Cancer incidence in children and young adults did not increase relative to parental exposure to atomic bombs

S Izumi*,1, K Koyama2, M Soda3 and A Suyama3
1Department of Statistics, Radiation Effects Research Foundation (RERF), 5-2 Hijiyama Park, Minami-ku, Hiroshima 732-0815 Japan; 2Department of Epidemiology, RERF, 5-2 Hijiyama Park, Minami-ku, Hiroshima, 732-0815 Japan; 3Department of Epidemiology, RERF, 1-8-6 Nakagawa, Nagasaki, 850-0013 Japan

We have examined whether parental exposure to atomic bomb radiation has led to increased cancer risks among the offspring. We studied 40,487 subjects born from May 1946 through December 1984 who were cancer-free in January 1958. One or both parents were in Hiroshima or Nagasaki at the time of the bombing and for childbirth. Using population-based tumor registry data we analyzed cancer incidence data from 1958 to 1997 by Cox regression models, and we examined the effects of both paternal and maternal irradiation with adjustment for city, sex, birth year, and migration. During follow-up, 575 solid tumor cases and 68 hematopoietic tumor cases were diagnosed. Median age at diagnosis was 39.7 years. Median doses were 143 millisieverts for 15,992 exposed (5 + millisieverts or unknown dose) fathers and 133 millisieverts for 10,066 exposed mothers. Cancer incidence was no higher for the offspring born in Hiroshima and Nagasaki. This finding is consistent with earlier studies of the cohort, which found no dose-dependent increases in mortality (Kato et al, 1966; Neel et al, 1974; Yoshimoto et al, 1991; Little et al, 1994), childhood cancer (Yoshimoto et al, 1990), cytogenetic abnormalities (Awa et al, 1987), or loss of enzyme activity (Neel et al, 1988). However, because cancers with high survival rates could not be adequately evaluated by mortality data, the effects of parental irradiation on cancer risks among the offspring need to be examined using the cancer incidence data.

In the present cohort study, we used population-based tumor registry data to examine whether parental exposure to atomic bomb radiation was associated with higher cancer incidence rates among the offspring born in Hiroshima and Nagasaki. We examined the effects of paternal and maternal irradiation on cancer risks among offspring both before and after they were 20 years of age.

Our long-term study of a large cohort of offspring of atomic-bomb survivors screens regularly for possible effects of parental preconception exposure to radiation. The latest mortality study (Izumi et al, 2003) suggested that such exposure did not lead to increased cancer mortality rates in childhood and young adulthood among the offspring born in Hiroshima and Nagasaki. This finding is consistent with earlier studies of the cohort, which found no dose-dependent increases in mortality (Kato et al, 1966; Neel et al, 1974; Yoshimoto et al, 1991; Little et al, 1994), childhood cancer (Yoshimoto et al, 1990), cytogenetic abnormalities (Awa et al, 1987), or loss of enzyme activity (Neel et al, 1988). However, because cancers with high survival rates could not be adequately evaluated by mortality data, the effects of parental irradiation on cancer risks among the offspring need to be examined using the cancer incidence data.

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METHODS

Study population

We analyzed a subset of the F1 mortality study cohort of the Radiation Effects Research Foundation (RERF), Japan (Kato and Schull, 1960; Yoshimoto et al, 1990), consisting of 40,487 Japanese offspring (20,743 men and 19,744 women) born from 1 May 1946 through 31 December 1984. They were conceived between 1 month and 38 years after the atomic bombing in August 1945 and one or both parents were in either city of Hiroshima or Nagasaki at the time of the bombing and for the childbirth. Almost two-thirds were born in Hiroshima, the majority between 1946 and 1959. Radiation dose was known for at least one parent. The subjects were alive and cancer-free in January 1958. Family and biological relationships were established from birth records, parental interviews, and maternal pregnancy data (Neel and Schull, 1956). The study sample did not include persons born to atomic-bomb survivors who had moved away from the cities after the bombings.

Follow-up/identification of cancer cases

We assessed cancer incidence from 1 January 1958 through 31 December 1997 through population-based tumor registries in Hiroshima and Nagasaki. These registries have collected information from local hospitals and death certificates since 1957 for Hiroshima and 1958 for Nagasaki. Tissue registries have been providing supplemental information about tumor cases to the tumor registries. Neither a nation-wide tumor registry nor access to other tumor registries has been established. Details of the
Statistical methods

We analyzed cancer incidence rates for subjects both before and after they were 20 years of age. We used Cox regression models to compute risk ratios and 95% confidence intervals for paternal and maternal radiation dose (using either groups or continuous values) with adjustment for the baseline rates for city, sex, year of birth, age at entry, and residency. Residence probabilities were estimated by city (Hiroshima, Nagasaki), sex (male, female), and calendar period (1958–60, 61–65, 66–70, 71–75, 76–80, 81–85, 86–90, 91–97). We also checked proportionality of hazard rates (Therneau and Grambsch, 2000). We found in a preliminary analysis that the results from Poisson regression models were similar to those from Cox regression models. Heterogeneity of risk ratios was tested among the groups of subjects whose parents were in either city of Hiroshima or Nagasaki at the time of the bombing. Evidence of any linear dose-response was also investigated among the subjects whose parents were in either city at the time of the bombing with known dose. We calculated two-sided P values, with values less than 0.05 indicating significance. EPICURE software was used for all statistical analyses (Preston et al, 1993).

RESULTS

During the 40-year period of follow-up (Table 2), 575 cases of solid tumors and 68 cases of hematopoietic tumors were diagnosed, representing a 1.4 and 0.2% cumulative incidence, respectively. Of these, 551 solid tumor and 44 hematopoietic tumor cases were diagnosed above age 20 years. For 3568 subjects with two exposed parents, 55 and 6 developed solid and hematopoietic tumors, respectively. Age at onset ranged from 0.8 to 50.9 years with a median of 39.7, and attained age for cancer-free subjects ranged from 0.003 to 51.7 years with a median of 44.9. Mean length of follow-up was 39.3 years. As subjects aged, the number of solid tumors increased far more than that of hematopoietic tumors, particularly in the digestive system. Other major tumor sites were breast, genital organ, and thyroid for female subjects and respiratory system, prostate, and urinary system for male subjects. In the course of follow-up, 77% of the subjects had passed their 40th year.

Cancer incidence rates were no higher among the subjects with one or two exposed parents than among the reference subjects (Tables 3 and 4). For the subjects with two exposed parents, the adjusted risk ratio was 0.97 (95% Confidence Interval (CI) 0.70–1.34) for all cancers, 0.97 (95% CI 0.69–1.36) for solid tumors, and 0.95 (95% CI 0.32–2.64) for hematopoietic tumors. Cancer incidence rates were not positively associated with either paternal or maternal radiation exposure (P > 0.1). Regarding a possible

Table 1 Distribution of parental radiation dose among 40,487 offspring of atomic-bomb survivors and controls

| Paternal dose                        | 0–4* | 5–49 | 50–149 | 150–499 | 500–4000 | Unknown | Not in city | Total |
|--------------------------------------|------|------|--------|---------|----------|---------|------------|-------|
| mSv (mean)                           | (0)  | (22) | (91)   | (290)   | (1148)   | (–)     | (0)        | (1148) |
| Maternal dose                        |      |      |        |         |          |         |            |       |
| 0–4*                                 | 5322 | 532  | 540    | 570     | 524      | 524     | 3279       | 11394 |
| 5–49                                 | 758  | 435  | 206    | 128     | 60       | 148     | 564        | 2073  |
| 50–149                               | 511  | 206  | 113    | 272     | 55       | 89      | 601        | 1814  |
| 150–499                              | 570  | 128  | 90     | 272     | 55       | 564     | 111        | 1848  |
| 500–4000                             | 430  | 60   | 45     | 111     | 564      | 601     | 667        | 1814  |
| Unknown                              | 524  | 148  | 89     | 148     | 564      | 601     | 667        | 1848  |
| Not in city                          | 11394| 2073 | 1814   | 1848    | 1814     | 1848    | 1848       | 1848  |
| Total                                | 11394| 2073 | 1814   | 1848    | 1814     | 1848    | 1848       | 1848  |

*Classified as the reference group.
linear dose-response, the adjusted risk ratio of all cancers at 100 mSv was 0.96 (95% CI 0.92–1.00) for paternal exposure and 1.01 (95% CI 0.98–1.04) for maternal exposure. No trend toward increasing cancer incidence was found for increasing dose ($P > 0.05$), but a decreasing incidence with increasing paternal dose was suggested ($P = 0.08$). The adjusted risk did not change with age, calendar period, sex, or parental age at the time of the bombing ($P > 0.1$). Findings were similar whether cancer occurred in childhood or young adulthood of the offspring.

**DISCUSSION**

The present study is the first to examine cancer risks in early adulthood of offspring born to one or two atomic bomb survivors in Hiroshima and Nagasaki. Our results suggest that cancer incidence in children and young adults did not increase relative to parental exposure to atomic bombs. The estimates and 95% confidence intervals of risk ratios provide an indication of the magnitude of possible effects for all levels of preconception exposure. For example, the 95% upper confidence bound of risk ratios indicates that there might be a 34% increase in cancer incidence rates among the subjects with two exposed parents relative to the reference subjects. Our results are consistent with those obtained in the latest study of cancer mortality in childhood and young adulthood for the same cohort members (Izumi et al., 2003). Our study is unique in certain respects. First, it involved a long-term follow-up of a large fixed cohort of a single ethnic group; second, the parents experienced single, whole-body exposures with

Table 2  Cancer incidence before and after 20 years of age among 40487 offspring of atomic-bomb survivors and controls

| Cancer site | ICD-9* | Male | Female | Total |
|-------------|--------|------|--------|-------|
| Solid tumors | 140–203, 225 | 15 | 9 | 234 | 317 | 575 |
| Digestive | 150–159 | 2 | 1 | 149 | 89 | 241 |
| Respiratory | 160–165 | 0 | 1 | 23 | 9 | 33 |
| Female breast | 174 | 0 | 0 | 0 | 88 | 88 |
| Female genital organ | 179–184 | 0 | 0 | 0 | 71 | 71 |
| Male genital organ | 185–187 | 1 | 0 | 14 | 0 | 15 |
| Urinary | 188–189 | 0 | 0 | 17 | 11 | 18 |
| Brain and nervous | 191,192,225 | 5 | 6 | 12 | 10 | 30 |
| Thyroid | 193 | 1 | 1 | 9 | 33 | 44 |
| Other | 6 | 3 | 10 | 16 | 35 |
| Hematopoietic tumors | 200–208 | 16 | 8 | 23 | 21 | 68 |
| Leukemia | 204–208 | 8 | 7 | 9 | 10 | 34 |
| Lymphoma | 200–202 | 8 | 1 | 14 | 11 | 34 |

Table 3  Adjusted risk ratio for solid tumor before and after 20 years of age in the offspring, according to parental preconception exposure to atomic bomb radiation

| Dose (mSv) | No. of cases* | Risk ratio | 95% CI | P-valueb | No. of cases* | Risk ratio | 95% CI | P-valueb |
|------------|---------------|------------|--------|----------|---------------|------------|--------|----------|
| Paternal exposure | | | | | | | | | |
| 0–4 (reference) | 4 | 1.00 | 0.78 | 156 | 1.00 | 0.60 |
| 5–49 | 3 | 0.80 (0.17–3.68) | 25 | 0.99 (0.63–1.49) |
| 50–149 | 23 | 0.89 (0.55–1.35) |
| 150–499 | 27 | 1.09 (0.71–1.63) |
| 500–4000 | 16 | 0.68 (0.39–1.10) |
| Unknown | 34 | 1.12 (0.76–1.61) |
| Continuous dose (100 mSv) | 1.03 (0.84–1.14) | 0.66 | 0.96 (0.92–1.00) | 0.07 |
| Maternal exposure | | | | | | | | | |
| 0–4 (reference) | 11 | 1.00 | 0.97 | 256 | 1.00 | 0.99 |
| 5–49 | 11 | 0.98 (0.42–2.31) | 43 | 0.89 (0.63–1.23) |
| 50–149 | 48 | 0.97 (0.70–1.31) |
| 150–499 | 49 | 1.02 (0.74–1.38) |
| 500–4000 | 34 | 1.02 (0.70–1.36) |
| Unknown | 43 | 0.99 (0.70–1.36) |
| Continuous dose (100 mSv) | 1.02 (0.88–1.12) | 0.73 | 1.01 (0.98–1.04) | 0.53 |

*International Classification of Diseases, 9th Revision.

In all, 55 offspring who developed solid cancer were conceived after both parents had been irradiated. *Test for homogeneity of risk ratios among dose groups or test for trend of linear dose response; baseline rates adjusted for city, sex, year of birth, residency, and age at entry.
Table 4  Adjusted risk ratio for hematopoietic tumor before and after 20 years of age in the offspring, according to parental preconception exposure to radiation

| Dose (mSv)          | Age 1–19 years | Age 20+ years |
|---------------------|----------------|---------------|
|                     | No. of cases* | Risk ratio   | 95% CI | P-value b | No. of cases* | Risk ratio   | 95% CI | P-value b |
| Paternal exposure   |                |              |        |           |                |              |        |           |
| 0–4 (reference)     | 7              | 1.00         | 0.47   |           | 11             | 1.00         | 0.86   |           |
| 5–49                | 7              | 1.07         | (0.36–3.13) | 0.58 | 3               | 1.68         | (0.37–5.60) | 0.58   |           |
| 50–149              | 1              | 0.58         | (0.03–3.06) | 0.63 | 2               | 1.10         | (0.17–4.21) | 0.63   |           |
| 150–499             | 2              | 1.10         | (0.03–3.28) | 0.63 | 1               | 0.63         | (0.03–3.28) | 0.63   |           |
| 500–4000            | 1              | 0.63         | (0.03–3.28) | 0.63 | 0               | Not estimated |        |           |
| Continuous dose (100 mSv) | 0.97         | (0.73–1.09) | 0.70   |           | 0.91           | (0.65–1.07) | 0.36   |           |
| Maternal exposure   |                |              |        |           |                |              |        |           |
| 0–4 (reference)     | 7              | 1.00         | 0.14   |           | 23             | 1.00         | 0.90   |           |
| 5–49                | 10             | 1.55         | (0.59–4.28) | 0.14 | 4               | 0.96         | (0.28–2.53) | 0.14   |           |
| 50–149              | 3              | 0.66         | (0.16–1.92) | 0.14 | 6               | 1.40         | (0.51–3.24) | 0.14   |           |
| 150–499             | 6              | 0.99         | (0.23–2.87) | 0.14 | 3               | 0.72         | (0.17–2.10) | 0.14   |           |
| 500–4000            | 3              | 0.72         | (0.17–2.10) | 0.14 | 0               | Not estimated |        |           |
| Continuous dose (100 mSv) | 1.04         | (0.89–1.13) | 0.58   |           | 0.97           | (0.83–1.07) | 0.63   |           |

*6 offspring who developed hematopoietic tumor were conceived after both parents had been irradiated. bTest for homogeneity of risk ratios among dose groups or test for trend of linear dose response; baseline rates adjusted for city, sex, year of birth, residency, and age at entry.
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