2022年 福島県立医科大学『県民健康調査』国際シンポジウム
公立大学法人福島県立医科大学放射線医学県民健康管理センター
国際シンポジウム事務局（広報・国際連携室）
✉ kenkani@fmu.ac.jp　Tel: 024-581-5454(平日9～17時)

2022 Fukushima Medical University International Symposium on the Fukushima Health Management Survey
Secretariat of International Symposium
Office of Public Communications and International Cooperation, Radiation Medical Science Center for the Fukushima Health Management Survey, Fukushima Medical University
✉ kenkani@fmu.ac.jp, TEL: +81-24-581-5454 (Weekday, 9a.m. - 5 p.m. JST)

Genetic Effects of Radiation
- Lessons learned from Hiroshima, Nagasaki, and Chernobyl -

Fukushima Medical University International Symposium
on the Fukushima Health Management Survey
March 5 (Sat), 2022

Radiation Effects Research Foundation (RERF)
Ohtsura Niwa

Genetic Effects of Radiation

Are there genetic effects in your children?

- Radiation induces mutation in somatic cells
- Such mutation caused cancer among A-bomb survivors.

⇩

- Mutation is thought to be heritable
- We expect the next generations to have cancer

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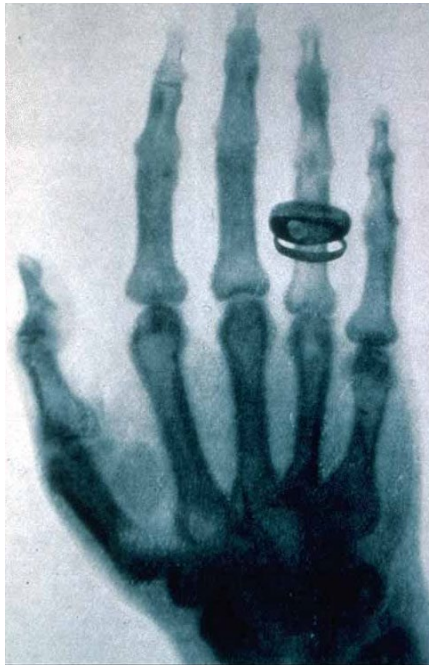
- How were Hiroshima/Nagasaki and Chernobyl?
- How do we understand past studies?

Basics of Radiation Health Effects: A Short History



1895: Discovery of X-rays by Roentgen and the X-ray photo
1896: Reports on induction of inflammation and ulcers
1904: Assistant of Edison developed sarcoma in his hand
1926: Discovery of radiation induction of mutations
1928: International Council of Radiation Protection established
1945: A-bombing and studies of the survivors initiated
～
1986: Chernobyl Nuclear Accident took place
～
2011: Fukushima F1 Nuclear Accident took place
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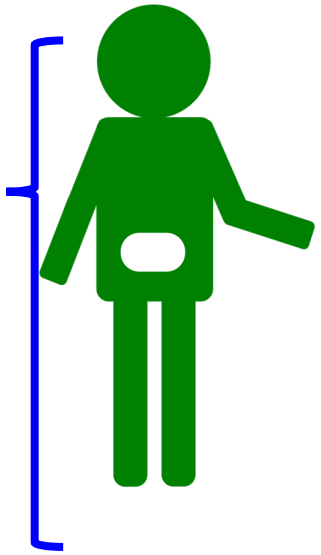
2022: The A-bomb survivors and their children continue

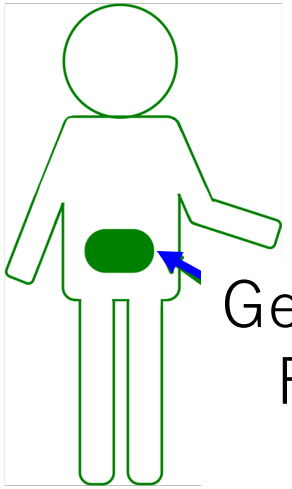
Today, we will learn genetic effects of radiation

Basics: Somatic Cells and Germline Cells

Somatic cells: 37 trillion



They are mortal and subject to be born, age, get sick and die



Germ cells

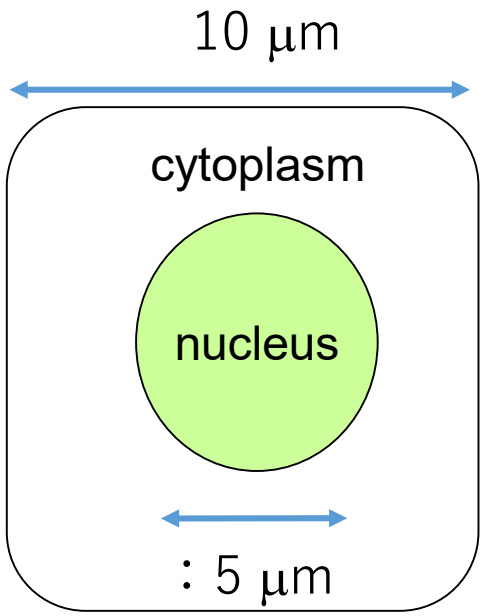
Female: 2 M cells,
500 ovulations in a lifetime

Male: 1 B cells, only a few used for real reproduction

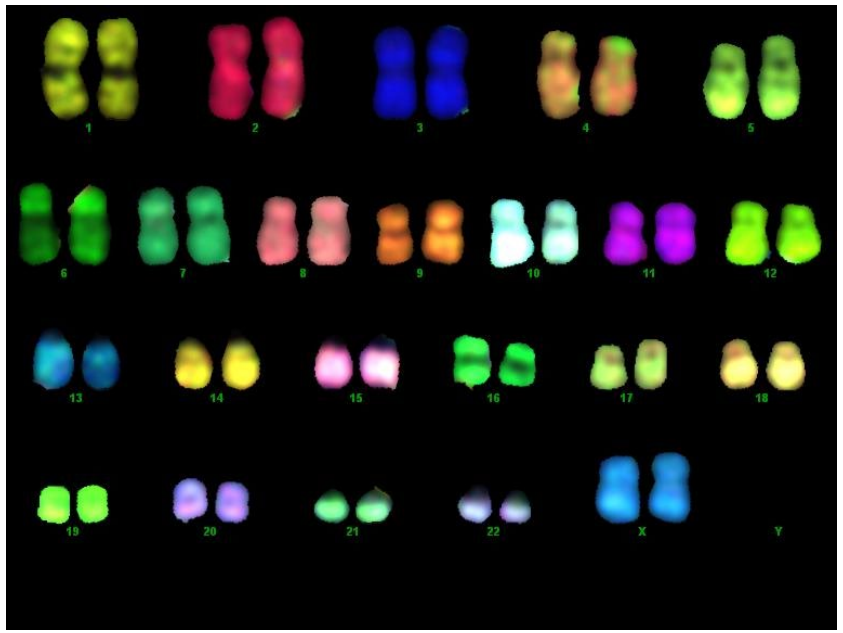
They are immortal and form the first cell of the next generation

They are made with extreme care, especially those of the female

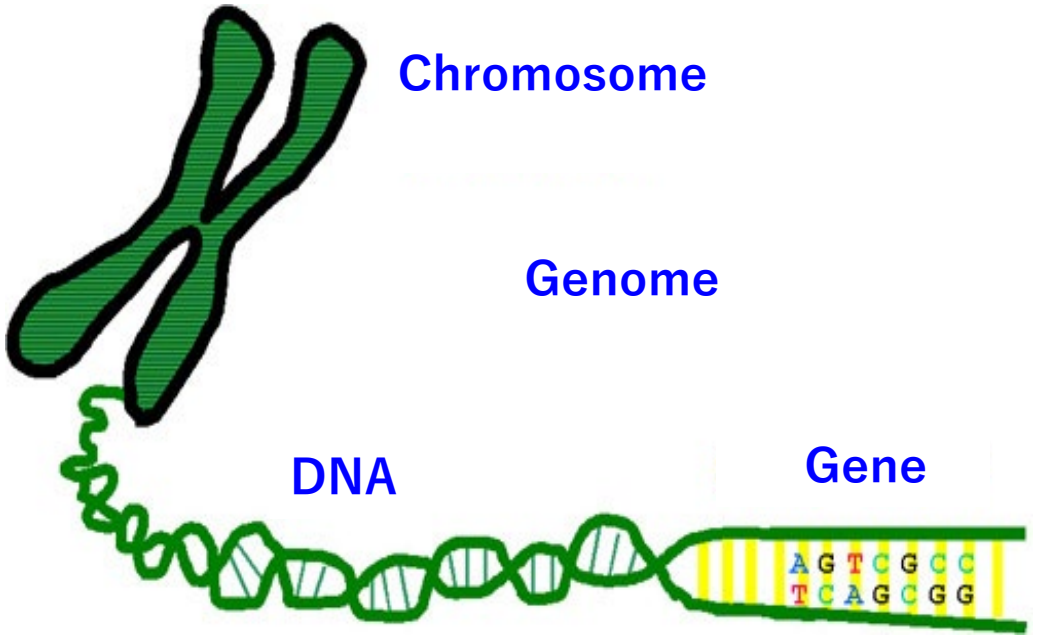
Basics: Cell, Chromosome, DNA , Gene and Genome



cell

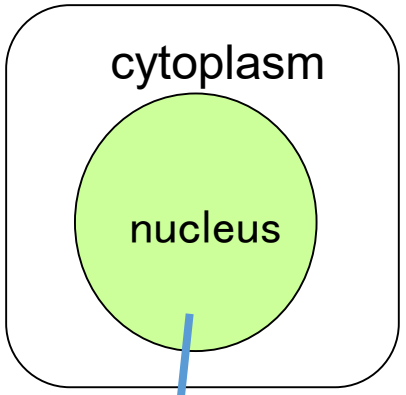


chromosome

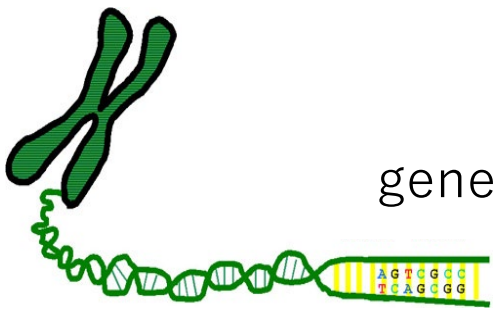


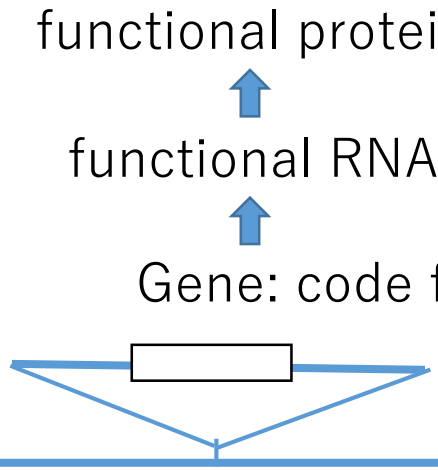
- Cell nucleus has two 23 **chromosome** sets; each comes from mother and father
- Chromosome consists of **DNA** strand packaged into chromatin structure
- DNA sequence of the 23 chromosome set is called **Genome**
- Genomic DNA contain gene which codes functional **RNA** and **protein**

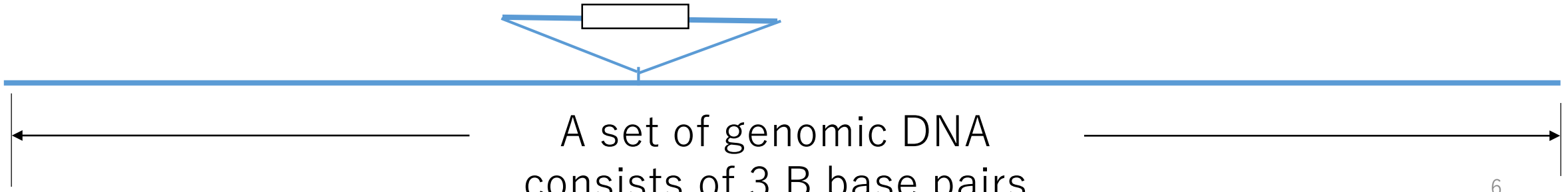
Basics: DNA, Protein, RNA and gene



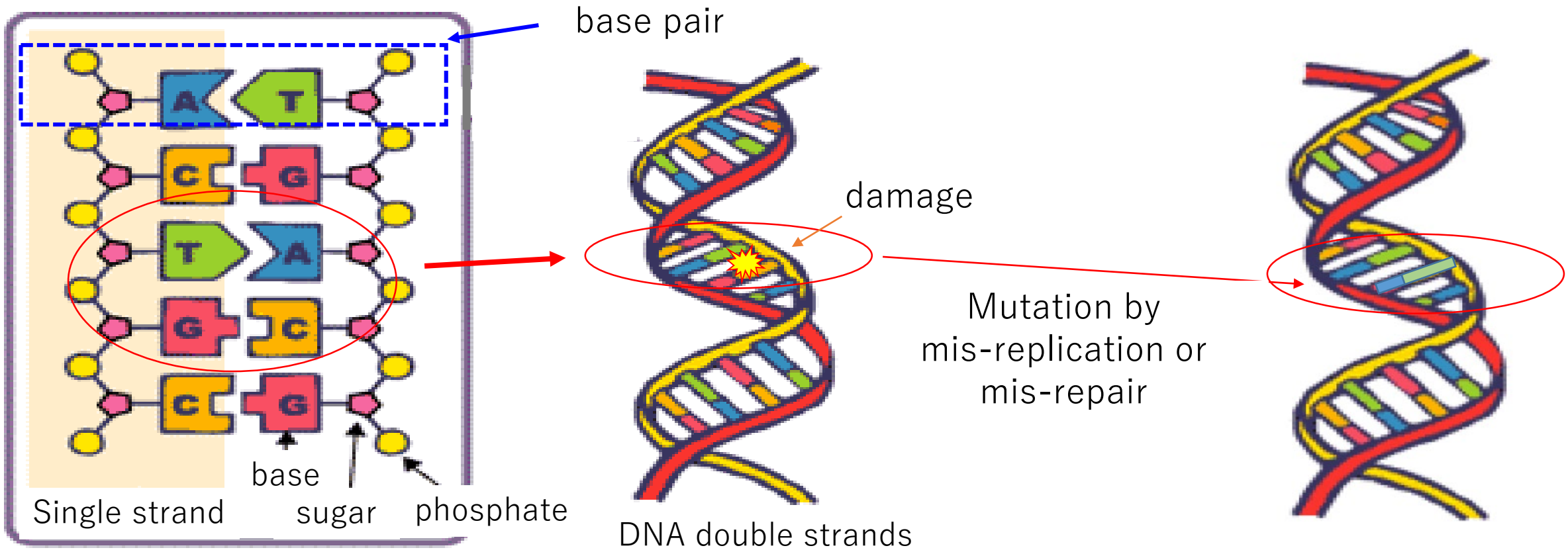
- Our genome from parents consists of 3 B base pairs of DNA
- Genes occupy only 2% of the 3 B base pairs of DNA
- Gene is a sequence element coding functional RNAs and functional protein
- Mutation taking place in a gene may have some effects





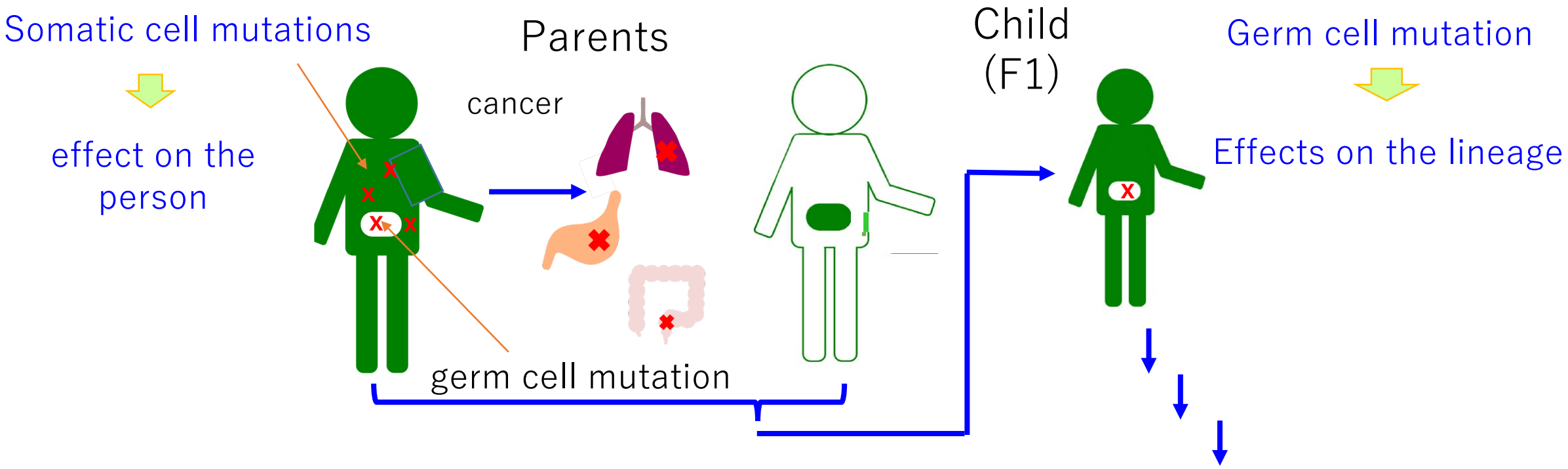


Basics: DNA is subject to mutation



- Our Cellular DNA is damaged daily by many causes
  Spontaneous (oxi-radical): some 10s of thousands/day
  Radiation: 4000 damages /1 Gy or 1000 mSv

Basics: Mutations in somatic cells and germ cells

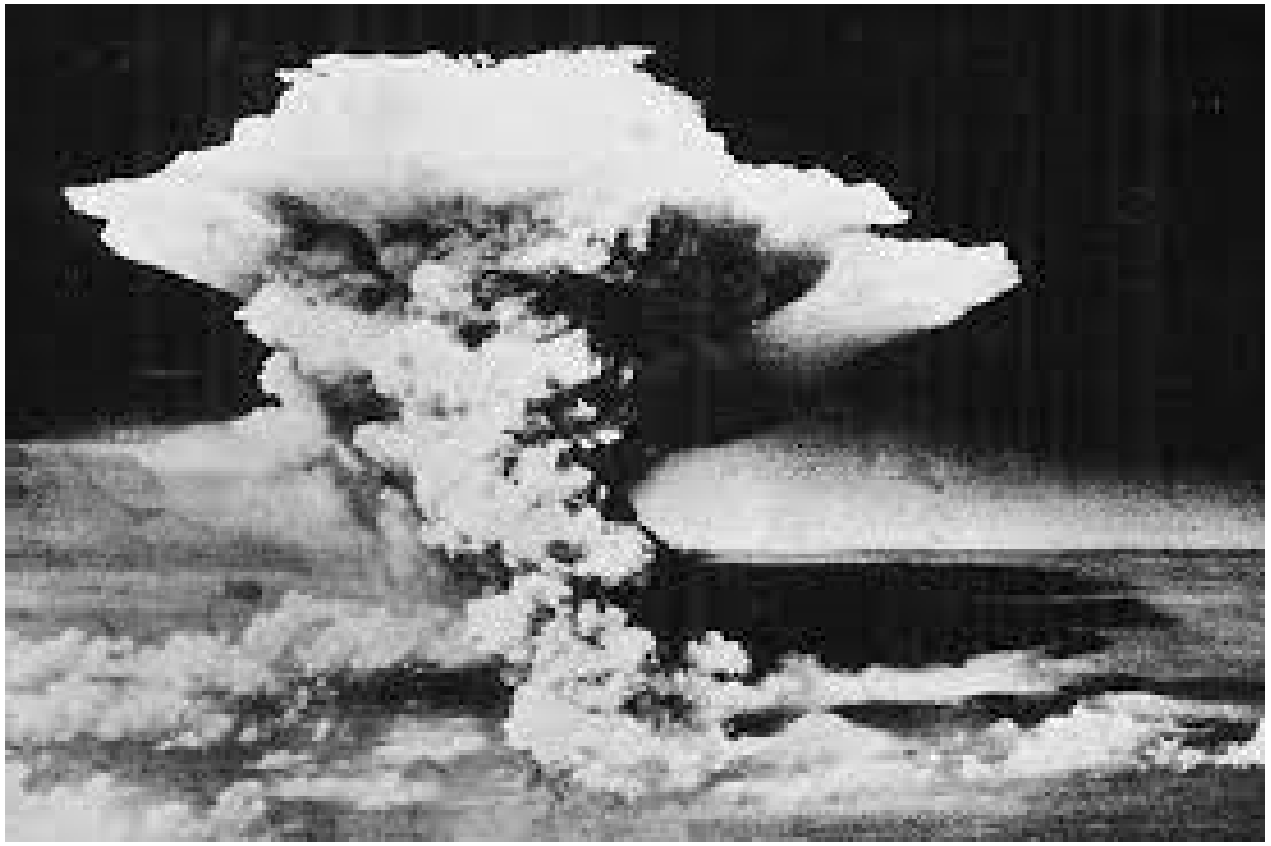


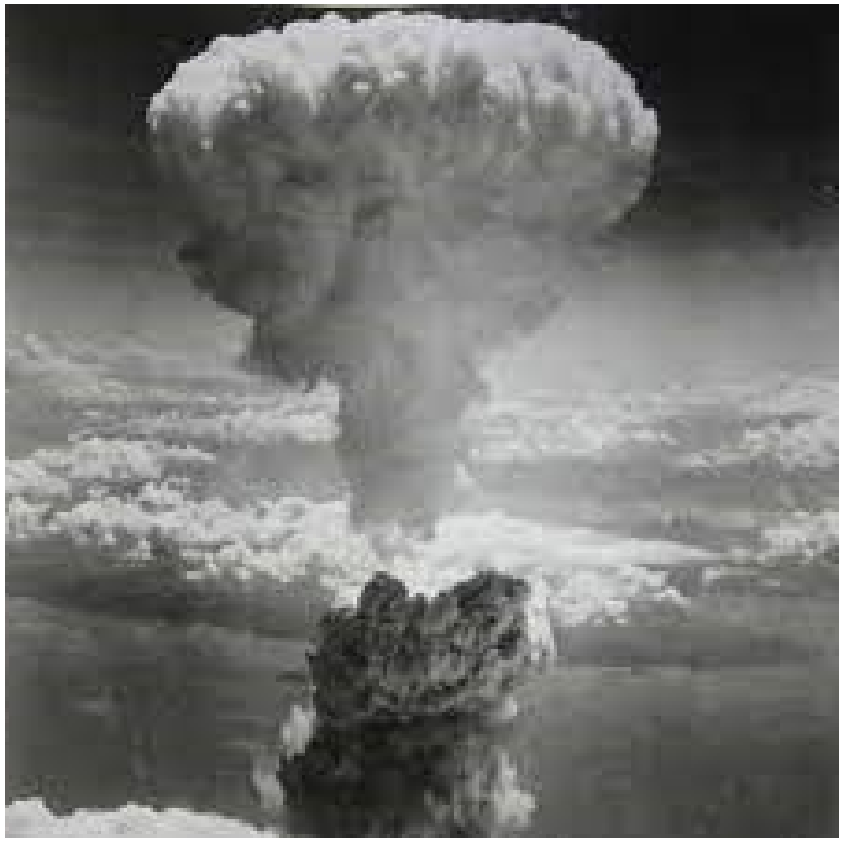
What is mutation: old definition vs current definition

- Mutation means gene mutation, and supposed to have bad effects

- Mutation means DNA mutation, and may not have any effect

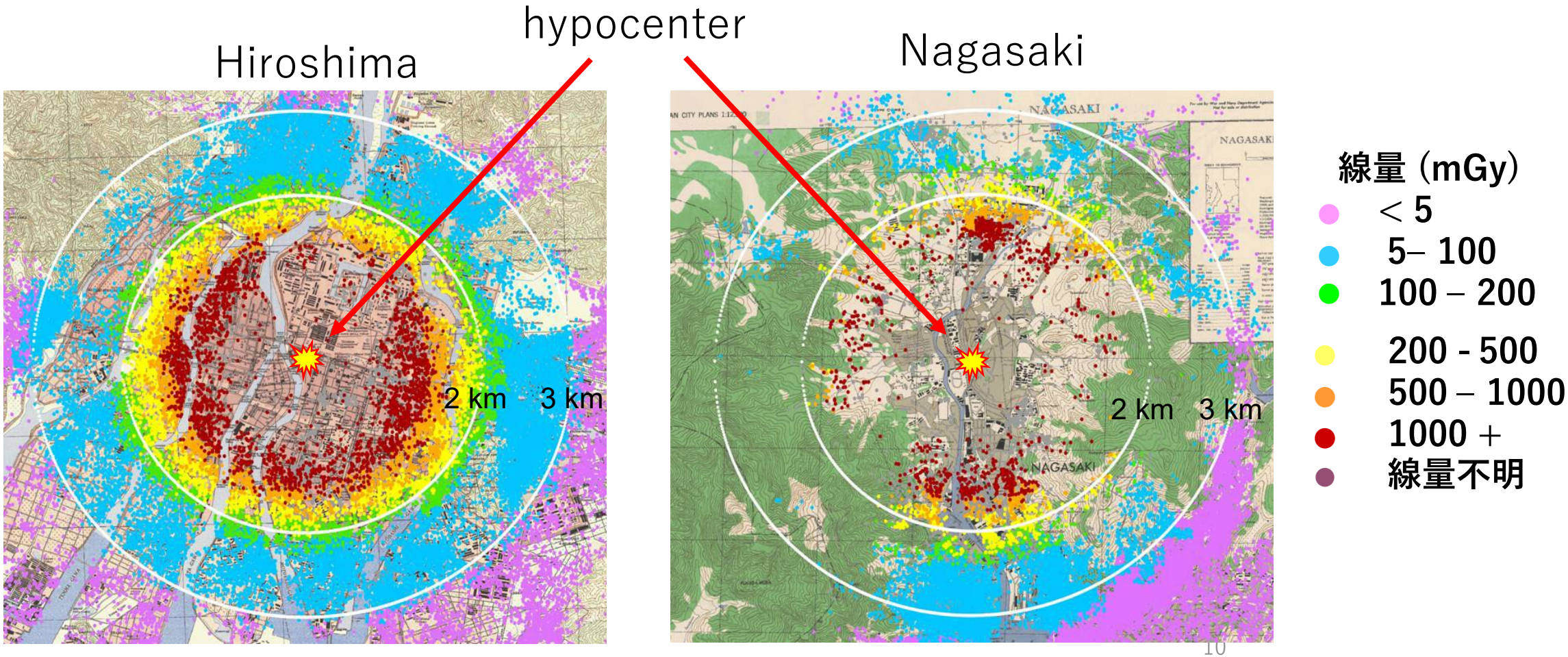
Genetic Effects of Radiation: Events





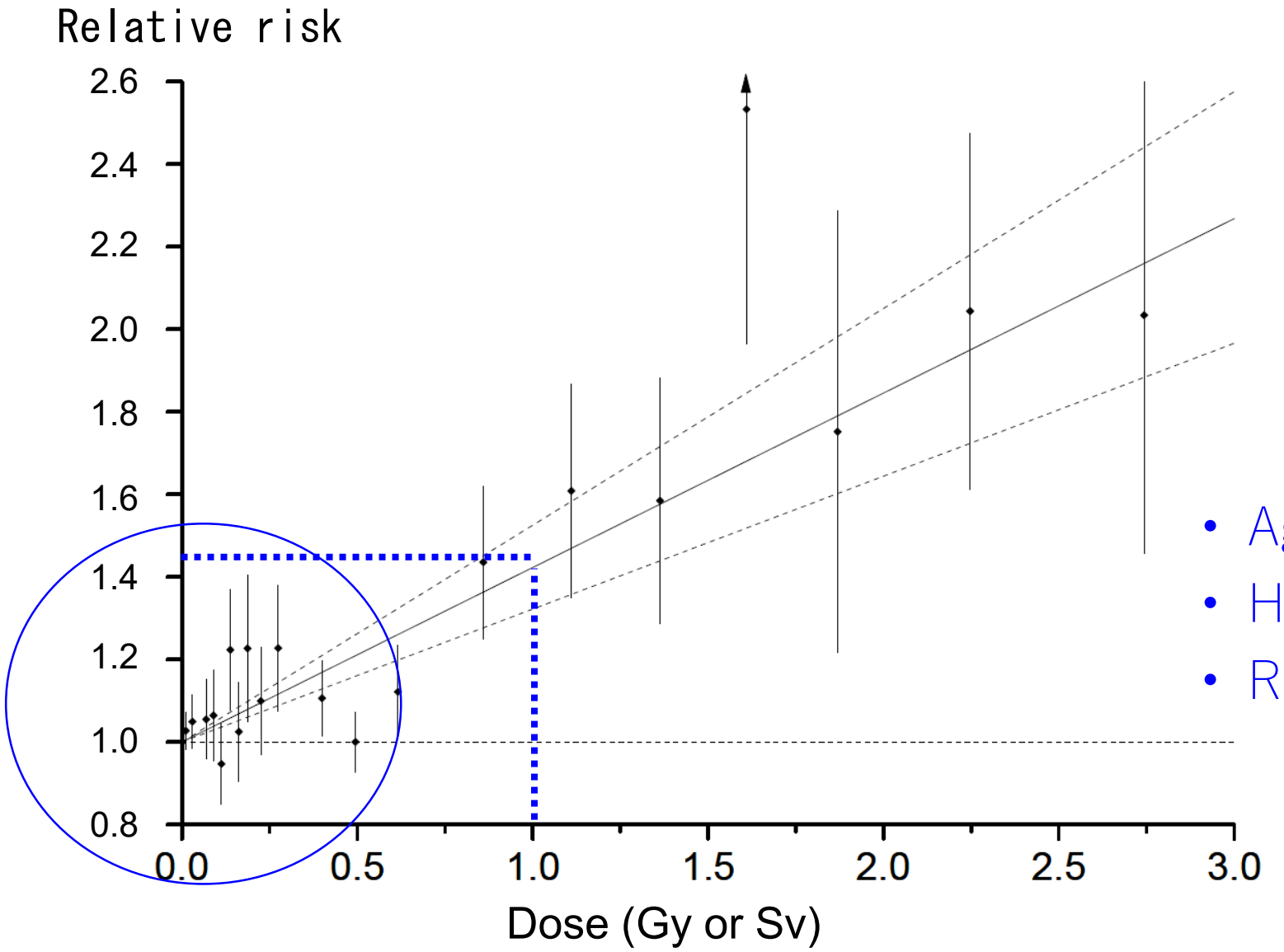
- Aug. 6, 1945: Hiroshima, Uranium bomb, killed 90,000
- Aug. 8, 1945: Nagasaki, Plutonium bomb killed 74,000
- 1947: ABCC was established. 120,000 survivors and their 77,000 children have been followed and will be until 2060.

RERF Study: Radiation Dose to the Survivors



- Dose was estimated from the energy of the bomb, place at the time of bomb, shielding conditions and other details
- Dose estimated matches well with the dose estimated by other methods

RERF Study: Famous study on Solid Cancer Mortality
Data are used for risk estimation for radiation protection



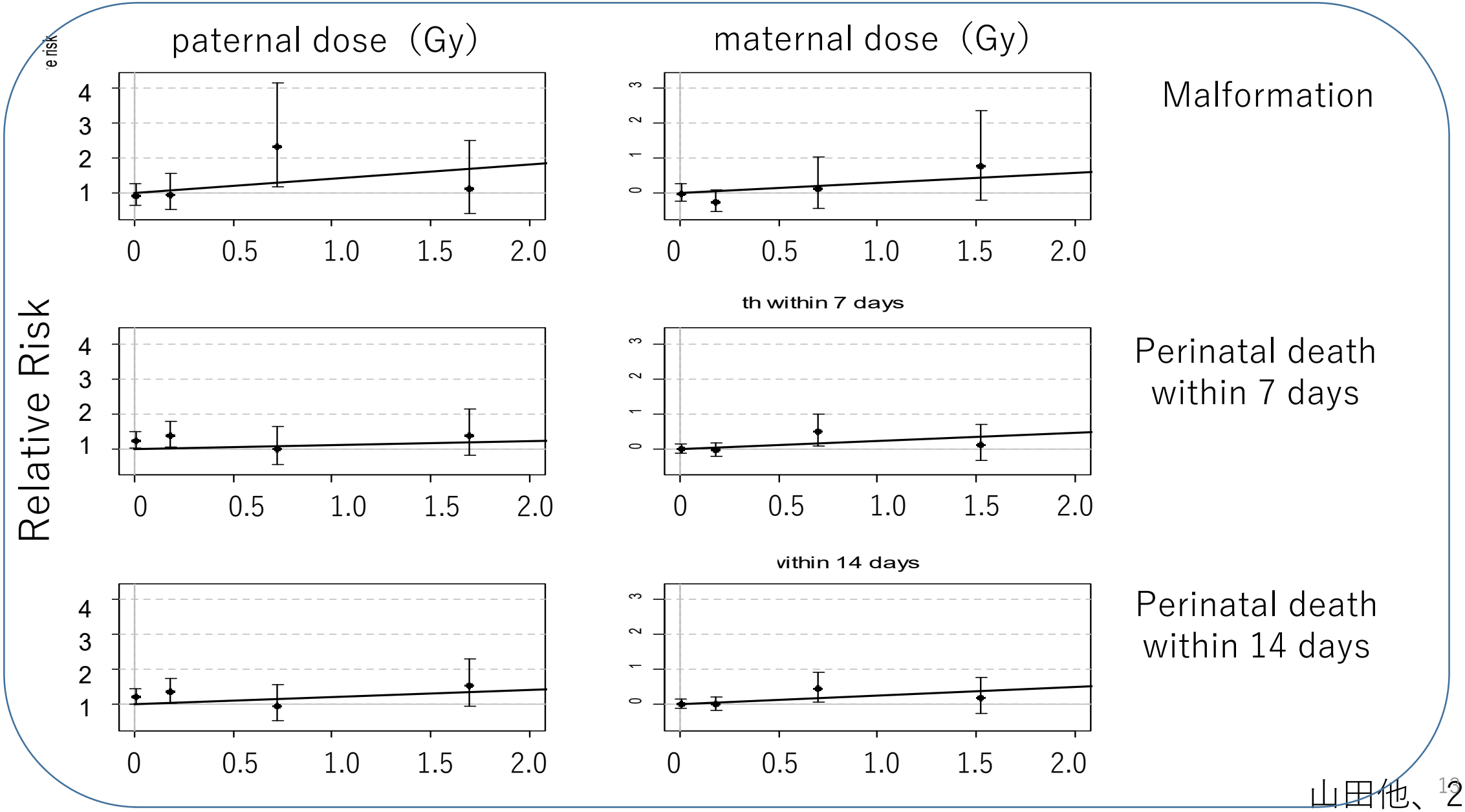
- Age 30 ATB and death at 70
- High uncertainty at low dose
- RR 1.5/ 1 Gy

Ozasa et al. 2012

RERE Study: Genetic effects on F1s

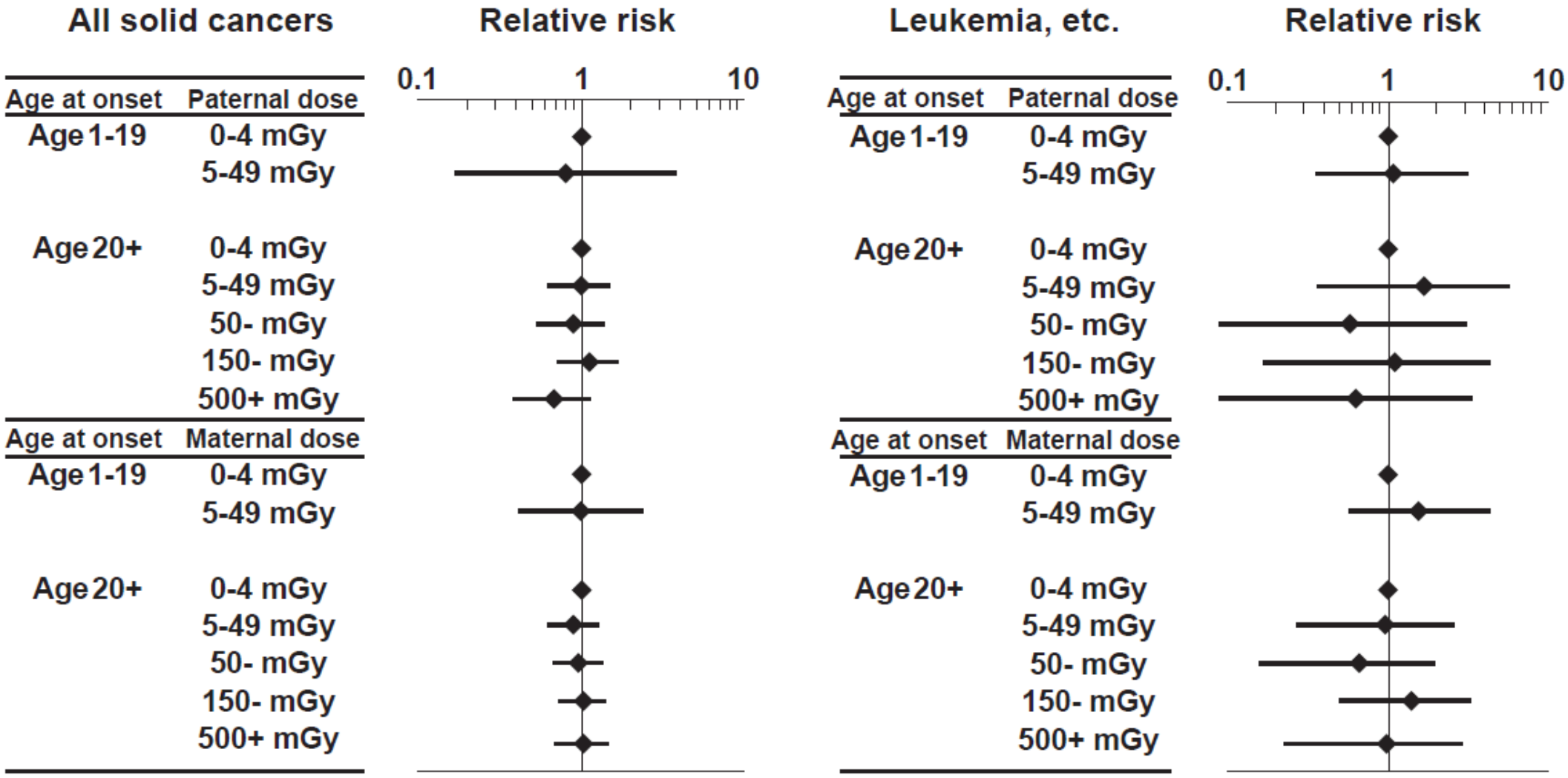
Study period	Study
① 1948-1954	Untoward pregnancy outcomes of 77,000 F1s
② 1948-1962	Sex ratio of children of the survivors
③ 1967-1985	Chromosome analyses on F1s
④ 1975-1985	Analyses of mutated serum proteins among F1s
⑤ 2021	Project ① revisited and reanalyzed
⑥ since 1948 till today	Mortality and incidence of cancer among F1 born to the survivors

F1 Study: Untoward Pregnancy Outcome Revisited



山田他、2021年

F1 Study: Cancer Incidence (2003 data)



ure 21. Parental radiation dose and risk of cancer incidence in A-bomb survivors' children born during 1946–1984 (follow-up period: 1958–1997).[100] The horizontal bars indicate 95% confidence intervals.

F1 Study: Cancer Mortality (2015 paper)

F1 born to maternally exposed			F1 born to paternally exposed		
dose (mGy)	No. dead	hazard ratio	dose (mGy)	No. dead	hazard ratio
0	806	1	0	1003	1
1-49	184	1.092	1-49	93	0.943
50-149	67	0.883	50-149	31	0.735
150 - 499	81	1.046	150 - 499	42	0.973
500 -	56	0.970	500 -	35	0.830
dose unknown	52	0.721	dose unknown	42	0.782

70,00 born between 1946–1984, followed from 1958 to 2009

Grant et al., 2015

F1 Study: Non-cancer Mortality (2015 paper)

母親被曝の二世			父親被曝の二世		
線量・mGy	死亡人数	ハザード比	線量・mGy	死亡人数	ハザード比
0	2525		0	3034	
1-49	548	1.045	1-49	315	0.972
50-149	232	0.969	50-149	140	0.986
150 - 499	236	0.962	150 - 499	140	0.966
500 -	176	0.991	500 -	145	1.061
線量不明	220	1.027	線量不明	163	0.987

70,00 born between 1946–1984, followed from 1958 to 2009

Grant et al., 2015

RERF F1 Study: Current Summary

- A clear dose-dependent increase in the risk of cancer and non-cancer diseases was observed in directly exposed survivors
- No such increase was observed among children born to exposed parent
- Currently, average age of F1s exceed 60 and they are coming to so called “cancer-prone age” so that careful and intense follow-up has to be made on them
- Past genetic studies at RERF were relying on health detriments. Now, how is it at the DNA level?

F1 Study outside of RERF

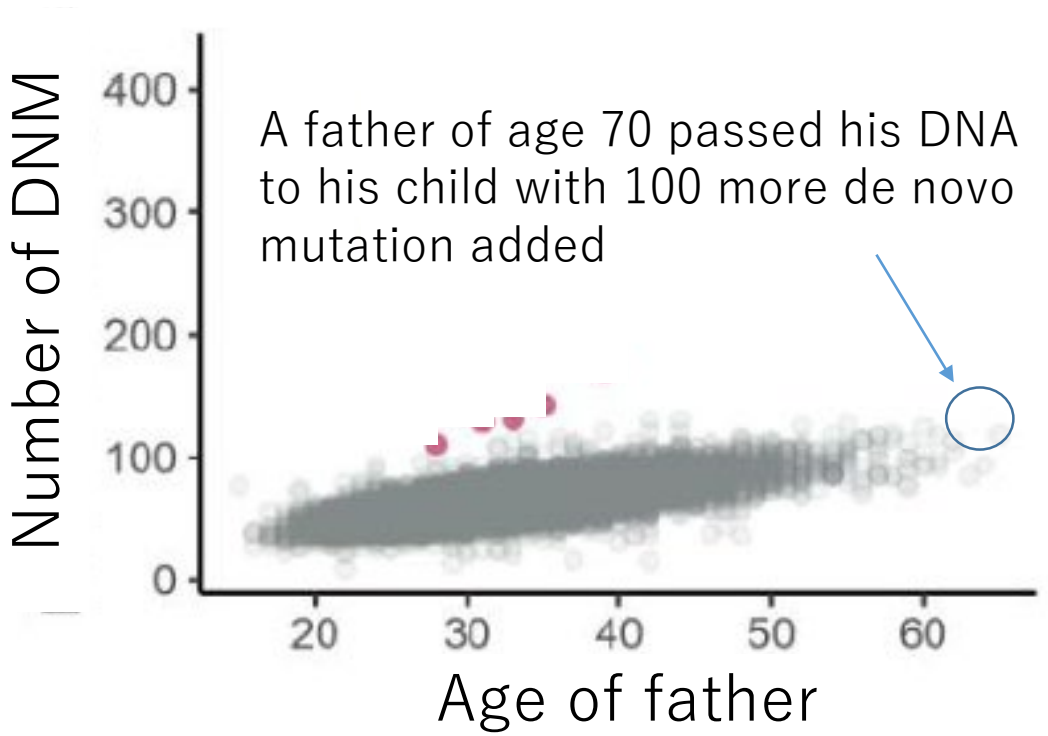
- Is there any study supporting RERF's results showing the lack relation between parental radiation dose and detriments in F1?

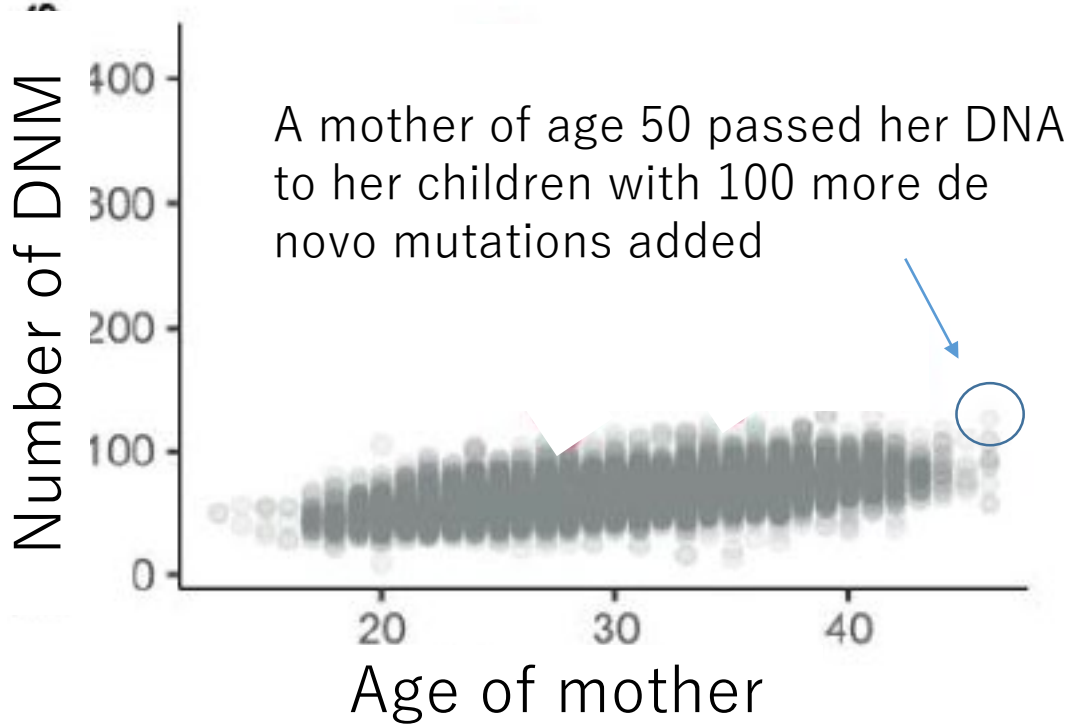
- Epidemiological studies of children born to radiotherapy survivors
  → Doses to the parental gonads is sometimes much higher than those for A-bomb survivors
  Yet, past publications show no health effect in their children

In order to confirm, we need DNA level studies

When you have your children: Spontaneous mutation

Analyses of 22,000 children for de novo mutation (DNM)

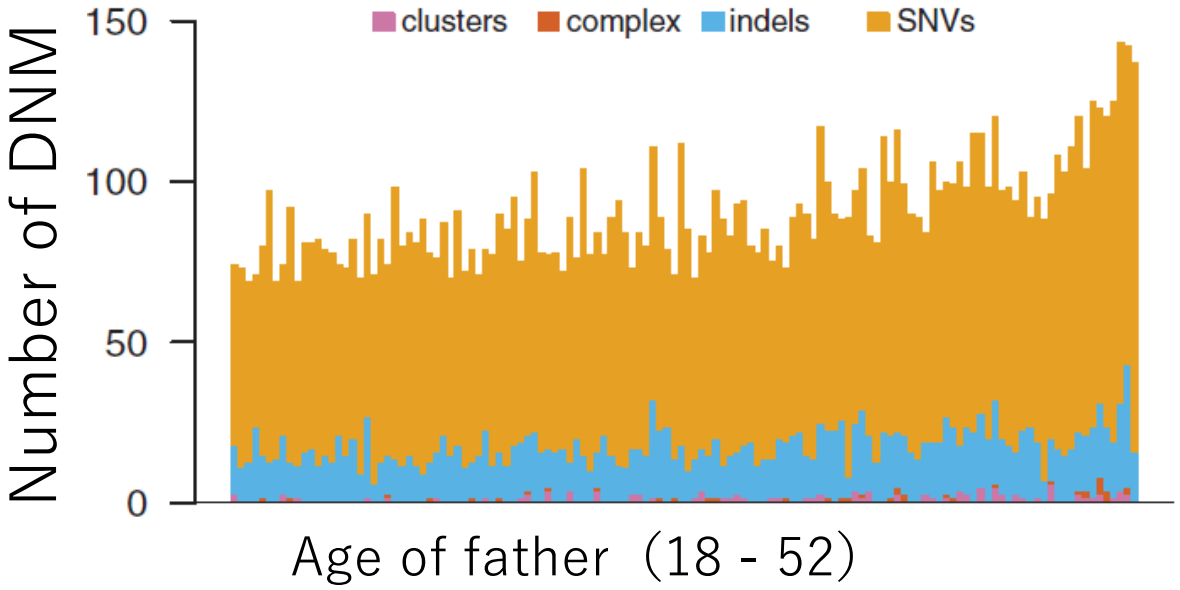


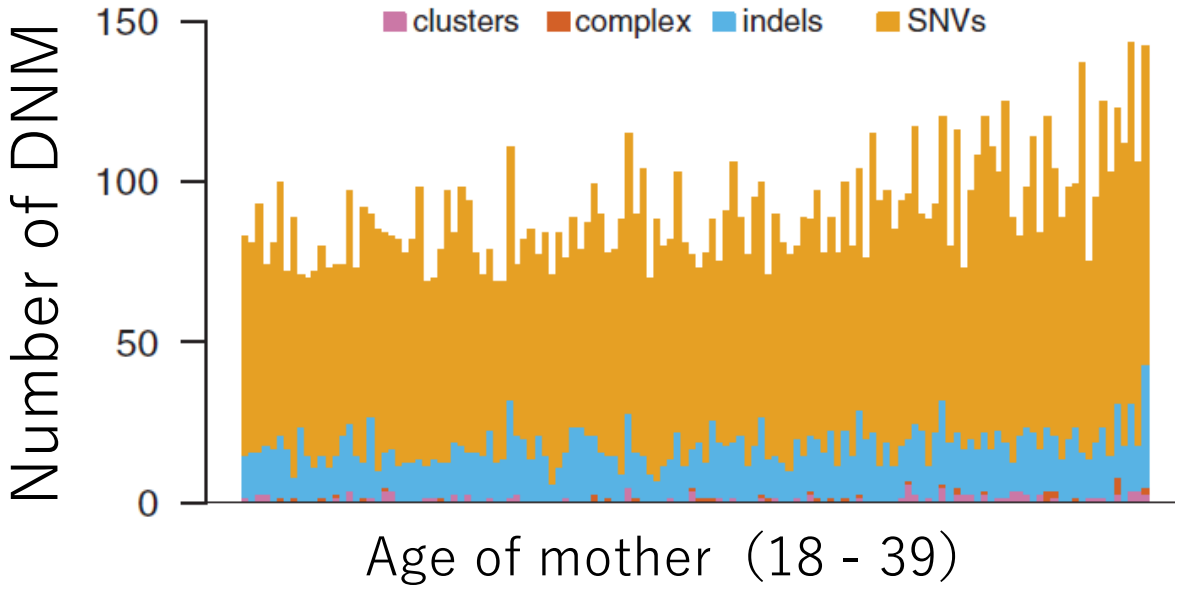


- Age dependent increases of de novo mutation by parental age
- Around 50 – 100 new mutations added for most of pregnancies
- These mutations rarely affect health of children

Kaplanis et al., 2021

Analyses of 130 Children born to Chernobyl workers
— Parental age at conception —

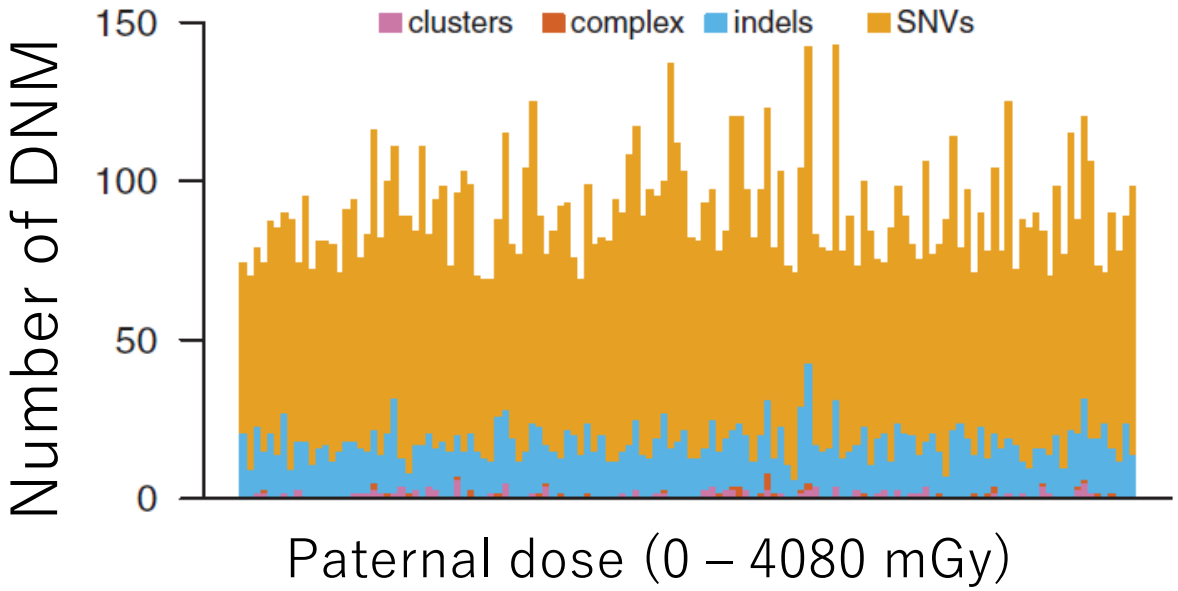


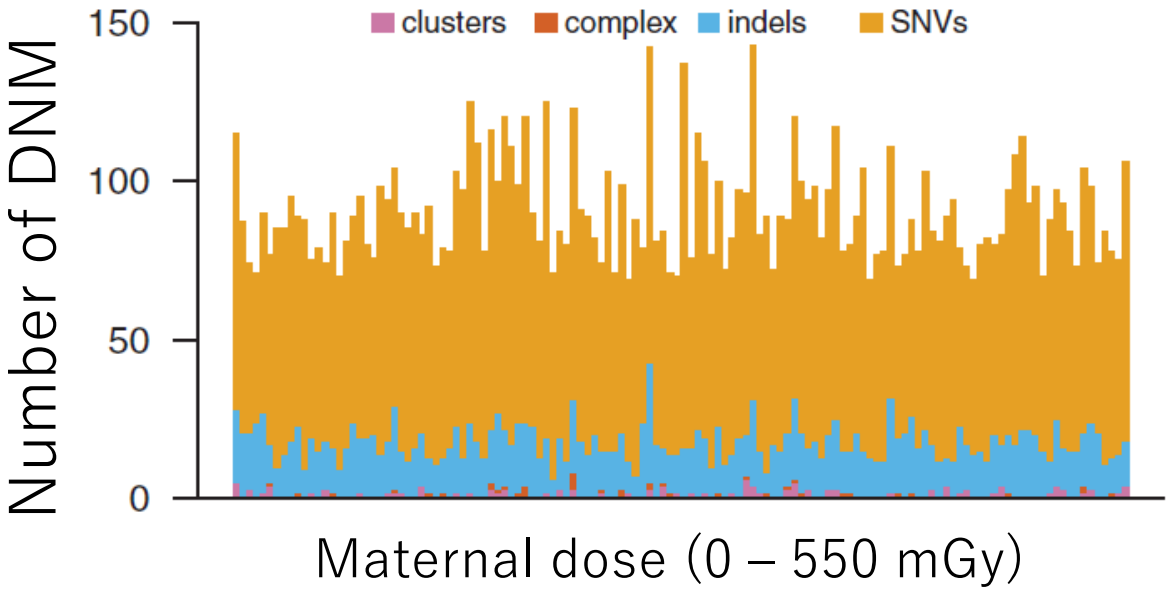


- Chernobyl works received relatively high dose and 34 of them died from acute effects of radiation
- Number of de novo mutations (DNM) increased in relation to the parental age at the time of conception

Chanock group, 2021

Analyses of 130 Children born to Chernobyl workers
— Parental dose —





- No relation was found for the number of de novo mutations and parental radiation dose, indicating these were spontaneous

Chanock group, 2021

Issues to be addressed

- No observation so far indicates any detriments among F1s born to the atomic bomb survivors
- Similarly, no observation was made of such detriments among children born to radiotherapy patients
- Genomic sequencing of children born to Chernobyl workers detected no increase in heritable DNA mutation
- At the same time, de novo mutations are occurring frequently in germ cells

Enigma to be clarified

- Why human data does not support radiation induced germ cell mutation while fruit fly and mice data do?

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