Genetic Effects of Radiation in Atomic-bomb Survivors and Their Children: Past, Present and Future

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Atomic bomb/Radiation/Genetic risk/Birth defects/Chromosome aberration.

Genetic studies in the offspring of atomic bomb survivors have been conducted since 1948 at the Atomic Bomb Casualty Commission and its successor, the Radiation Effects Research Foundation, in Hiroshima and Nagasaki. Past studies include analysis of birth defects (untoward pregnancy outcome; namely, malformation, stillbirth, and perinatal death), chromosome aberrations, alterations of plasma and erythrocyte proteins as well as epidemiologic study on mortality (any cause) and cancer incidence (the latter study is still ongoing). There is, thus far, no indication of genetic effects in the offspring of survivors. Recently, the development of molecular biological techniques and human genome sequence databases made it possible to analyze DNA from parents and their offspring (trio-analysis). In addition, a clinical program is underway to establish the frequency of adult-onset multi-factorial diseases (diabetes mellitus, high blood pressure, and cardiovascular disease etc) in the offspring. The complementary kinds of data that will emerge from this three-pronged approach (clinical, epidemiologic, and molecular aspects) promise to shed light on health effects in the offspring of radiation-exposed people.

INTRODUCTION

In 1927, Muller reported that X rays induced mutations in germ cells of fruit flies.1) Since then, a large number of studies have been conducted on the mutagenicity of ionizing radiation in various organisms.2) These studies have demonstrated that ionizing radiation has the potential to induce mutations in any species, and that there is no reason to suspect that humans are exceptional. On the other hand, it is also true that no study has conclusively demonstrated a detrimental genetic effect of radiation in the offspring of radiation-exposed people. (It is noted that detrimental effects of radiation to fetuses, such as miscarriage, malformation, or mental retardation are known but these are not due to genetic effects of radiation and hence will not be included in this report.)

In 1945, the people of Hiroshima and Nagasaki were hit by atomic bombs and suffered from various health problems due to damage not only from the blast and heat (or fire) but also from radiation. By the end of 1945, most of the early deaths related to acute radiation damage had occurred, and the survivors started to reconstruct their new post-war lives. One of the immediate concerns then was the possibility of radiation-induced genetic effects in the children of the survivors who were going to have children. Since, at that time, there was no scientific knowledge on humans, rumors sprang up that malformations often occurred in the offspring of survivors. The Atomic Bomb Casualty Commission (ABCC) was also concerned with this possibility and planned and initiated in February 1948 the first genetic study designed to assess the frequency of birth defects in children born to exposed parents (no reliable information on miscarriage could be obtained, though). This was a monumental scientific accomplishment during the chaotic postwar era. The finding of this initial study was that there was no increase in birth defects which helped to defuse some of these rumors.3) However, rumors persisted fueled in part by the movies and popular press.

To obtain additional and more convincing data, ABCC and later the Radiation Effects Research Foundation (RERF), conducted additional large-scale surveys. No increase in genetic effects was found in any of these studies.4) Having said this, it should be noted that the mean dose to the survivors was generally much smaller compared to the doses usually employed in animal studies. For example, the fraction of survivors who had an estimated dose of 2 Gy or higher consist of only 1.4% among the members of a large epidemiologic cohort (Life Span Study, LSS) with doses of >0.005 Gy (679/50,113), while genetic studies in mice mostly used radiation dose of 3 Gy or larger.5) Therefore, detec-
tion of genetic effects in the offspring of the survivors depends ultimately on the sensitivity of the methods used and the number of subjects studied. In this report I briefly describe our past and present studies, and introduce plans for future analysis with new, molecular techniques which promise greatly to increase the sensitivity of our analysis.

PAST STUDIES OR ACHIEVEMENTS

Most of the studies in early years of ABCC are best presented in a book edited by Neel and Schull. Table 1 shows a list of the major genetic studies at ABCC and RERF.

Untoward Pregnancy Outcome (UPO)

The endpoints of this study included congenital malformations, stillbirth, and perinatal death (death within 1 week after birth). Because the study was initiated in 1948, the survivor cohorts which were established in the late 1950s did not exist so that the study used identified pregnancies from a food-ration system. Since pregnant women who appeared at the city hall for registration following completion of the fifth months of gestation could obtain special food rations, it became possible by this method to identify and follow more than 90% of pregnancies that occurred in the contacting areas of Hiroshima and Nagasaki.

At the time of termination of the pregnancy, the midwife or Japanese physician completed a questionnaire regarding the delivery. If the newborns appeared normal by visual inspection, the midwife kept the questionnaire until it was collected weekly by ABCC. If the newborns appeared abnormal, the midwife informed the Commission by telephone as soon as possible. Regardless of the outcome, a Japanese physician examined the child and made a detailed report to ABCC. If the physician encountered an unusual abnormality, he could arrange, if the parents were willing, for an American pediatrician at ABCC to see the babies. This method worked well so that about 77,000 newborns were examined from 1948 to 1954. Also an autopsy program was initiated in 1948 in Hiroshima and several years later in Nagasaki. Information on radiation exposure conditions of both parents and certain other relevant facts such as genetic relationship of the parents was collected through questionnaires but needless to say estimations of individual dose were not possible. Therefore, exposure conditions for each

Table 1. Summary of large-scale surveys at ABCC-RERF

| Study                                | No. of study subjects or cohort members | Study period        | Note on analysis                          |
|--------------------------------------|----------------------------------------|---------------------|-------------------------------------------|
| Birth defects (Untoward pregnancy outcome) | 77,000                                 | 1948–1954           | Congenital malformation, stillbirth, perinatal death |
| Sex ratio                            | 140,000                                | 1948–1966           | Search for X-chromosomal recessive lethal mutations |
| Cytogenetics                         | 16,000                                 | 1967–1985           | Solid Giemsa method                       |
| Biochemical genetic study            | 23,000                                 | 1975–1984           | Electrophoretic variants and erythrocyte enzyme activity |
| Epidemiologic follow-up              | 77,000                                 | 1946–present        | Mortality from any cause and cancer incidence |

Table 2. The observed cases of major malformation in relation to dose groups (ref. 4)

| Mother’s radiation statusa) | Unexposed | Low dose | Moderate dose | High dose |
|-----------------------------|-----------|----------|---------------|-----------|
| Unexposed                   | 294/31,904(0.92%) | 121/14,684(0.82%) | 23/2,932(0.78%) | 19/1,676(1.1%) |
| Low dose                    | 28/3,670(0.76%) | 62/5,994(1.0%)  | 7/703(1%)   | 3/318(0.9%)  |
| Moderate dose               | 12/839(1.4%) | 4/658(0.6%)  | 6/615(1%)   | 3/146(2%)  |
| High dose                   | 6/534(1%) | 4/422(0.9%)  | 1/192(0.9%) | 1/145(0.7%) |

a) Low dose = exposed at > 3 km, any shielding at 2.0–2.9 km, heavy or moderate shielding at 1.5–1.9 km, heavy shielding at < 1.4 km. Moderate dose = no shielding at 2.0–2.9 km, light shielding at 1.5–1.9 km, moderate or light shielding at 1.0–1.4 km, moderate shielding at < 1.0 km. High dose = no shielding at 1.0–1.9 km, light or no shielding at < 1.0 km, or presence of acute radiation symptoms at any distance < 3 km.
person were classified into five groups according to distance from the hypocenter, shielding conditions (heavy, moderate, or light shielding), and the presence or absence of acute radiation symptoms. No individual doses were used in the analysis.

Fortunately, deleterious effects of parental exposure to radiation were not found for any individual endpoints measured or as UPO in total.4) For example, among 31,904 live births to unrelated parents in the unexposed group (i.e., consanguineous marriages were excluded), 294 (0.92%) had severe malformations (Table 2). The frequency of malformations in children of survivors was almost the same as that of a control population of babies born in the Tokyo Red Cross Maternity Hospital during 1922-1940 (cited in ref. 4) (456 with severe defects of 49,645 newborns or 0.92%) although the definition of severe malformation was somewhat different between the two studies.4) The results were later reanalyzed using DS86 doses which gave estimated doses to individuals.6) No effect of parental exposure to radiation was uncovered by this re-analysis.5) The summary data of UPO using DS86 dose is shown in Table 3. Since the frequency of observed congenital malformation depends on the clinical methods employed as well as the years of follow-up, about 19,000 newborns from Hiroshima and Nagasaki were clinically re-examined at 9 months of age with again no indication of a radiation-related effect.4)

### Table 3. Summary of untoward pregnancy outcome in relation to DS86 dose to the parents (ref. 7).

| DS86 dose of mothers (Gy)a | <0.01 | 0.01–0.5 | 0.5–1.0 | >1.0 |
|---------------------------|-------|----------|---------|------|
|                           | 2,257/45,234 (5%) | 260/5,445 (4.8%) | 44/651 (6.8%) | 19/388 (4.9%) |
|                           | 81/1,614 (5%) | 54/1,171 (4.6%) | 1/43 (2.3%) | 2/30 (7%) |
|                           | 12/238 (5%) | 4/68 (6%) | 1/49 (9%) | 1/9 (11%) |
|                           | 17/268 (6.8%) | 2/65 (3%) | 1/17 (6%) | 1/15 (7%) |

a) Parental dose means gamma-ray dose plus 20 times the neutron dose.

### Sex ratio

When the genetic study was initiated in the 1940s, most of the knowledge in genetics was based on studies in Drosophila. Since sex-linked recessive mutations were well known in Drosophila, it was expected that such mutations would occur also in humans. Therefore, it was hypothesized that if a detrimental, recessive mutations were induced in the X chromosome of oocytes by radiation exposures, more male fetuses would be lost since males carry single X chromosomes derived from the mother. (In the case of fathers’ exposure, the conditions are more complicated and I will not consider them here). Later studies revealed, however, that the hypothesis was too naive and human geneticists no longer believe it possible to estimate radiation effects from sex ratio data. This is mainly because, in contrast to Drosophila in which both X chromosomes are active in females, it was found in 1961 that one of the two X chromosomes in female mice is inactivated in somatic cells (Lyonization).8) This means that the recessive mutation would not be silenced in the female somatic cells when the mutation-carrying X chromosome is active (hence, the normal X chromosome is inactivated), which raised the question of whether X-chromosomal recessive mutations are really completely hidden in heterozygous female mammals. In fact, later studies in mice could not find any induced sex-linked recessive mutations.5) Searle concluded in his review article as that “any induced lethals are likely also to have a deleterious effect in the heterozygote...so may well be lost before their hemizygous effects can be detected”.5) Further, inactivation of the X chromosome in placenta of human female fetuses varies, i.e., either random, or preferentially maternal, or paternal.9) Additionally, sex chromosome aneuploidies, e.g., XXY Kleinfelter syndrome and XO Turner syndrome, were not known at that time (the frequency is currently estimated as 0.25% among live births7).

A brief outline is that initial results obtained in 1953 seemed to support the notion of a sex-ratio shift. Since this was not statistically significant, data collection was continued until 1966 to accumulate 140,542 births. It turned out, however, that the results did not confirm the initial trends. Table 4 shows the summary of maternal exposure cases.4)

### Table 4. Sex ratios in the offspring born to exposed mothers (ref. 4).

| Mother’s dose | Male birth | Female birth | Sex ratio |
|--------------|------------|--------------|-----------|
| 0            | 34,559     | 31,989       | 108.0     |
| 8 rep        | 15,447     | 14,410       | 107.2     |
| 75 rep       | 3,096      | 2,949        | 105.0     |
| 200 rep      | 1,799      | 1,660        | 108.4     |

rep = old dose unit, roentgen equivalent physical; i.e., equivalent to 1R of X or gamma rays.

### Cytogenetic study

In this study, the solid Giemsa staining method was used to examine blood lymphocytes from 8,322 offspring born to exposed parent(s) (i.e., within 2 km from the hypocenter) and 7,976 offspring born to unexposed parents (or exposed beyond 2.5 km from the hypocenter) who were selected from the F1 cohort for epidemiologic mortality study. The
mean age at the time blood samples were collected was 24 years. Extensive efforts were made to attain a high participation rate of 75% among the 60% of the offspring who could be contacted (5% of the cohort member had already died and 35% had migrated out from contacting areas in Hiroshima and Nagasaki). The prevalence of chromosome aberrations was the same in both the exposed and unexposed groups (Table 5). The overall frequency of individuals with any cytogenetic abnormality (either numerical or structural) was 0.5–0.6% in both groups, which agrees closely with results obtained in studies of newborns in different places in the world. Table 6 summarized the data on the origin of structural rearrangements, which indicates that the majority of the aberrations were inherited. The de novo mutation rate was calculated as about 0.02%, which is close to the estimated rate from other studies of 0.018%.

**Table 5.** Summary of cytogenetic analysis of chromosome abnormalities in offspring of exposed and unexposed populations (refs. 4, 10)

| Parental conditions                  | Exposed | Control |
|-------------------------------------|---------|---------|
| No. of offspring                    | 8,322   | 7,976   |
| Sex chromosome anomaly              | 19      | 24      |
| Autosomal structural change          | 23 (18) | 27 (25) |
| Autosomal trisomy                   | 1       | 0       |
| Total                               | 43 (0.52%) | 51 (0.64%) |

\(^a\) Number in the parentheses indicates stable-type aberrations.
\(^b\) Down’s syndrome.

**Table 6.** Summary of the origin of stable-type aberrations (autosomal structural rearrangements) (refs. 4, 10)

| Origin of the rearrangement         | Exposed | Control |
|-------------------------------------|---------|---------|
| De novo (both parents were normal)  | 1       | 1       |
| Inherited                           | 10      | 15      |
| Parents not tested                  | 7       | 9       |
| Total                               | 18      | 25      |

**Biochemical genetic study**

In this study, 30 different proteins in plasma and erythrocytes were examined to detect electrophoretic variants which mostly originated from amino acid substitutions but could also be derived, at least in theory, from small deletions or insertions. After examination of more than one million genes, only three mutations were detected in each of the exposed and control groups. Obviously, no indication of radiation effect was seen. Although the technique was cutting edge in those days, it is now accepted that ionizing radiation induces predominantly deletion type mutations in mammalian cells (which the technique was not set up to detect) rather than base-change mutations which lead to amino-acid substitutions. In order to detect deletion mutations, reduction of enzymatic activity of 11 erythrocyte enzymes was also looked at but only one mutation was observed among about 10,000 offspring (5,000 each in the control and exposed groups).

**Mortality and cancer incidence**

Recent studies on mortality and cancer incidence in the offspring, covering a follow-up period of 54 years (1946–1999), showed no indication of an effect on these endpoints of parental exposure to radiation. As the authors noted, these results are very preliminary and inconclusive since the cohort analyzed is still young (mean age was about 45 years in 1999) so that the cumulative mortality was still very low, only about 5%. Further follow-up is needed for several more decades before valid conclusions can be made.

**Establishment of lymphoblastoid cell lines from parents and offspring of 1,000 families**

We spent nearly 10 years collecting blood from both parents and their offspring from which to establish lymphoblastoid cell lines by Epstein-Barr virus infection. So far, cell lines have been established from about 1,500 offspring and from about 2,000 parents, of which about 300 were born to parents exposed to > 1Gy, about 600 to < 0.01 Gy (controls). The remaining cases received doses of between 0.01 and 1 Gy. In addition, uncultured lymphocytes and white blood cells are also stored. These materials are unique resources for studying radiation-induced mutations in humans.

**CURRENT STUDIES**

**Two-dimensional DNA electrophoresis in the offspring of the survivors and of mice**

This technique uses a combination of restriction enzymes to end-label DNA fragments with $^{32}$P. The labeled-DNA is subjected to first dimensional gel followed by in gel digestion with the third restriction enzyme and subjected to second two-dimensional electrophoresis to separate the fragments. Subsequently, autoradiograms are developed to show more than 1,000 spots most of which are derived from auto-
somal DNA fragments having two copies per genome. Detection of mutations at autosomal genes consists of identifying spots that have half the density among the two-copy spots. A 50% reduction in spot intensity indicates the possibility of a deletion mutation that resulted in loss of one copy of autosomal genes. Analysis is carried out using computer-assisted image analysis. The advantages of the method include: no exogenous probe is required; mutations at any of about 1,000 sites (or genes) in the genome can be screened at a time; the nature of mutation can be assessed by cloning and sequencing of the putative mutant spot, or its normal counterpart.

A pilot study on 100 families (50 highest dose of > 1Gy and 50 control families) of atomic bomb survivors was conducted but only one mutation was found in the offspring of the control group. Results in mouse offspring derived from irradiated spermatogonia indicate that the mean mutation induction rate (mutations per generation per unit dose of radiation) at about 1,000 loci (GC-rich Nof restriction sites) in the genome is considerably lower than the mean rate found at the 7 genes that were widely used at Oak Ridge National Laboratory by Russell and coworkers. The discrepancy between our results and those of Russell and coworkers is due to the inclusion of the s and d loci (which turned out to be extremely sensitive to radiation induced mutations) among the 7 loci; this inflated the average induced mutation rate estimated with the 7-loci method. The mean mutation induction rate at the remaining 5 loci is similar to the mean rate at 1,000 genes.

Minisatellite mutation

Micro- or minisatellites are composed of multiple short-sequence units (i.e., of 1-5 or 6-100 nucleotides, respectively, but with a rather arbitrary border) repeated in tandem and arranged in arrays, and range from 0.5 kb to >30 kb in length in the case of minisatellites. Some minisatellites are known to be hypervariable, i.e., the number of repeat unit varies extensively among individuals as a result of high spontaneous mutation rate in germ cells. Further, studies in mice indicated that both low-LET radiation and fast neutrons induced mutations at a rate of nearly 10% per Gy at some minisatellites in male germ cells, which is too high to be induced by direct hit of the loci by irradiation. Thus, the minisatellite mutations are considered as originating from genomic instability induced by radiation exposure although the underlying mechanisms for the instability are not known. Although Dubrova’s group repeatedly observed radiation effects in germ cells of people who were exposed to chronic and/or low level radiation, we could not find such an effect in our pilot study which includes 49 offspring born to parents exposed to a mean estimated dose of 1.7 Gy. The reasons for the discrepancy remain to be resolved.

Microarray-based comparative genomic hybridization (CGH)

In 2000, we introduced a microarray system (Affymetrix@417) and started to create microarrays for detecting deletion mutations in the genome by means of CGH. We obtained 2,500 bacterial clones bearing DNA fragments from different regions in the human genome (about 1.2 Mb apart) as bacterial artificial chromosomes (BAC), cultured them to isolate the BAC DNA, and spotted the DNA on glass slides. A pilot study on 80 offspring of the survivors (40 with highest parental dose and 40 in the control) is currently in progress to evaluate both the spontaneous and radiation-induced rates of deletions. Studies from other laboratories using the array CGH technique are revealing that genomic gain or loss is frequent in normal individuals. We expect that a similar situation will hold also for the Japanese population. If this is in fact the case, the high background rate of deletion will complicate attempts to identify and quantify radiation-induced deletions among the offspring of the A-bomb survivors and in other populations exposed to radiation.

F1 clinical health study

The study was planned to ascertain the frequency and prevalence of adult-onset life-style diseases (multifactorial diseases) such as diabetes mellitus, high blood pressure, and cardiovascular disease etc. in the offspring of atomic bomb survivors in relation to the radiation dose to the parents. More than 10,000 individuals will be examined in 5 years (2002–2006). Plans have been formulated to gain support to expand this population and to extend these studies for many more years.

F1 epidemiologic study

Collection of data on both mortality from any causes and cancer incidence is in progress on a cohort population of 77,000 to clarify health effects of radiation in the offspring of survivors. This study will be continued until this population (current median age is about 45 years) reaches the age at which cancer and other pathologies will be more prevalent. The cancer incidence is expected to reach a peak in about 30 years so that to gain maximum insights it will be necessary to continue this study until at least 2030–2040.

FUTURE STUDIES

Future studies will comprise three facets; clinical study, epidemiologic study, and molecular study.

One of the molecular studies that we plan to initiate is to create an animal model system to shed light on genetic risk of exposed human females. In this regard, past studies which used mice were not appropriate because immature oocytes, the target cells at risk in humans, are highly sensitive to death by apoptosis after irradiation, while human immature

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oocytes are far less radiosensitive. We have recently found that rat immature oocytes are only moderately sensitive to radiation and thus the rat may be a good model for human exposure.

Another study relates to mutations at microsatellite loci, which is under preparation as a small-scale collaborative investigation with Dr. T. Nomura at Osaka University. Microsatellites are defined as tandem arrays of repeated short sequences varying from single to a few bases, and compared with minisatellite which spans a few kb, microsatellites sequences are much shorter and hence can be subjected to direct sequencing to detect genetic alterations. The study will clarify if there are any microsatellite loci that are suitable as biomarkers for genetic study in humans.

We also plan to apply multicolor FISH techniques to quantify translocations in the offspring. Although our previous study using the solid Giemsa method did not show any effect of radiation on induction of chromosome aberrations, FISH appears to offer a more sensitive method of detection, especially in detecting translocations involving telomeric regions.

CONCLUSION

It is worth reiterating here that the mean radiation dose to the A-bomb survivors is small (the mean parental dose in the exposed group of the epidemiologic F1 cohort is on the order of 0.4 Gy compared to the doses frequently used in mouse germ cell mutagenesis experiments which is usually 3 Gy or larger. Therefore, it will continue to be a difficult task to observe a genetic effect in the F1 cohort of the survivors. However, it is unlikely that humans are the exception as to be free from induction of germ cell mutations by irradiation. Therefore, it would not be appropriate to ask if there is any possibility of detecting radiation effect but rather to ask how large the effect could be. In this context, we hope there are still ways to contribute to scientific understanding of genetic effects of radiation in humans.

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J. Radiat. Res., Vol. 47, Suppl. B (2006); http://jrr.jstage.jst.go.jp
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