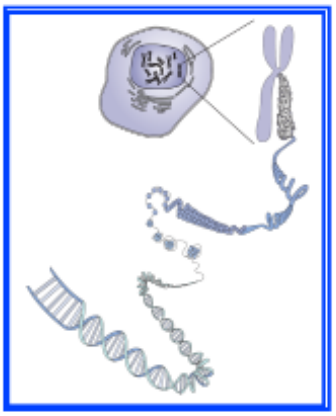
Heritable Effects

Risks of Heritable Effects for Human Beings



- Radiation effects on gonads (reproductive cells)
  - ◎ Gene mutations
    Changes in genetic information in DNA (point mutation)
  - ◎ Chromosome aberrations
    Structural chromosomal aberrations
    * Increases in hereditary diseases in the offspring have not been proved among human beings.
- Risks of heritable effects (up to children and grandchildren)
  = Approx. 0.2%/Gy (Two out of 1,000 people per gray)
  (2007 Recommendations of the International Commission on Radiological Protection (ICRP))

  This value is indirectly estimated using the following data:
  - Spontaneous incidences of hereditary diseases among a group of human beings
  - Average spontaneous gene mutation rate (human beings) and average radiation-induced mutation rate (laboratory mice)
  - Correction factor for extrapolating potential risks of induced hereditary diseases among human beings based on radiation-induced mutation rate among laboratory mice
- Tissue weighting factor for gonads (ICRP Recommendations)
  0.25 (1977) → 0.20 (1990) → 0.08 (2007)

In animal testing, when parents are exposed to high-dose radiation, congenital disorders and chromosomal aberrations are sometimes found in their offspring. However, there has been no evidence to prove that parents' radiation exposure increases hereditary diseases in their offspring in the case of human beings. The ICRP estimates risks of heritable effects as 0.2% per gray. This is even less than one-twentieth of the risk of death by cancer. Furthermore, the ICRP assumes that the exposure dose that doubles the spontaneous gene mutation rate (doubling dose) is the same at 1 Gy for human beings and laboratory mice. However, heritable effects have not been confirmed for human beings and there is the possibility that this ICRP estimate is overrated.

Targeting children of atomic bomb survivors, life-span surveys, health effects checks, and surveys on various molecular levels have been conducted. Results of these surveys have made it clear that risks of heritable effects had been overestimated. Accordingly, the tissue weighting factor for gonads was reduced in the ICRP Recommendations released in 1990 and further in the ICRP Recommendations released in 2007.

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Chromosomal Aberrations among Children of Atomic Bomb Survivors

Stable chromosome aberrations among children of atomic bomb survivors

Sources of aberrations	Number of children with chromosome aberrations (percentage)	
	Control group (7,976 children)	Exposed group (8,322 children) Average exposure dose: 0.6 Gy
Derived from either of the parents	15 (0.19%)	10 (0.12%)
Newly developed cases	1 (0.01%)	1 (0.01%)
Unknown (Examination of parents was not possible.)	9 (0.11%)	7 (0.08%)
Total	25 (0.31%)	18 (0.22%)

Source: Prepared based on "Chromosomal Aberrations among Children of Atomic Bomb Survivors (1967 - 1985 surveys)" on the website of the Radiation Effects Research Foundation (https://www.rerf.or.jp/programs/roadmap/health_effects/geneefx/chromeab/)

Surveys of health effects on children of atomic bomb survivors examine incidence rates of serious congenital disorders, gene mutations, chromosome aberrations and cancer, as well as mortality rates from cancer or other diseases. However, no significant differences were found between the survey targets and the control group regarding any of these.

Stable chromosome aberrations do not disappear through cell divisions and are passed on from parents to their offspring. As a result of a survey targeting 8,322 children (exposed group), either or both of whose parents were exposed to radiation within 2,000 m from the center of the explosion (estimated exposure doses: 0.01 Gy or more), stable chromosome aberrations were found in 18 children. On the other hand, among 7,976 children (control group), both of whose parents were exposed to radiation at locations 2,500 m or farther from the center of the explosion (estimated exposure doses: less than 0.005 Gy) or were outside the city at the time of the atomic bombing, stable chromosome aberrations were found in 25 children.

However, a later examination of their parents and siblings revealed that most of the detected chromosome aberrations were not those newly developed but those that had already existed in either of their parents and were passed on to them. Given these, it was made clear that radiation effects, such that stable chromosome aberrations newly developed in parents' reproductive cells due to radiation exposure were passed on to the offspring, have not been found among atomic bomb survivors.

(Related to p.89 of Vol. 1, "DNA→Cells→Human Body")

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Survey of Children of Childhood Cancer Survivors

- An epidemiological survey to compare children of childhood cancer survivors in the United States and Canada (average gonadal dose is 1.26 Gy for females and 0.46 Gy for males) and children of those survivors' siblings does not show any increases in chromosome aberrations and Mendelian disorders expected from the average gonadal doses.*

Source: Green DM et al: J Clin Oncol Vol.27, 2009: 2374-2381

* Based on a study on hereditary influences using mice, the ICRP estimated the doubling dose** for genetic diseases due to radiation as 1 Gy.

** The doubling dose here means the gonadal dose that increases the incidence rate of genetic diseases twofold.

According to the results of the survey of children of childhood cancer survivors in the United States and Canada, as in the case of the surveys targeting children of atomic bomb survivors, excess incidence of chromosome aberrations, Mendelian disorders and malformation was not observed. Based on the study on heritable effects among laboratory mice, the International Commission on Radiological Protection (ICRP) estimates the doubling dose for hereditary disorders to be 1 Gy. However, these survey results do not show any increases in chromosome aberrations and Mendelian disorders expected from the average gonadal doses.

Source

• D.M. Green et al.: J. Clin. Oncol. 27: 2374-2381, 2009.

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Abnormalities at Birth among Children of Atomic Bomb Survivors (Malformations, Stillbirths, Deaths within Two Weeks)

		Father's dose (Gy)			
		<0.01	0.01-0.49	0.5-0.99	>=1
Mother's dose (Gy)	<0.01	2,257/45,234 (5.0%)	81/1,614 (5.0%)	12/238 (5.0%)	17/268 (6.3%)
	0.01-0.49	260/5,445 (4.8%)	54/1,171 (4.6%)	4/68 (5.9%)	2/65 (3.1%)
	0.5-0.99	44/651 (6.8%)	1/43 (2.3%)	4/47 (8.5%)	1/17 (5.9%)
	>=1	19/388 (4.9%)	2/30 (6.7%)	1/9 (11.1%)	1/15 (6.7%)

Source: M. Ohtake et al.: Radiat. Res. 122: 1-11, 1990.

Surveys targeting newborns of atomic bomb survivors were conducted between 1948 and 1954 in order to examine the possibility that genetic mutations in the genome of germ-line cells induced by radiation exposure due to the atomic bombing may impair growth of fertilized embryos, fetuses or newborn babies. However, radiation effects were not observed.[1]

Furthermore, in the United States and Canada[2,3] and in Denmark,[4,5] abnormalities at birth among children of childhood cancer survivors were epidemiologically surveyed (p.110 of Vol. 1, "Survey of Children of Childhood Cancer Survivors"). These surveys also do not show any risks of congenital anomalies or stillbirths caused by fathers' radiation exposure. On the other hand, it was found that mothers' exposure to radiation exceeding 10 Gy in the ovary or womb increased premature births and stillbirths caused by deterioration of uterine function.[3]

1. M. Ohtake et al.: Radiat. Res. 122: 1-11, 1990.
2. L.B. Signorello et al.: J. Clin. Oncol. 30: 239-45, 2012.
3. L.B. Signorello et al.: Lancet 376(9741): 624-30, 2010.
4. J.F. Winther et al.: J. Clin. Oncol. 30: 27-33, 2012.
5. J.F. Winther et al.: Clin. Genet. 75: 50-6, 2009.

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Heritable Effects — Other Epidemiological Surveys of Children of Atomic Bomb Survivors

- **Deaths from malignant tumors, etc. developed by the age of 20**

  The follow-up survey of 41,066 subjects revealed no correlation between parents' gonadal doses (0.435 Sv on average) and their children's deaths.

  (Source: prepared based on Y. Yoshimoto et al.: *Am J Hum Genet* 46: 1041-1052, 1990.)

- **Incidence rate of cancer (1958 - 1997)**

  As a result of the follow-up survey of 40,487 subjects, development of solid tumors and blood tumors was found in 575 cases and 68 cases, respectively, but no correlation with parents' doses was observed (the survey is still underway).

  (Source : prepared based on S. Izumi et al.: *Br J Cancer* 89: 1709-13, 2003.)

- **Deaths from cancer**

  As a result of the follow-up survey of 75,327 subjects conducted from 1946 to 2009, there were 1,246 deaths from cancer, but no correlation with parents' doses was observed.

  (Source : prepared based on E. Grant et al.: *Lancet Oncol* 16: 1316-23, 2015.)

- **Prevalence rates of lifestyle-related diseases (2002 - 2006)**

  The clinical cross-sectional survey of approx. 12,000 subjects revealed no correlation between parents' doses and their children's prevalence rates of lifestyle-related diseases (the survey is still underway).

  (Source : prepared based on S. Fujiwara et al.: *Radiat Res* 170: 451-7, 2008.)

The Radiation Effects Research Foundation has been conducting follow-up surveys to ascertain whether parents' radiation exposure increases their children's incidence or prevalence rates of lifestyle-related diseases, which are multifactorial disorders. The Foundation has so far conducted a survey of development of malignant tumors by the age of 20,[1] a survey of cancer,[2,3] and a survey of lifestyle-related diseases,[4] but none of them revealed specific radiation effects.

1. Y. Yoshimoto et al.: Am J Hum Genet 46: 1041-1052, 1990.
2. S. Izumi et al.: Br J Cancer 89: 1709-13, 2003.
3. E. Grant et al.: Lancet Oncol 16: 1316-23, 2015.
4. S Fujiwara et al.: Radiat Res 170: 451-7, 2008.

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