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

Persistent concerns about possible genetic risks of radiation exposure coupled with society's increased focus on medical radiation and radiation accidents prompted RERF scientists to reexamine—with reference to recent findings—historical data related to untoward pregnancy outcomes (UPO) using the latest statistical techniques and updated dosimetry information.

A study of nearly all pregnancies in the cities of Hiroshima and Nagasaki was conducted by ABCC (RERF's predecessor organization) during the period 1948–1954 to determine whether there were increases in occurrence of the UPO categories of congenital malformations, stillbirths, and neonatal deaths among the children of atomic bomb survivors at the time of birth. Association between radiation exposure and each of the three outcome categories, and the three categories together, had been analyzed in past studies (1956, 1981, 1990), but no associations of statistical significance were found.

This most recent reanalysis of the original ABCC study defines UPO into three categories: [1] congenital malformations observed at birth; [2] perinatal deaths—relating to immediately before and after birth, including stillbirths—within 7 days from birth; and [3] perinatal deaths within an expanded timeframe of 14 days from birth. With 71,603 children of A-bomb survivors, selected from the original ABCC study, this reanalysis looked at the effects of parental exposure dose (in the mother, or father, or both combined) in each of the three UPO categories, totaling 9 combinations (the 3 UPO categories multiplied by the 3 different dose groups).

This study reanalysis reworked[1] the data from the previous ABCC studies to minimize biases[2] arising from the original data-collection process, after adjusting[3] for risk factors besides radiation (e.g., age of parents, consanguineous parents [marriage with a related individual], and so on) in all study participants. However, since information about economic status and the like was available for only some of the children, adjusting for those factors was not possible. The reanalysis showed that increased doses in mothers, fathers, and both parents resulted in increased trends for each of the UPO markers, but the increases were not statistically significant for most of the categories, except for 1 of the 9 patterns (combined dose, and deaths within 14 days). It is known that congenital

malformations and perinatal mortality were affected by socio-economic factors other than radiation, such as poverty. Given the important influence of factors other than radiation from the atomic bombings such as socio-economic conditions, radiation effects might have been overestimated. The increased trends of risks observed in this study, therefore, likely cannot be interpreted to be only the result of radiation—or genetic—effects. In addition, since it is conceivable that UPO findings might have been affected by socio-economic conditions and the harsh living environment following the war caused by the atomic bombings, these reanalysis results cannot be applied to people exposed to radiation other than A-bomb radiation, such as medical exposures.

At the same time, since in the reanalysis an increase was observed for each of the three UPO markers, further investigation regarding the direct effects of radiation in the children of A-bomb survivors is considered essential. The rapidly advancing field of life sciences is thought to offer great promise with respect to continued research into this area. Utilization of whole-genome sequencing for analyses of biosamples donated by A-bomb survivors and their surviving children, for example, is anticipated to help clarify much of the uncertainty about genetic effects of parental radiation exposure.

Notes

[1] The methods used in the past analyses differed from those utilized in this reanalysis. The major differences involved the source data and exclusion criteria. The 1981 and 1990 analyses included newly diagnosed congenital malformations from about 30% of the children initially surveyed at birth who were reexamined in the ABCC pediatric program about 9 months later. Our most recent reanalysis, however, considered only malformations present at birth. By so doing, diagnosis of congenital malformations for all children were carried out under the same conditions. The reanalysis also differed in terms of conditions used for determining exclusion from analysis. For example, about 500 individuals whose birthweight was unknown were excluded from the past analyses. In this most recent reanalysis, however, understanding the effect of exposure on birthweight was not an objective, and thus birthweight, even if unknown, was included in analysis. Such differences in conditions for exclusion from analysis represented one factor leading to an increased number of individuals in this reanalysis compared with past analyses. In this way, the data were reworked to respond to changes and differences in analysis methodologies.

[2] For example, in cases when autopsies are conducted, more congenital malformations are likely to be found. Most congenital malformations found at birth are visible, such as an excess number of fingers and/or cleft palate. However, autopsies allow investigation of malformations that are not visible at birth and would not be diagnosed as malformations at that time, including those of internal organs. Even without differences in frequency of malformations at birth between group “A” and group “B” before autopsy, more events (malformations) would occur in the autopsied group if more autopsies were to be

conducted for individuals in group A, for example. This would represent inaccurate analysis results due to a "bias" in diagnosis of congenital malformations, leading to an increase in frequency of malformations for group A. In such analysis, therefore, it is important to first consider whether any bias exists in the population or group being studied and whether there is a way to minimize the bias if present. For the above reasons, the main analyses in this paper did not include congenital malformation cases identified only by autopsy.

[3] Using age as an example, it is known that the older the age of the mother, the more likely congenital malformations and perinatal deaths will occur at the birth of offspring. Hypothetically, when comparing exposed group "C" to unexposed group "D" without considering age, analysis might indicate people unexposed to radiation have serious events (such as malformations and deaths) in offspring if the average age of the mother is high, even without any association between severe events at birth and parental radiation exposure. To avoid such inaccuracies, this reanalysis used the latest statistical analysis with age taken into consideration (in what is called age-adjusted analysis).

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RERF's objective with this brief outline is to succinctly explain our research for the lay public. Much of the technical content of the original paper has been omitted. For further details about the study, please refer to the full paper published by the journal.