3 Second-generation Survivors (Genetic Effects)

A Birth disorders (stillbirth, malformation, neonatal mortality)

Summary

To investigate the possibility that A-bomb radiation affected germ cells of the A-bomb survivors and led to an increased frequency of birth defects, a large-scale study of newborns was conducted over the period 1948-54, during which physicians examined more than 77,000 newborns within two weeks of birth. The survivors (fathers and mothers) were divided into five dose groups depending on distance from the hypocenter and degree of shielding at the time of bombing, and their data were analyzed with respect to stillbirth, malformation, neonatal mortality, and so on. The results did not indicate an increased frequency of birth defects with increasing parental radiation dose. Later, when individual doses (assessed by DS86) became available the results were reanalyzed, but the conclusion remained the same. In the years, with improvements in the cure rate of childhood cancers (radiation therapy contributed substantially to this result), many such patients are able to marry and have children. Studies of the offspring of former cancer patients do not suggest increased frequency of malformation, even in cases of extremely high parental gonadal doses from radiation therapy employing up to 25 Gy.

B Sex ratio

Summary

Parental exposure to the atomic bombings had the potential to alter the sex ratio in the offspring, due to induction of lethal mutations in the X chromosome of sperm and egg. Initial studies seemed to provide evidence of that possibility, but the results were not statistically significant. Thus, collection of sex-ratio data was continued even after termination of the study on birth defects. Ultimately, however, information obtained from more than 140,000 offspring did not support the initial hypothesis of alteration in the sex ratio.

C Chromosomal aberrations

Summary

Ionizing radiation has the potential to induce double-strand breaks in DNA. Cells, on the other hand, are endowed with the capacity to repair such DNA breaks. The repair process is not complete, however, with the wrong strand ends sometimes being joined together, resulting in chromosomal abnormalities (structural abnormalities). When such abnormalities occur in the chromosomes of reproductive cells (sperm and egg cells), there is the potential for an increased rate of offspring bearing structural chromosome aberrations. A study was thus conducted of chromosomes in the blood lymphocytes of 8,322 offspring with at least one parent exposed to an estimated dose of 0.01 Gy or greater (according to T65D dose) within 2,000 m of the hypocenters (exposed group), and in the blood lymphocytes of 7,976 offspring in an unexposed control group with both parents exposed to less than 0.01 Gy (exposure at distances of greater than 2,500 m or persons not in either Hiroshima or Nagasaki at the time of the bombings). The study did not reveal effects of

parental exposure to radiation, confirming only one case with a new chromosomal aberration in each of the two groups of offspring.

D Studies of protein-level genetic effects, and later DNA studies

Summary

One of the concerns immediately following the dropping of the atomic bombs was whether exposure to radiation in the parents causes genetic effects in the offspring. For that reason, different genetics studies, from those at the clinical level to those at the DNA level, have been carried out up to the present time. Such studies include ones now deemed inadequate despite the fact that the methods were considered advanced at the time of investigation or ones that studied an insufficient number of genes. In any case, fortunately, none of the studies has been suggestive of effects of parental exposure to radiation. Starting in the early 2000s, genome analysis technology started to be used even in non-specialized labs, and as a result, individual genome studies using high-density microarrays were begun. An era of research based on whole-genome sequencing is now nearly upon us.

E Mortality rate

Summary

Genetic effects of parental radiation exposure have been studied as indices of the rates of mortality in the offspring of A-bomb survivors (second-generation survivors). No effects of parental radiation exposure have been observed in the studies carried out to date regarding mortality at birth or in childhood, mortality under the age of 20 years, or mortality in those 20 years and older (average age: 46 years). However, the proportionate mortality in such cohorts is still 3.5%, and thus it is too early to derive any conclusions. In studies other than those of A-bomb survivors, studies investigating effects of parental exposure to radiation from radiotherapy of childhood cancers are important, as the radiation doses to the gonads are high. In male ex-patients (former patients), increased risk of stillbirth or perinatal mortality has not been found in the offspring, but in female ex-patients, an increased risk of stillbirth or neonatal mortality has been observed although the risk is limited to instances of treatment prior to menarche. As such effects have not been observed in post-menarche treatment and because increased risk of low birth weight in the offspring of female ex-patients has been known for some time, it is now considered that such results are likely due to radiation exposure affecting the uterus, not genetic effects of exposure of the ovaries.

F Cancer incidence

Summary

Radiation has the potential to induce cellular mutations, and hence when such mutations occur in reproductive cells, they may lead to increased risk of cancers in the offspring of people exposed to radiation. However, in research that investigated the offspring (F1 generation) of mice exposed to X rays, the results are not concordant: some reports showed that tumor frequency increased while others did not, with no progress made in terms of understanding the underlying mechanisms behind such processes. Mortality and cancer incidence rates have been investigated continuously in about 77,000 offspring of

A-bomb survivors since 1959, the year of establishment of the cohort. Since some childhood cancers are known to occur as a result of inheritance of cancer-susceptible genes from the parents (for example, retinoblastoma), the possibility exists of an increased frequency of early onset malignancies should a mutation occur that inactivates tumor-suppression genes in reproductive cells. Nevertheless, no effects of parental exposure to radiation have been found in follow-up studies spanning around 40 years. Studies targeting persons other than A-bomb survivors mainly involve offspring of childhood cancer survivors who were exposed to radiation for medical purposes, but there also no effects of parental exposure have been observed. In other words, apart from cases of in-utero exposures (increased risks of childhood leukemia and childhood cancers are reported but their causal relationship is still under debate), no evidence exists of genetic effects of parental exposure to radiation regarding increased risk of childhood leukemia and cancers in the offspring. With respect to the risk of solid cancers in the offspring, which generally increases with aging, continued study is important.

G Multifactorial disease prevalence

Summary

Epidemiological research investigating effects on adult-onset multifactorial diseases (excluding cancers) as a genetic result from radiation exposure is limited at present (May 2011) to one study conducted between 2002 and 2006 by RERF. The study included 11,951 offspring of A-bomb survivors exposed in Hiroshima and Nagasaki and examined whether there was any association between prevalence of adult-onset multifactorial diseases (hypertension, diabetes, hypercholesterolemia, myocardial infarction, angina, and stroke) and parental radiation exposure. The study found no evidence indicating increased risk of such multifactorial diseases overall (combined as a single endpoint) in the offspring in association with parental radiation exposure.