Low-Dose Radiation Research in Japan

1) **Tatsuhiko Imaoka (QST)** Low-dose radiation research in Japan: an overview
2) **Shizuko Kakinuma (QST)** Low-dose radiation research at QST
3) **Yoshiya Shimada (IES)** Low-dose radiation research at IES

Low-Dose Radiation Research in Japan: an overview

Tatsuhiko Imaoka

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National Institutes for Quantum Science and Technology
Japan

Brief history of low dose radiation research in Japan

	SOCIETY	ACADEMIA	RESEARCH PROJECTS
Dawn of nuclear energy use	1945 Atomic bombing	1947 ABCC established (later RERF)	1950s+ Atomic bomb survivor studies
		1951 CRIEPI established	
	1954 Lucky Dragon incident	1957 NIRS established	1960s+ NIRS projects on radioecology/biology
	1955 Atomic Energy Basic Law	1959 JRRS established	
		1961 JHPS established	
		1958-1976 Radiation institutes/ labs placed in universities	1970s+ KAKEN 'radiobiology'
Fuel cycle R&D	1985 Location of fuel recycling facilities agreed	1990 IES established	1989 MEXT Nuclear Crossover Research (later Nuclear Initiative)
	1999 JCO criticality accident		2001 NIRS low dose effect project
			2006 NIRS radiobiology for children's health
Post-Fukushima	2011 Fukushima accident		2012 NIRS Fukushima restoration project
			2012 MOE radiation health effects research
			2014 MEXT Project Wisdom
	2022 Fuel reprocessing starts	2016 NIRS reorganized as QST	2016 Joint Usage/Research Center for Radiation Disaster Medical Science

ABCC Atomic Bomb Casualty Commission
CRIEPI Central Research Institute of Electric Power Industry
IES Institute for Environmental Sciences
JRRS Japanese Radiation Research Society
JHPS Japanese Health Physics Society
MEXT Ministry of Education, Culture, Sports, Science and Technology
MOE Ministry of the Environment
NIRS National Institute of Radiological Sciences
QST National Institutes for Quantum Science and Technology
RERF Radiation Effect Research Foundation

All Japan

Overview of low-dose radiation research, with emphasis on cutting-edge technologies

Overview of low-dose radiation research in Japan

Epidemiology

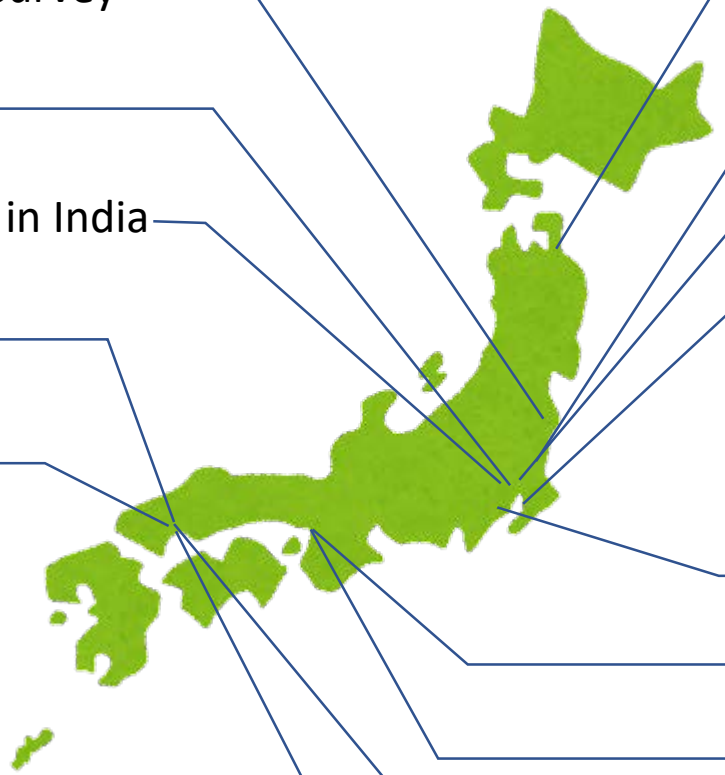
FMU: Fukushima Health Management Survey

REA: Nuclear worker study (J-EPISODE)

CRIEPI: High background radiation area in India

RIRBM: CT biodosimetry study

RERF: A-bomb study
Nuclear Emergency Worker Study



Radiobiology

IES: Animal carcinogenesis
Low dose rate irradiation facility
(presented by Shimada)

Ibaraki Univ: Tritium radiotoxicology

CRIEPI: Cell competition

QST: Radiation signature mutation
Animal carcinogenesis
Prevention of cancer
Archive of past experiments
(presented by Kakinuma)

Tokai Univ: Hereditary effect

Kansai Univ: Mathematical model

Osaka Univ: Cesium radiotoxicology

RIRBM: Animal carcinogenesis

RERF: Hereditary effect

CRIEPI Central Research Institute of Electric Power Industry
FMU Fukushima Medical University
IES Institute for Environmental Sciences
QST National Institutes for Quantum Science and Technology
(formerly, National Institute of Radiological Sciences, NIRS)
REA Radiation Effect Association
RERF Radiation Effect Research Foundation
RIRBM Research Institute for Radiation Biology and Medicine, Hiroshima University

Nuclear Emergency Worker Study (NEWS) @RERF

- Epidemiological study of health effects in Fukushima nuclear emergency workers.
- The potential subjects are ~20,000 workers engaged in emergency operations at the Fukushima Daiichi Nuclear Power Plant.
- QST collaborates in dosimetry.
- Clinical study: General health examination, thyroid cancer, cataract, psychology, mortality, cancer incidence, radiobiology (biomarkers of chronic inflammation, oxidative stress, miRNA)
- Dose construction: physical (and biological for subjects with 70+ mSv)

Kitamura et al. Radiat Prot Dosimetry 182:40-48 (2018) https://doi.org/10.1093/rpd/ncy136

Nuclear worker study (J-EPISODE) @REA

- Japanese nuclear workers with questionnaire on smoking.
- Mortality followed up for 71,733 males for 8.2 y (avg.) during 1999-2010; the mean cumulative dose is 25.5 mSv
- ERR/Sv significant on all non-cancer (1.87, 95% CI: [0.47, 3.49]) and liver cancer (4.78 [0.09, 11.68]) before adjustment for smoking.
- ERR/Sv were no longer significant after adjustment for smoking (1.28 [-0.03, 2.79]and 3.89 [-0.46, 10.34])
- Direct adjustment for confounding by smoking reduces radiation-related cancer risk estimates of mortality among male nuclear workers in Japan (i.e., distortion of risk estimates by smoking in the previous report was demonstrated).

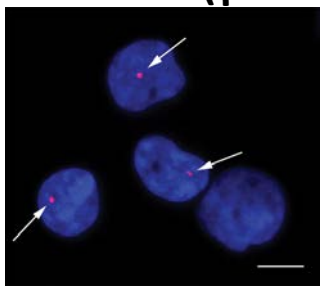
Kudo et al. J Radiol Prot 38:357-371 (2018) https://doi.org/10.1088/1361-6498/aaa65c
Furuta et al. Radiat Prot Dosimetry 190:372-391 (2020) https://doi.org/10.1093/rpd/ncaa111
Furuta et al. Health Phys 121:471-483 (2021) https://doi.org/10.1097/hp.0000000000001454

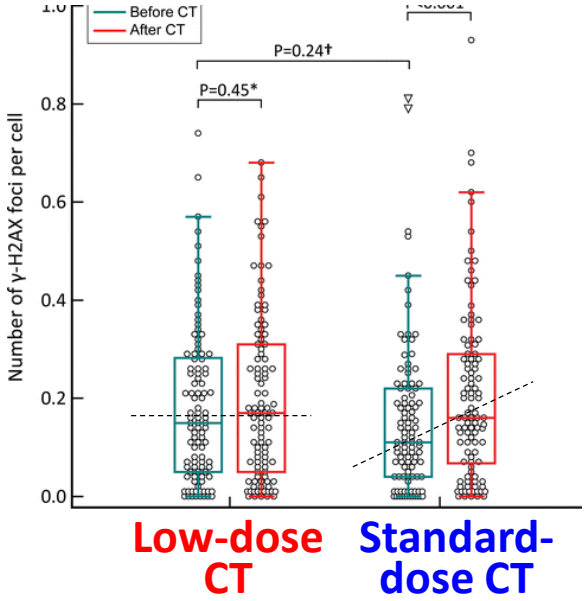
CT biological effect study @RIRBM

Biological effects of low-dose chest CT on chromosomal DNA were studied in peripheral blood cells of patients.

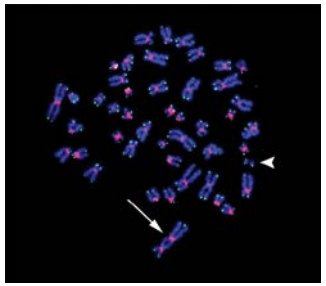
- DNA double-strand breaks and chromosome aberrations significantly increased 15 minutes after a single standard-dose chest CT examination (~5 mSv), but not after a single low-dose chest CT examination (~1.5 mSv, effective dose).

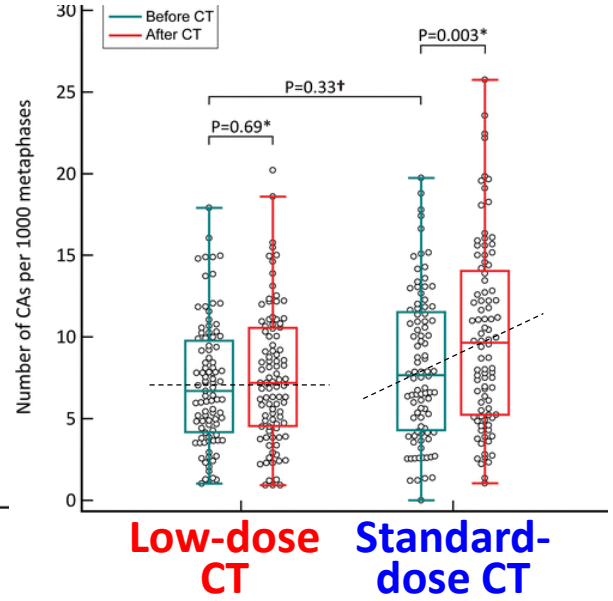
DNA breaks (γH2AX foci)





Chromosome aberrations





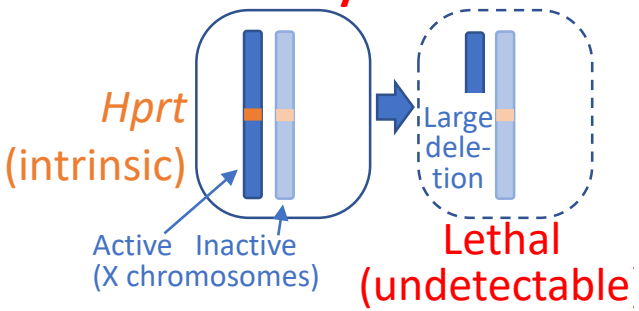
Sakane et al. Radiology 295(2): 439-445 (2020) https://doi.org/10.1148/radiol.2020190389

Tritium radiotoxicology study @Ibaraki Univ (Dr Tauchi)

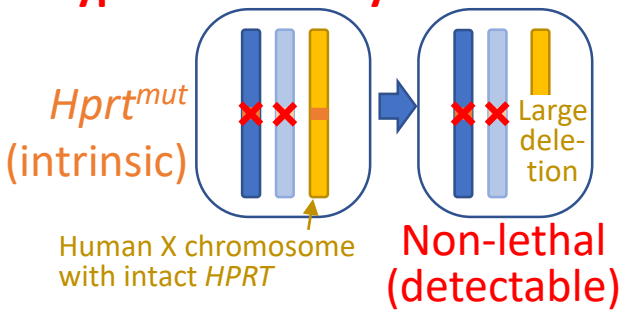
- Hypersensitive measurement of somatic mutations induced by various levels of tritiated water (HTO) provides evidence for the possible existence of a dose-rate threshold

Hypersensitive mutation assay system

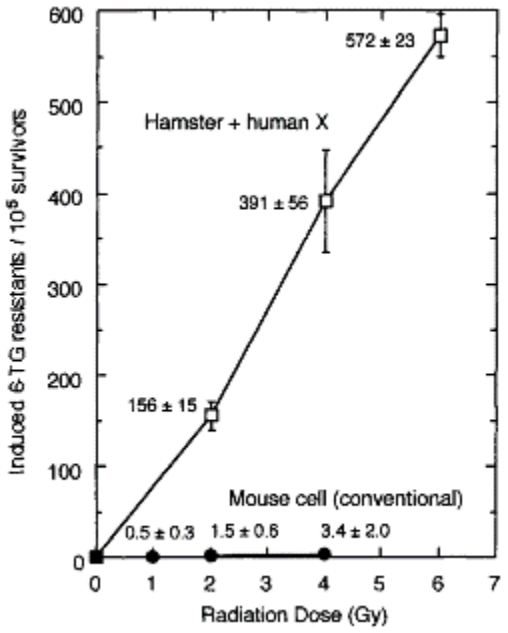
Conventional system



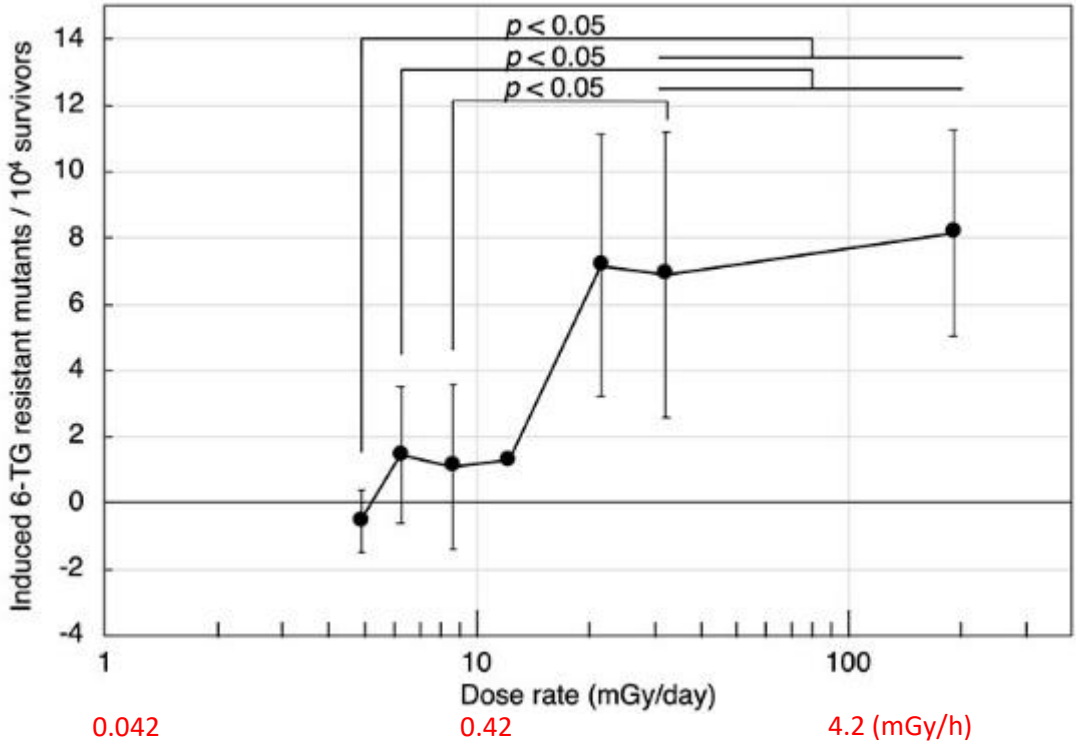
Hypersensitive system



Tauchi et al. doi: 10.13182/FST02-A22622



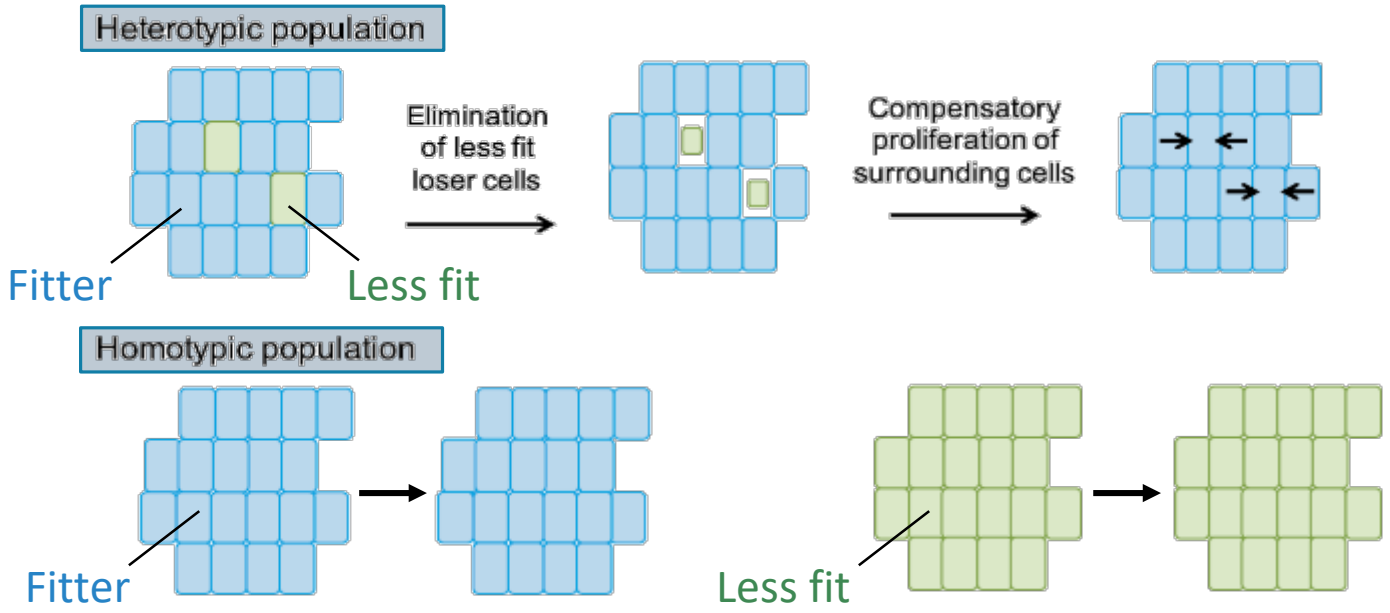
Effect of incubation in HTO



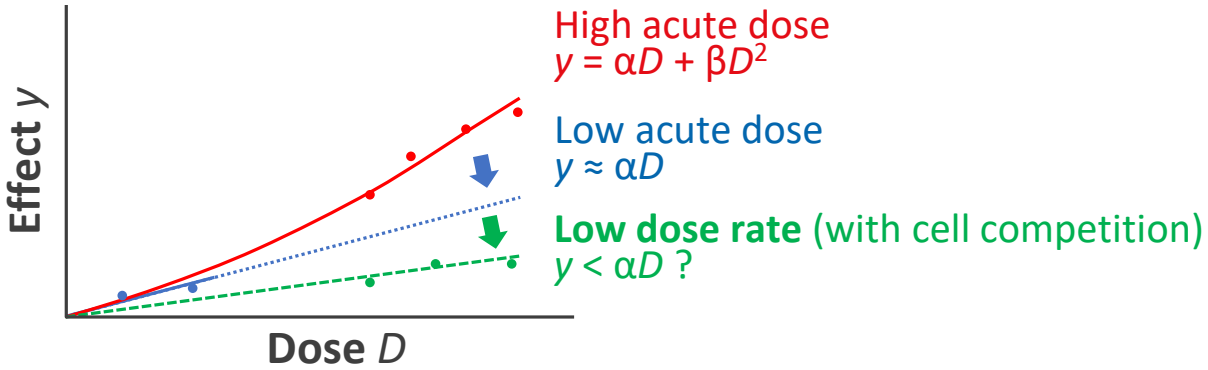
Nagashima et al. J Radiat Res 62:582-589 (2021) https://doi.org/10.1093/jrr/rrab022

Cell competition study @CRIEPI

- "Cell competition" was first discovered in *Drosophila* as a mechanism to exclude rare mutant cells from tissue
- Postulated (by ICRP Pub 131) as a possible mechanism to reduce radiation-induced cancer risk from chronic radiation exposure at low dose rates



(Adapted from Gregorio et al. Dev Cell 38: 621-34, 2016)



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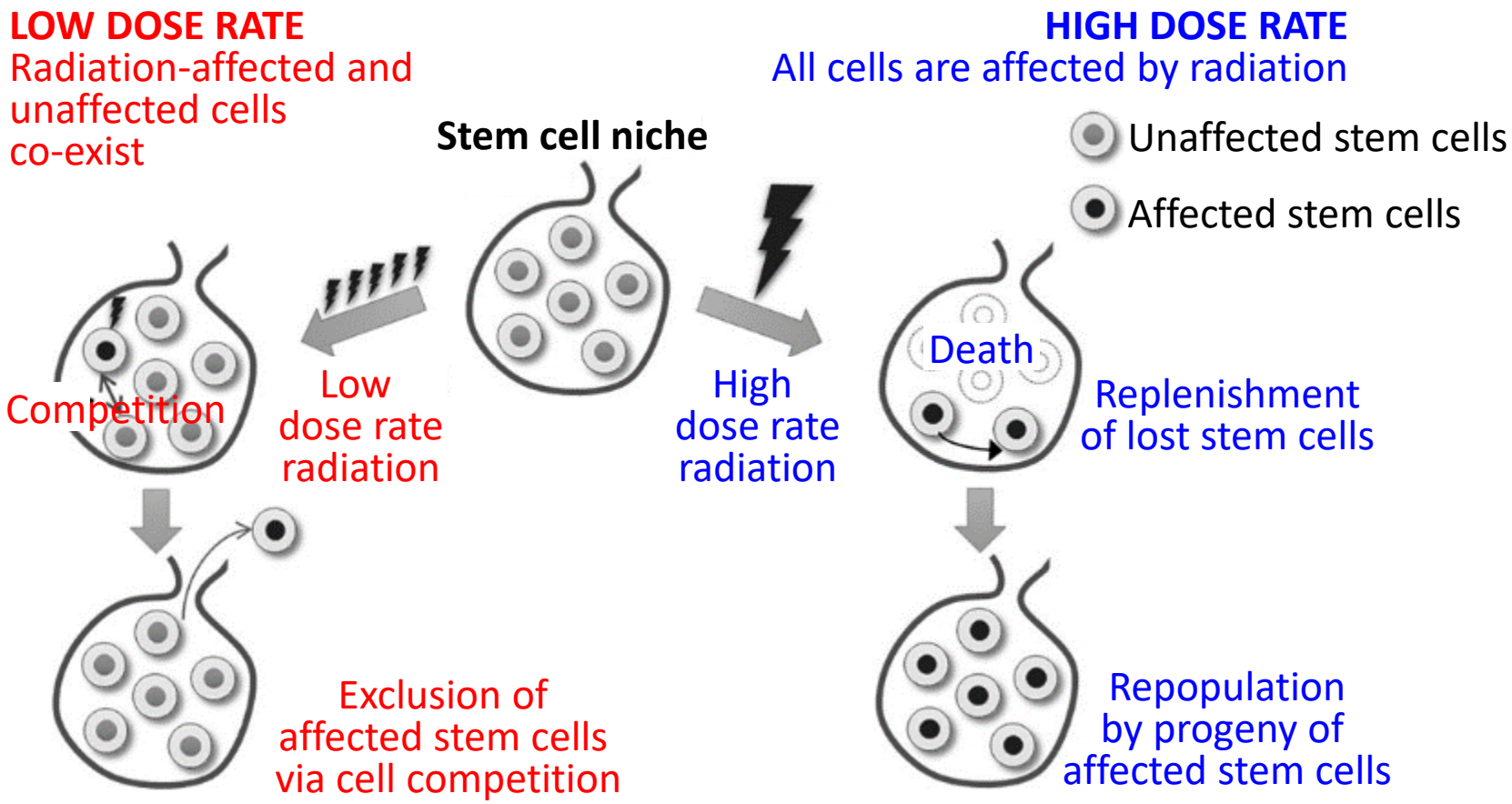
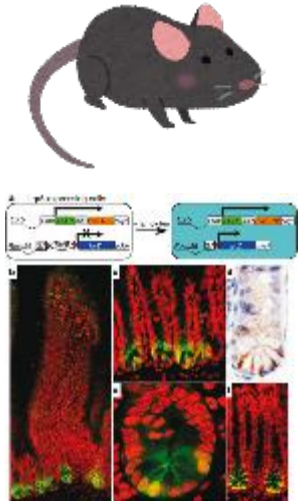


Fujimichi (2019) J Atomic Energy Soc Jpn 61:788-792 [publication in Japanese]

Cell competition study @CRIEPI (biology)

- Lgr5-GFP mice are mice that express GFP in their intestinal stem cells.
- Red and non-red stem cells were isolated, irradiated/non-irradiated, mixed at fixed ratios, and cultured to form intestinal organoids.
- Measurement of the ratios of cells in the organoids indicated outcompetition of non-irradiated cells.

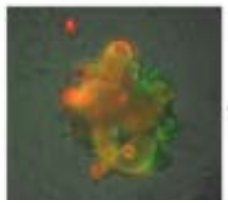
Lgr5-GFP mice
(intestinal stem cells express GFP)



Stem cells
(non-irradiated)

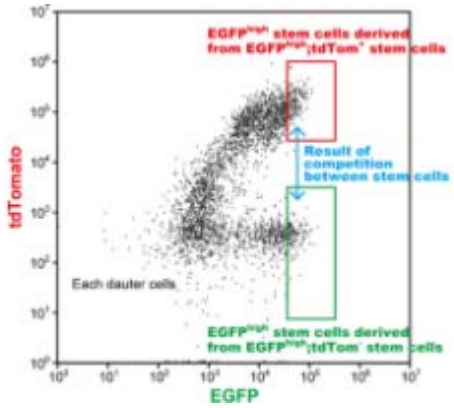
Mixed

Stem cells
(non-irradiated
or 1 Gy–irradiated)

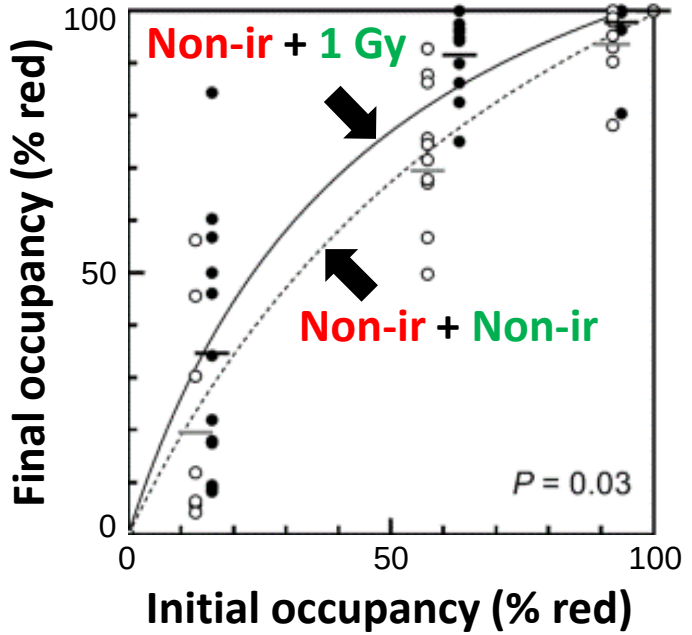


Intestinal organoid
(10-day culture)

Measure occupancy of red (non-irradiated) cells



Non-irradiated cells outcompete 1 Gy–irradiated cells in organoids

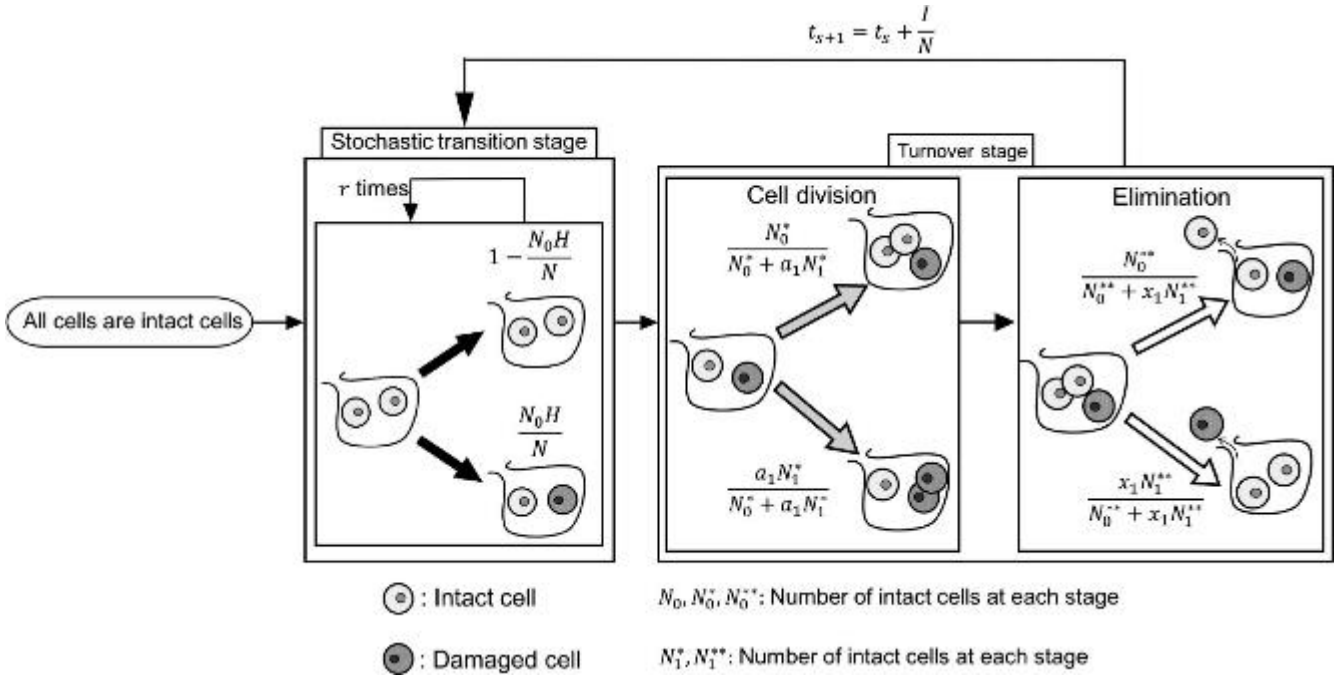


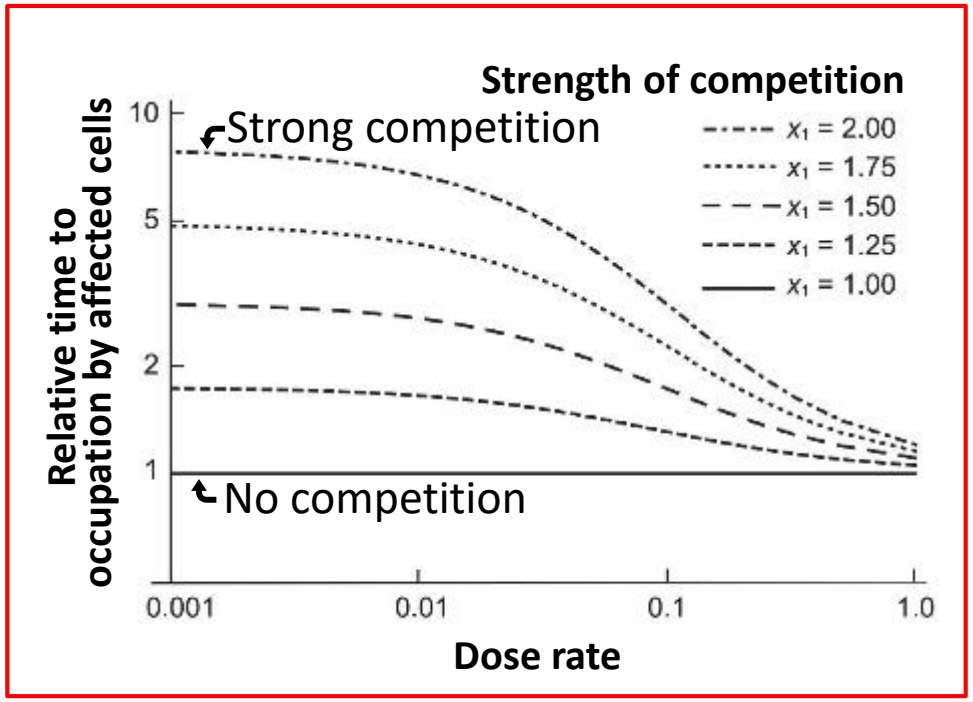
Fujimichi et al. Sci Rep (2019) 9:20297 https://doi.org/10.1038/s41598-019-55824-1

Cell competition study @CRIEPI (mathematical model)

- A mathematical model was constructed that describes the accumulation of affected cells in the stem cell pool in the presence of cell competition.
- Under very low-dose-rate conditions, this model showed that radiation damage to the stem cell pool was strongly suppressed in conditions where the damaged cells were less reproductive and easier to be eliminated compared to the unaffected cells.

$$\begin{bmatrix} D_0(s+1) \\ D_1(s+1) \\ \vdots \\ D_N(s+1) \end{bmatrix} = \begin{bmatrix} q_0^0 & q_1^- & 0 & \cdots & 0 & 0 & 0 \\ q_0^+ & q_1^0 & q_2^- & \cdots & 0 & 0 & 0 \\ 0 & q_1^+ & q_2^0 & \cdots & 0 & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & 0 & \vdots & \vdots \\ 0 & 0 & 0 & \cdots & q_{N-2}^0 & q_{N-1}^- & 0 \\ 0 & 0 & 0 & \cdots & q_{N-2}^+ & q_{N-1}^0 & q_N^- \\ 0 & 0 & 0 & \cdots & 0 & q_{N-1}^+ & q_N^0 \end{bmatrix} \begin{bmatrix} 1-\kappa_0 & 0 & 0 & \cdots & 0 & 0 & 0 \\ \kappa_0 & 1-\kappa_1 & 0 & \cdots & 0 & 0 & 0 \\ 0 & \kappa_1 & 1-\kappa_2 & \cdots & 0 & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots \\ 0 & 0 & 0 & \cdots & 1-\kappa_{N-2} & 0 & 0 \\ 0 & 0 & 0 & \cdots & \kappa_{N-2} & 1-\kappa_{N-1} & 0 \\ 0 & 0 & 0 & \cdots & 0 & \kappa_{N-1} & 1-\kappa_N \end{bmatrix}^I \begin{bmatrix} D_0(s) \\ D_1(s) \\ \vdots \\ D_N(s) \end{bmatrix}$$



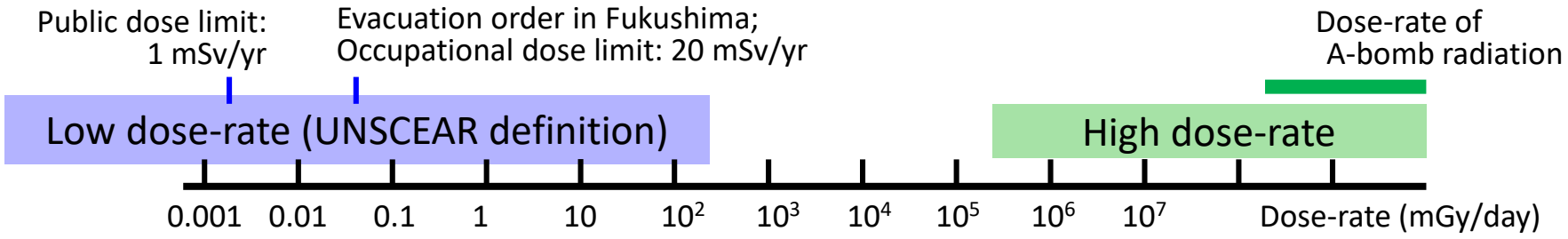


Uchinomiya et al. Radiat Res (2020) 194 (4): 379–389. https://doi.org/10.1667/RADE-20-00034.1

All Japan

Radiation facilities and accessibility

Radiation facilities and accessibility



	Joint usage	In-house usage (contract-based usage possible)	Mouse (SPF)	Rat (SPF)	Mouse (non-SPF)	Cell culture
IES, Japan, 1995		✓	✓			✓
MICADO, IRSN, France, 2017						
RBC, Kyoto Univ, Japan, 1996	✓					✓
CNL, Canada, 1994						
QST, Japan, 2003		✓	✓	✓		
RIRBM, Hiroshima Univ, Japan, 1984	✓				✓	✓
SCK-CEN, Belgium, 1980s						
CRIEPI, Japan, 2000		✓			✓	✓
FIGARO, NMBU, Norway, 2003						
Argonne, USA（closed in 1992）						

(By the courtesy of Dr. Komura, IES)

Radiation facilities and accessibility

- **Microbeam**

Facility	Specification	Accessibility
Microbeam X-ray Cell Irradiation System (CRIEPI)	X rays	In-house only
PF (KEK)	Synchrotron (X rays)	Joint usage
SPICE (QST)	Electrostatic (proton)	Joint usage
W-MAST (WERC)	Electrostatic (proton)	Contract-based
TIARA (QST)	Heavy ions (cyclotron)	Joint usage

- **High LET radiation**

Facility	Specification	Accessibility
KUR (Kyoto U)	Reactor (neutrons)	Joint usage
UTR-KINKI (Kindai U)	Reactor (neutrons)	Joint usage
NASBEE (QST)	Electrostatic (neutrons); animals, cells	Joint usage (suspended)
HIMAC (QST)	Synchrotron (He–Fe ions); animals, cells	Joint usage
TIARA (QST)	Cyclotron (H–Au ions, cluster ions); cells, plants	Joint usage
RIBF (RIKEN)	Cyclotron (H–U ions); plants	Joint usage

All Japan

Competitive funding sources

Relevant competitive funds in Japan

1. KAKEN (Grant-in-aid for Scientific Research) (MEXT)

(MEXT, Ministry of Education, Culture, Sports, Science and Technology)

- Covers all fields of science (humanities and social sciences to natural sciences)
- Competitive fund of a bottom-up nature, aiming at promoting academic research based on researchers' unfettered interest.
- Proposals are peer-reviewed in individual research categories.

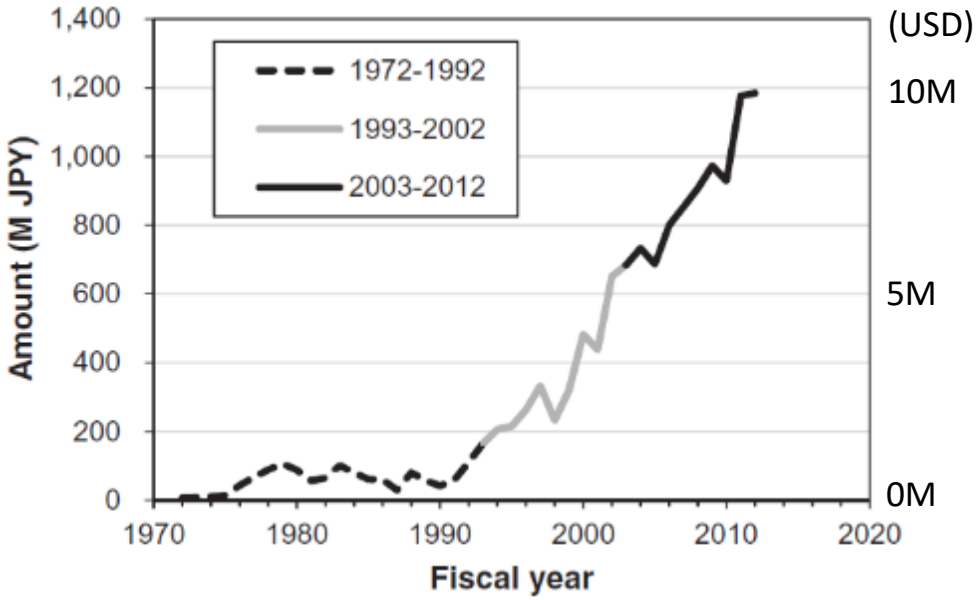


Fig. Total amount of KAKEN for the category of 'radiobiology' (1972–1992), 'environmental effects assessment (including radiobiology)' (1993–2002), and 'risk sciences of radiation/chemicals' (2003–2012).

Cho, Imaoka et al. INT J RADIAT BIOL 95: 816-840 (2019)

Relevant competitive funds in Japan

2. Collaborative nuclear energy research (MEXT)

- Aiming at investing in collaborative research on fundamental and innovative R&D on relevant research areas that were indicated in a top-down manner by the Japan Atomic Energy Commission.
- 'Crossover Research' (1989–2008), 'Nuclear Initiative' (2008–2013) and 'Project Wisdom' (2013+).
- Relevant research fields include health and environmental effects of radiation (JPY 100 M/y [USD 0.9 M/y], 2006–2014), utilization of radiation and laser technologies, materials science, and computational sciences.
- Shifted toward nuclear-decommissioning research (2018+).

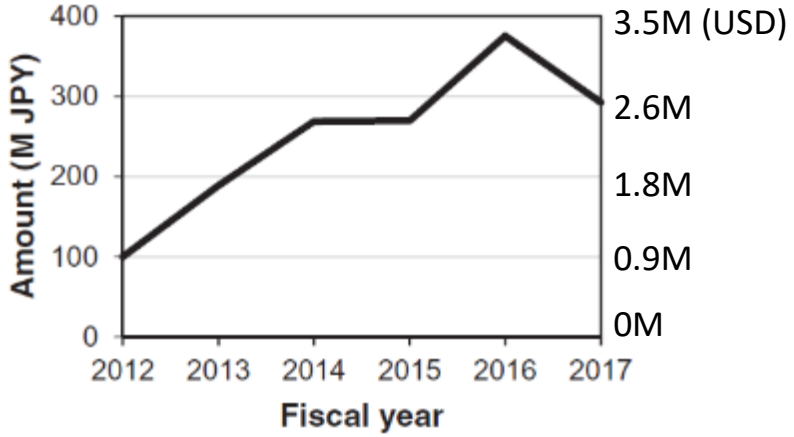
Cho, Imaoka et al. INT J RADIAT BIOL 95: 816-840 (2019)

Relevant competitive funds in Japan

3. Research on the Health Effects of Radiation (MOE)

(MOE, Ministry of the Environment)

- Objectives include health management and securing the reassurance of people affected in the Fukushima accident.
- The project invests in researches on
  1. Dose assessment techniques,
  2. Biological effects of radiation,
  3. Countermeasures against anxiety in affected areas,
  4. Assessment of initial radiation dose of the accident, and
  5. Morbidity trend in the affected areas
- Researchers are encouraged to use the research outcome in MOE's communication projects (see below) (2022+)



Cho, Imaoka et al. INT J RADIAT BIOL 95: 816-840 (2019)

All Japan

Communication of research findings with expert and non-expert groups

Communication among expert groups

Communication between academic societies

- Japanese Radiation Research Society (1959+)
  - Many members of JRRS are also members of Japan Society for Radiation Oncology (JASTRO), Japanese Environmental Mutagen and Genome Society (JEMS), Japanese Society for Biological Sciences in Space (JSBSS), Japanese Cancer Association (JCA), Japanese Health Physics Society (JHPS), etc.
  - The societies sometimes have joint academic meetings.

Communication among research institutions

- Radiation Research Institutions Council Japan (2005+)
  - Council of executives and/or high-level managers of QST-NIRS, RERF, Nagasaki University, IES, Kyoto University, Fukushima Medical University, Hirosaki University, Fukushima University, Hiroshima University, CRIEPI
  - Aims to deepen mutual understanding and cooperation among major radiation research institutions in Japan.
  - Annual meeting is held to share information on the activities of each organization and to plan the activity of the Council.

Communication with non-expert groups

Educational projects

- Primary/secondary education: 'Supplemental texts on radiation' (MEXT 2011, 2014, 2018) and training of school staff (2012+)
- Higher education: 'Proposal: enhancement of radiation health risk science education, including making it compulsory in medical education' (Science Council of Japan, 2014) and activities in response by national medical schools

Governmental projects (MOE)

- Consolidation of information: "BOOKLET to Provide Basic Information Regarding Health Effects of Radiation" (2014+), an easy-to-understand, annually revised document consolidating information provided by relevant ministries and agencies (subcontractor: QST)
- Science literacy and communication: "The GuGuRu Project" (2021+) aims to increase people's critical thinking on radiation effects to protect themselves against misinformation.
  - Named after Japanese words *tsumugu* [building knowledge], *tsunagu* [connecting people] and *tsutawaru* [transmitting knowledge].
  - The 5 main activities are: KNOW (developing skills to accurately understand scientific facts), LEARN (opportunities to learn about radiation), DECIDE (leaflets offering decision-making information), LISTEN (providing a consultation system), and RESEARCH (website to answer questions and concerns).

Reference MEXT textbook, https://www.mext.go.jp/b_menu/shuppan/sonota/detail/1409740.htm [Japanese only]
SCJ proposal, https://www.scj.go.jp/ja/info/kohyo/pdf/kohyo-22-t197-3.pdf [Japanese only]
MOE booklet, https://www.env.go.jp/en/chemi/rhm/basic-info/; GuGuRu, https://www.env.go.jp/en/headline/2534.html.

Communication involving expert/non-expert groups

Activities of researchers, motivated by the '*scientific*' misinformation after the Fukushima accident

- JRRS projects (2011+): Q&A website, seminars for citizens, radiobiology lectures, educational support in schools, training for officers of local governments
- JHPS project: Q&A website (2011–2014), now archived in National Diet Library.
- JRRS/JHPS collaboration: Consolidation of the experts' consensus on low dose effects (published as an open access paper)
- NPO '*Einstein*' (president, Prof. Bando at Osaka Univ., 2009+)
  - An NPO on expert-citizen interaction announced the foundation of JMELODI (Japan Multidisciplinary Effects-of-Low-Doses Initiative) in 2015 to gather relevant scientists in Japan.
  - The researchers are running the 'JSPS University-Industry Cooperative Research Committee 195' (2019 to 2024), for discussions on the biological effects of radiation and related regulations.

Reference JRRS, https://www.jrrs.org/faqpage/seminar/ [Japanese].
JHPS, https://warp.da.ndl.go.jp/info:ndljp/pid/8699165/radi-info.com/ [Japanese]
Consensus paper, *Radiat Biol Res Commun* 55 (2020) http://rbrc.kenkyuukai.jp/special/index.asp?id=33566 [Japanese]
'*Einstein*', JMELODI https://jein.jp/jmelodi.html; JSPS committee, https://www.jsps.go.jp/english/e-soc/list/195.html.

All Japan

Coordination of organizations within Japan or elsewhere

Coordination of organizations

- **J-RIME** (alliance of 18 associations, 2010+): medical exposure

  'Japan Network for Research and Information on Medical Exposure' (secretary: QST)

  - **Collects and shares information** on the actual situation of medical radiation exposure and related researches, to contribute to the research on medical radiation exposure.

- **PLANET** (a QST project, 2016+): low dose effect research

  'Planning and Acting Network for Low Dose Radiation Research' (secretary: QST)

  - Gathers relevant experts in Japan, **collects and analyzes information** on radiation effects, risks, and protection, and **provides it to stakeholders** (public, regulatory bodies, etc).
  - Organizes **research agenda** for assessment of low dose radiation risks.

- **UMBRELLA** (an NRA project, 2017+): radiation protection

  'Formation of problem-solving network and umbrella-type integrated platform in the field of radiation protection research' (secretary: QST)

  - Provides a platform to bring together stakeholders in the field of radiation protection.

NRA, Nuclear Regulation Authority

Reference J-RIME, http://www.radher.jp/J-RIME/ [Japanese].
PLANET, https://www.qst.go.jp/uploaded/attachment/2910.pdf [Japanese]
UMBRELLA, https://www.nirs.qst.go.jp/usr/umbrella-rp/ [Japanese], Kanda et al. Jpn J Health Phys 53:176-180 (2018) [English]

Low-Dose Radiation Research at QST

Shizuko Kakinuma

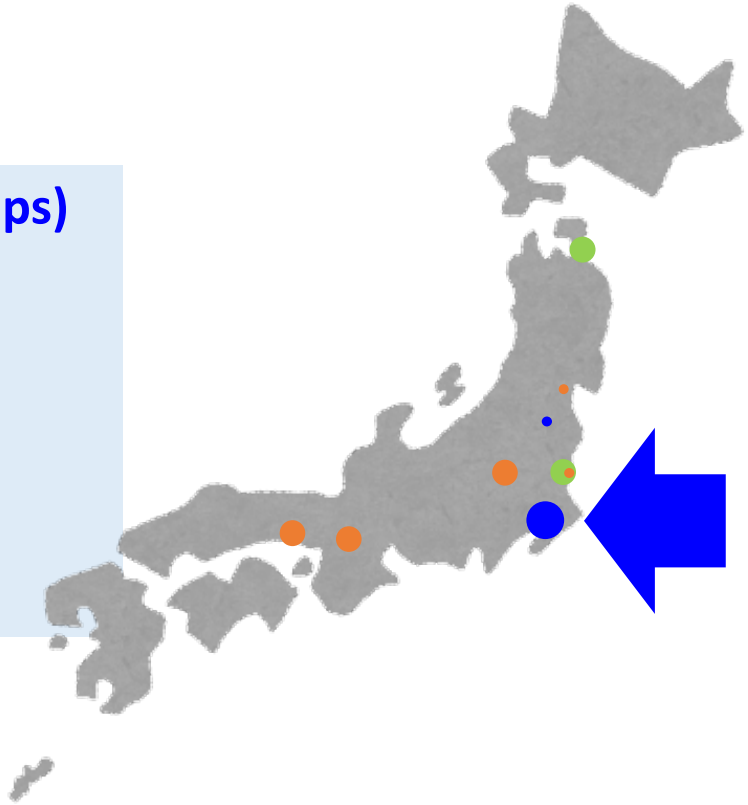
Director, Dept of Radiation Effects Research

National Institutes for Quantum Science and Technology
Japan

Organization of QST

Headquarter

- Quantum Life and Medical Science Directorate (4 institutes)
  - Institute for Quantum Medical Science (5 departments, 25 groups)
  - **National Institute of Radiological Sciences (6 departments, 22 groups)**
    - **Department of Radiation Emergency Medicine**
    - **Department of Radiation Emergency Management**
    - **Department of Radiation Measurement and Dose Assessment**
    - **Department of Radioecology and Fukushima Project**
    - **Department of Radiation Effects Research**
    - **Department of Radiation Regulatory Science Research**
  - QST Hospital (4 departments, 15 sections)
  - Institute for Quantum Life Science (0 departments, 19 groups)
- Quantum Beam Science Research Directorate (3 institutes)
- Fusion Energy Directorate (2 institutes)



Department of Radiation Effects Research

✓**People** (as of Nov 2021)

- **Employees**
  - 10 tenured researchers
  - 10 fixed-term researchers
  - 27 fixed-term technical staff
- **Research groups**
  - Radiobiology for Children's Health Research Group
  - Stem Cells and Effect Modifiers Research Group
  - Chronic Exposure, Cancer and Pathology Research Group
  - Dietary Effects Research Group
  - Carcinogenesis Dynamics Research Group
  - Biospheric Radionuclide Migration Research Group

✓**Budget** (as of Nov 2021)

- Grant for administrative expense
- External funds (KAKENHI, MEXT, MOE)

QST

Overview of low-dose radiation research, with emphasis on cutting-edge technologies

Radiation signature, Animal model,

Low-Dose Radiation Research in QST

- **Evaluation of cancer risk**

  Animal models, low dose rate effect

- **Research using cutting-edge technologies**

  'Radiation signature' mutations in tumors

  - Low dose and low dose rate, RBE of neutrons
  - Next generation sequencing, CGH microarray, LOH analysis

- **J-SHARE**

  Archive system of animal experiment (pathology images, samples, …)

- **PLANET** (presented by Imaoka)

  Planning and Acting Network for Low Dose Radiation Research

Animal models used in QST: mouse models

Mouse models	Genetic background	Tumors	Low doses tested	Low dose rate tested
B6C3F1 (wild-type)	C57BL6/N (B6) × C3H/HeN (C3) (hybrid)	Lymphoma (thymic, B-cell), liver, lung, thyroid	200 mGy	Ongoing
***Ptch1*$^{+/-}$**	C3B6F1 (hybrid)	Medulloblastoma, skin (basal cell carcinoma)	50, 100 mGy	1 mGy/h
***Apc*$^{Min/+}$ (also Min)**	C3B6F1 (hybrid)	Intestinal (carcinoma of small intestine, colon)	50, 100 mGy (ongoing)	Ongoing
***Mlh1*$^{+/-}$, *Mlh1*$^{-/-}$**	C57BL/6J	Colon, lymphoma (thymic)	Not yet	Not yet

B6C3F1 mice (200 mGy)

- Yamauchi et al. Mutat Res. 2008 Apr 2;640(1-2):27-37.
- Kakinuma et al. Mutat Res. 2012 Sep 1;737(1-2):43-50.

Ptch1 mice (50 mGy, 100 mGy, 1 mGy/h)

- Ishida et al. Carcinogenesis. 2010 Sep;31(9):1694-701.
- Tsuruoka et al. Radiat Res. 2016 Oct;186(4):407-414.
- Tsuruoka et al. Radiat Res. 2021 Aug 1;196(2):225-234.

Animal models used in QST: rat models

Rat models	Genetic background	Tumors	Low dose tested	Low dose rate tested
Sprague-Dawley (wild-type)	Jcl:SD	Mammary	200 mGy	3 mGy/h
(SD × COP)F_1 (wild-type)	Jcl:SD × COP/Hsd (hybrid)	Mammary	Not yet	Not yet
***Tsc2*$^{+/-}$ (also Eker)**	F344 and Long-Evans (hybrid)	Kidney (renal cell carcinoma)	500 mGy	Not yet
Wistar (wild-type)	WM/Nrs	Lung, mammary	Not yet	Not yet

Sprague-Dawley rats (200 mGy, 3 mGy/h)

- Imaoka et al. Int J Radiat Oncol Biol Phys. 2013 Mar 15;85(4):1134-40.
- Imaoka et al. Int J Cancer. 2014 Apr 1;134(7):1529-38.
- Imaoka et al. Radiat Res. 2019 Mar;191(3):245-254.

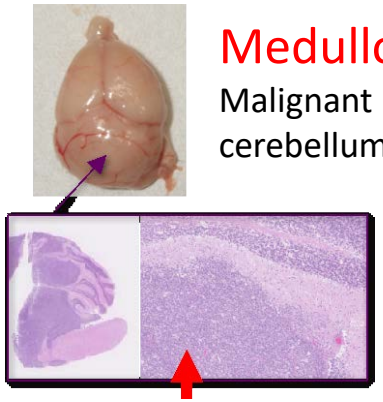
Tsc2$^{+/-}$ (Eker) rats (500 mGy)

- Kokubo et al. Cancer Sci. 2010 Mar;101(3):616-23.

‘Radiation signature’

- Radiation related genomic alteration:
  Interstitial deletion (real risk of radiation exposure)
- Ptch1 heterozygous mice, medulloblastoma
  →low dose exposure, low dose rate exposure
  →RBE for neutron exposure
- Other animal models
  a mutation of tumor suppressor and interstitial deletion
  → Eker rat (Tsc2 heterozygous kidney tumor)
  → B6C3F1 thymic lymphoma (mutation of Ikaros, interstitial deletion)
  →Rat mammary tumor (Interstitial deletion related radiation exposure)

Radiation signature in *Ptch1* heterozygous mouse



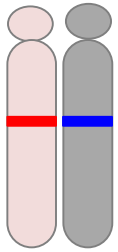
Medulloblastoma (MB)

Malignant brain tumors in cerebellum of childhood

Ptch1 heterozygous normal cell

Ptch1 mutation

Ptch1 wild-type

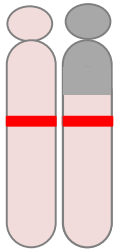


Chromosome 13

Spontaneous MB

Ptch1 mutation

Ptch1 mutation

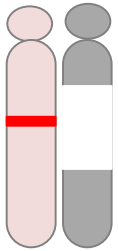


Mitotic recombination:
Both *Ptch1* allele were mutated

Radiation-induced MB

Ptch1 mutation

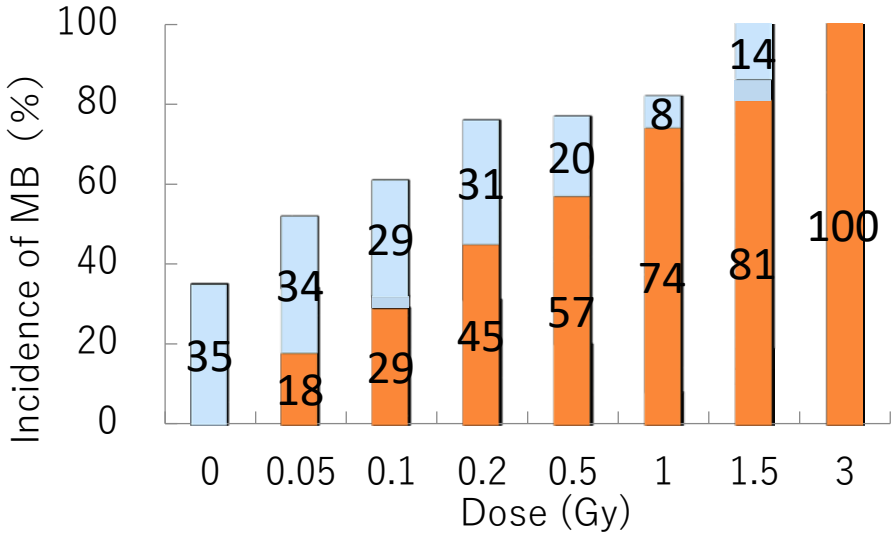
Interstitial deletion



Interstitial deletion:
Loss of wild-type *Ptch1* allele

Incidence of MB

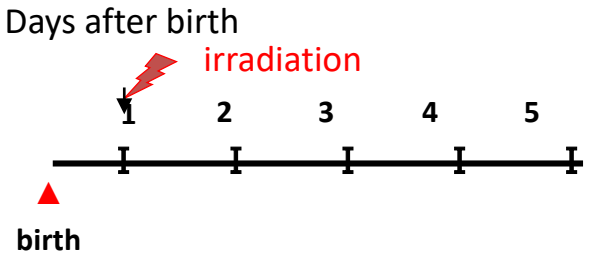
Irradiated age: Postnatal day 1
Radiation: X-rays, 250 days after birth



Ishida et al. Carcinogenesis, 2010.

Irradiation conditions

Acute exposure

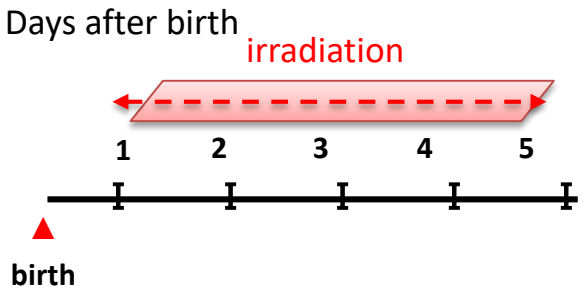


Dose rate ：540 mGy/min
（32,400 mGy/hr）

Total dose ：100 mGy

500 mGy

Protracted exposure (4 consecutive days)



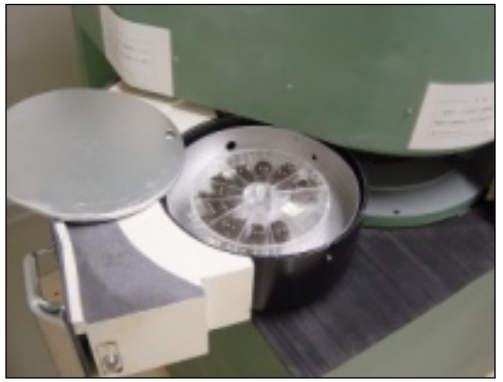
Dose rate ：1.1 mGy/hr

Total dose ：100 mGy

Dose rate ：5.4 mGy/hr

Total dose ：500 mGy

Facility in QST



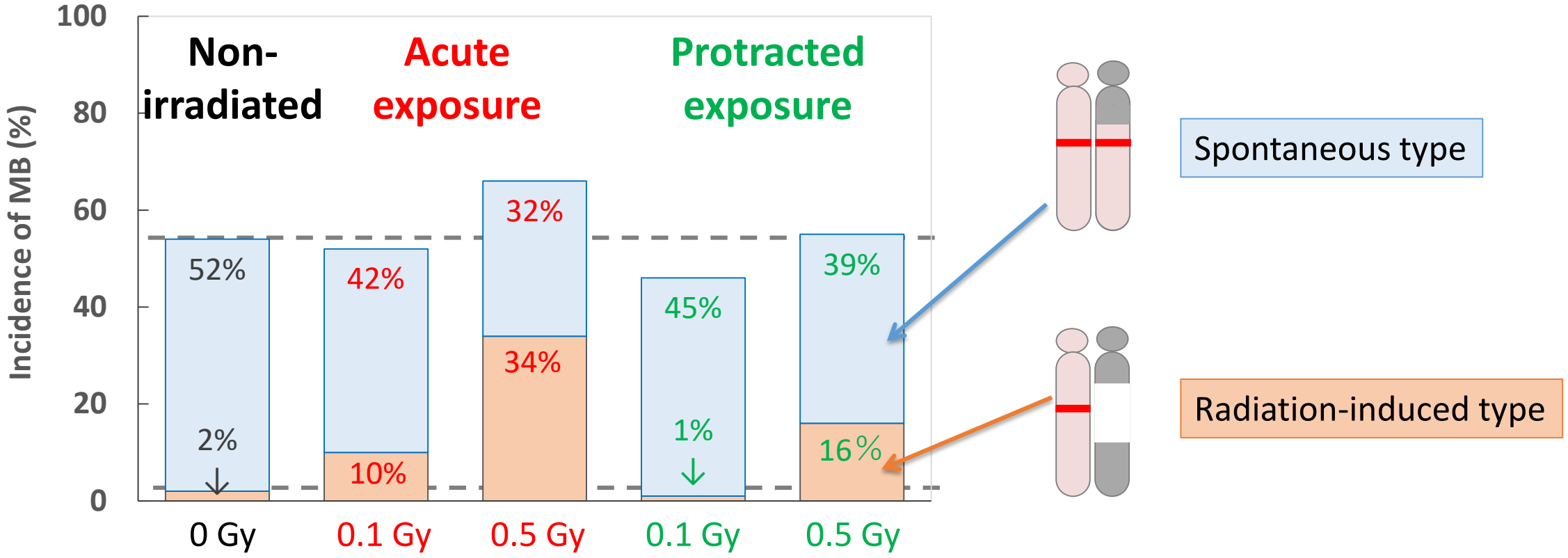
GAMMACELL 40

^{137}Cs (115 TBq), 30 Gy/h
Nordion International,
Ottawa, Canda

Low-dose-rate radiation system

^{137}Cs (1.11 and 0.111 TBq),
0.05–60 mGy/h
Pony Industry Co., Ltd.,
Osaka, Japan

Incidence of radiation-induced MBs



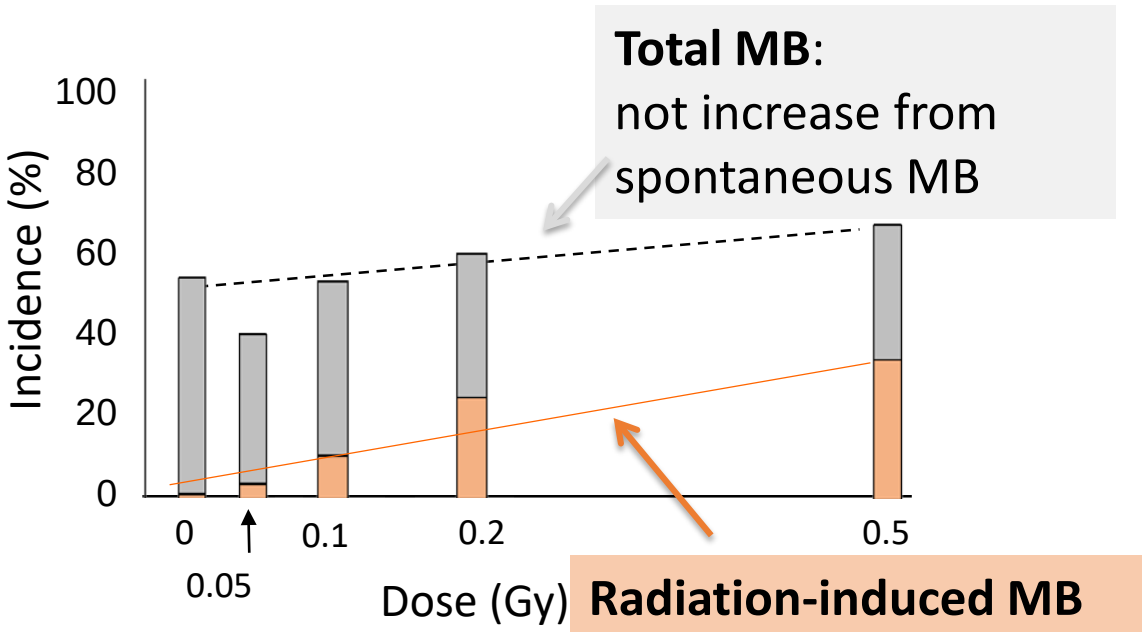
"Protracted exposure":
Incidence of radiation-induced MB was observed at 0.5 Gy, although it decreased below the incidence of acute exposure. When total dose was reduced to 0.1 Gy, incidence of radiation-induced MB decreased to background level.

Tsuruoka et al. *Radiat. Res.*, 2016

RBE of neutron for MB induction in Ptch1 mice

Incidence of MB

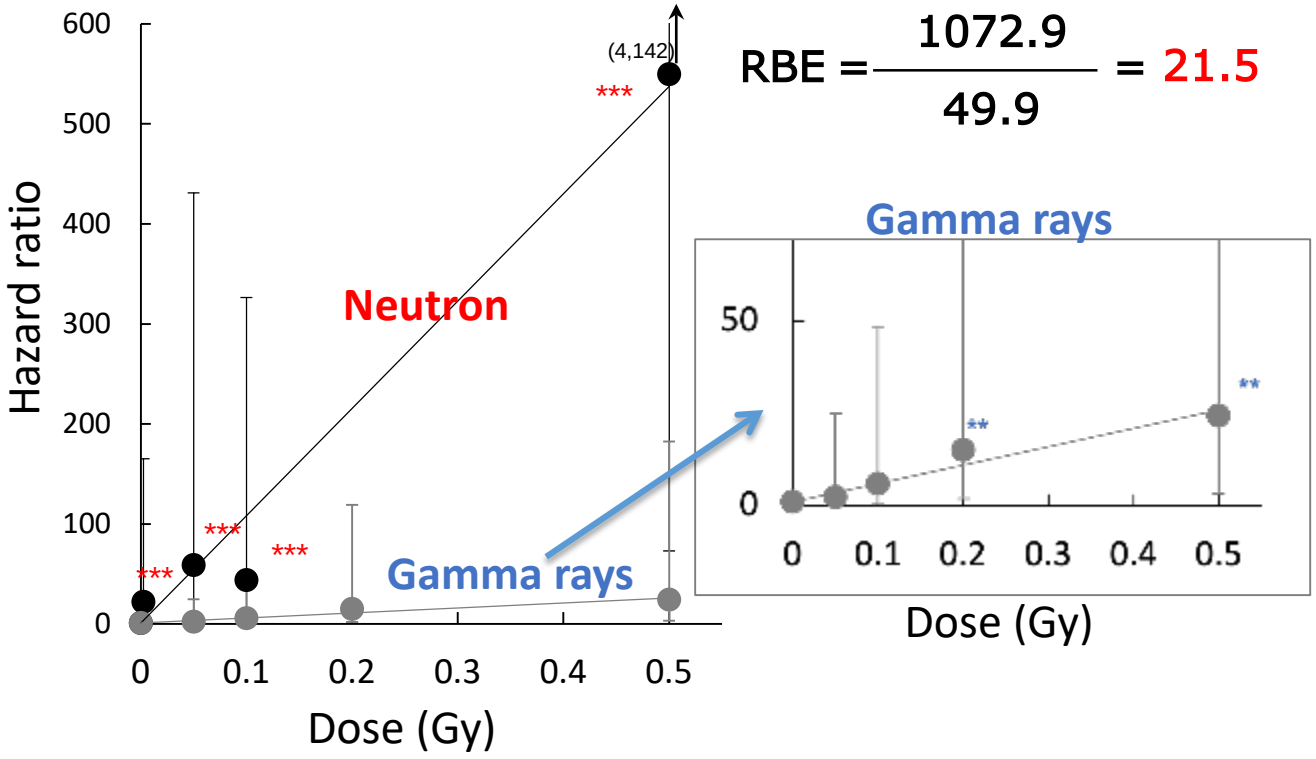
Total MB and radiation-induced MB



Total MB:
not increase from spontaneous MB

Radiation-induced MB
increases dose dependently with low dose exposure.

Risk of MB induction by gamma-rays or neutron exposure



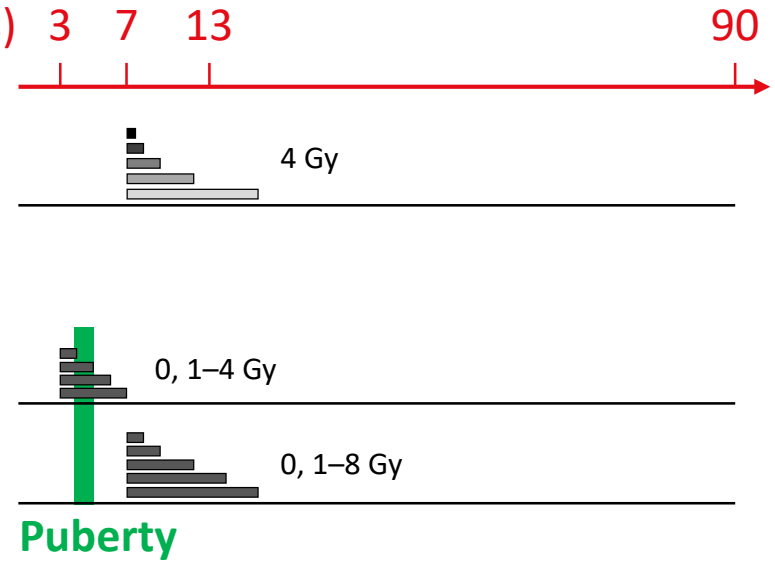
Tsuruoka et al, Radiat Res (2021) 196, 225-234.

Dose rate and age effects for mammary tumor in SD rats

Expt. 1 Dose rate
(3–60 mGy/h)

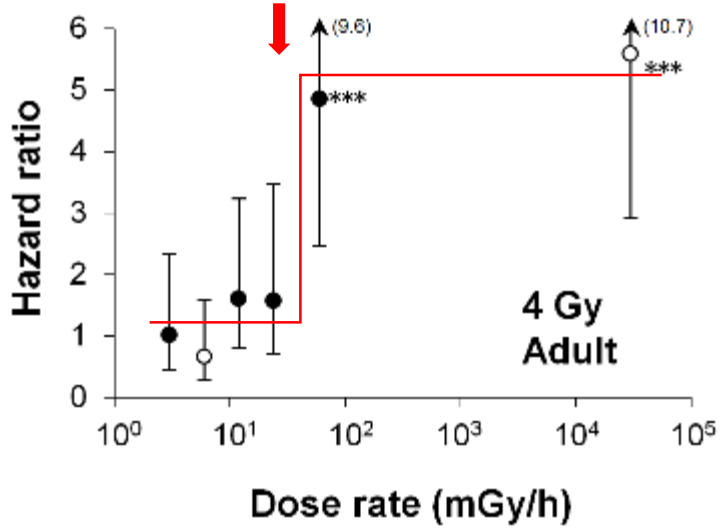
Expt. 2 Age
(6 mGy/h)
Around puberty
As adults

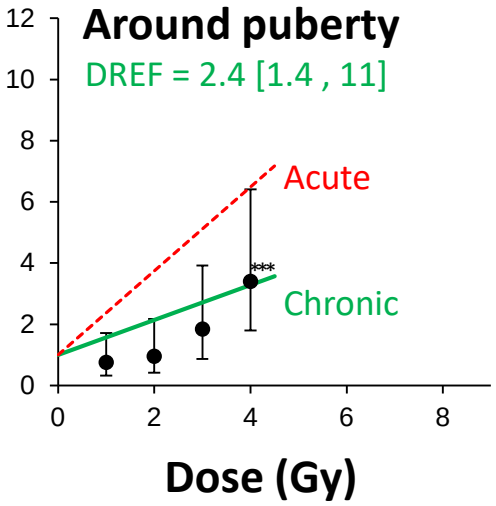
Acute (30 Gy/h)
3 weeks
7 weeks
13 weeks

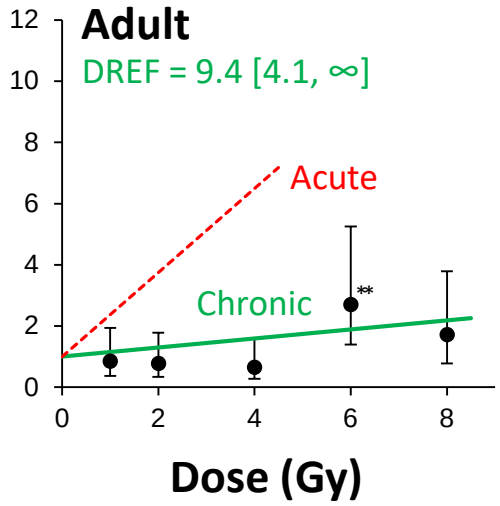


Female Jcl:SD rat (Clea Japan), n = ~24/group
30 kGy CE-2 diet fed *ad libitum*, 3 rats/cage, SPF
Approved by Institutional Animal Care & Use Committee (10-1035)

Threshold: between 24 and 60 mGy/h



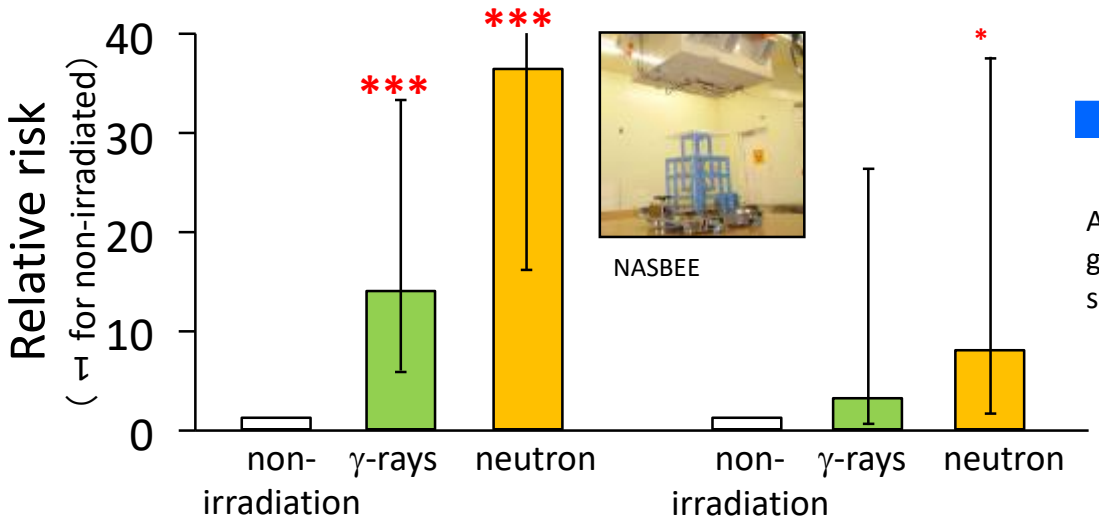




Imaoka, Nishimura, Daino et al. Rad Res 191: 245-254 (2019) https://doi.org/10.1667/rr15094.1

Risk and molecular biological characteristics for mammary tumor caused by radiation exposure

Luminal type mammary tumor increase by irradiation



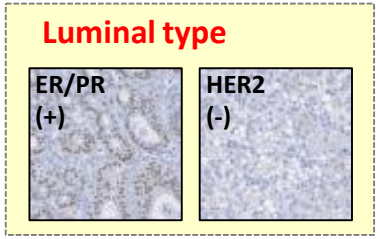
NASBEE

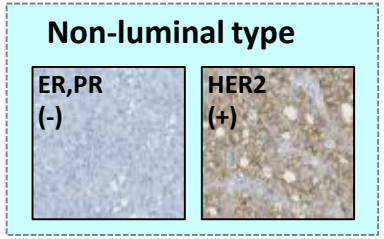
Analysis by Next generation sequencer

28検体の乳がん（各8～10検体）を解析

(Dose)

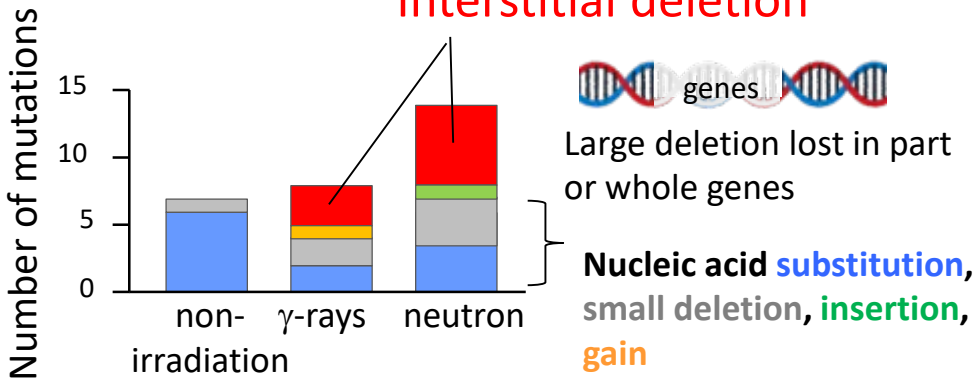
γ-rays :4 Gy
neutron:1 Gy
(2 MeV, fast neutron)





Number and types of mutations

Important mutant genes found in human （*Cdkn2a, Pik3r1 etc*） identified 23 genes

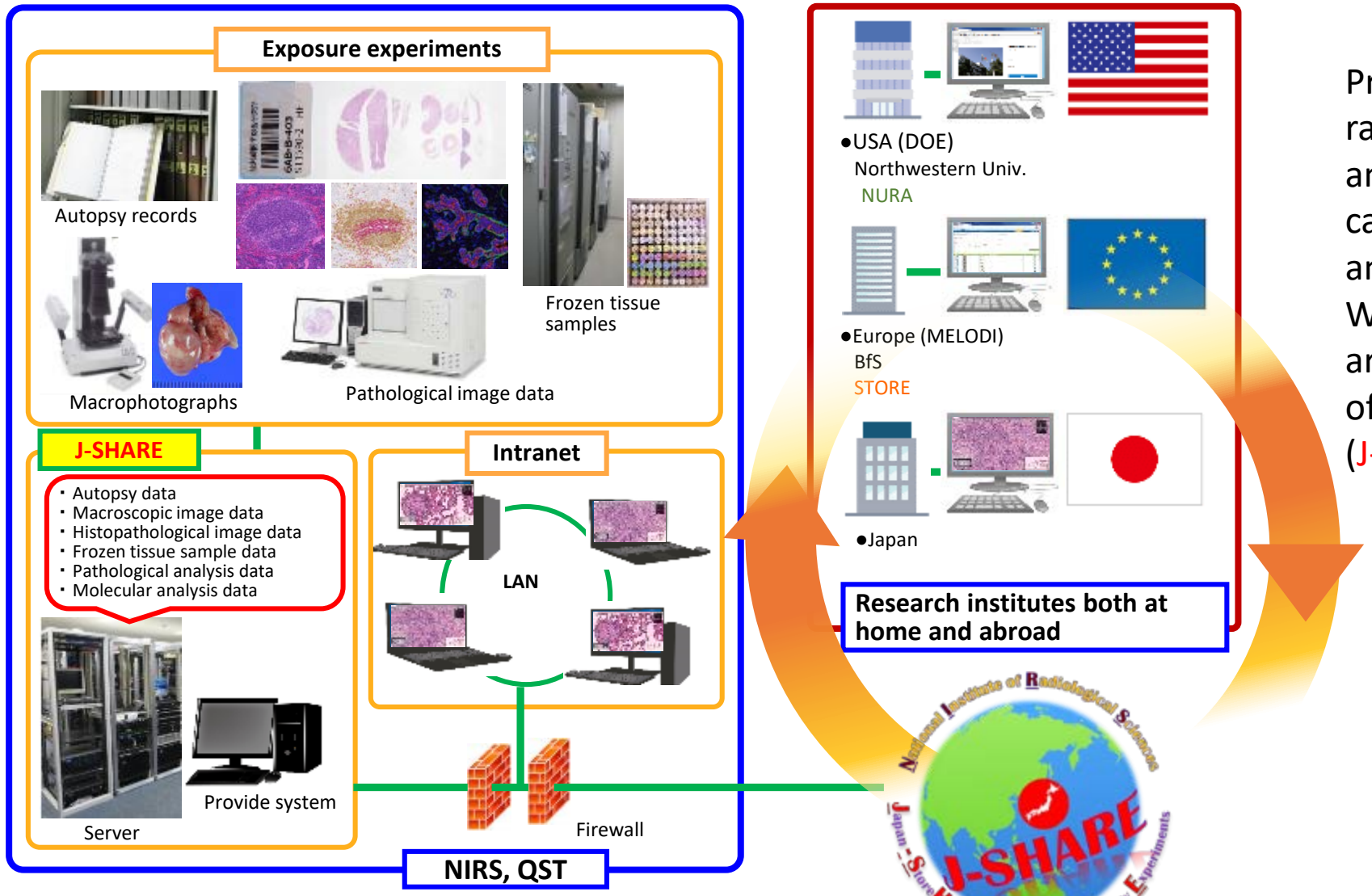


Interstitial deletion is characteristic in irradiated group.

This result suggests the possibility of more accurate risk assessment for radiation effects using radiation-related molecular signature.

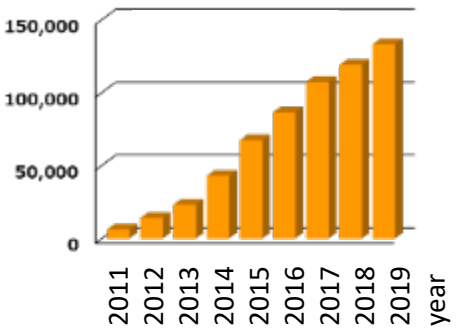
Moriyama et al. Anticancer Res. 2021 Jan;41(1):55-70.

J-SHARE (the Japan-Storehouse of Animal Radiobiology Experiments)



Projects to evaluate the effects of radiation has since focused on risk analyses for life shortening and cancer prevalence using laboratory animals within NIRS-QST.
We are now constructing such an archive called the Japan-Storehouse of Animal Radiobiology Experiments (J-SHARE).

Number of slides



Morioka, et al. (2019), Int J Radiat Biol *95*, 1372-1377.

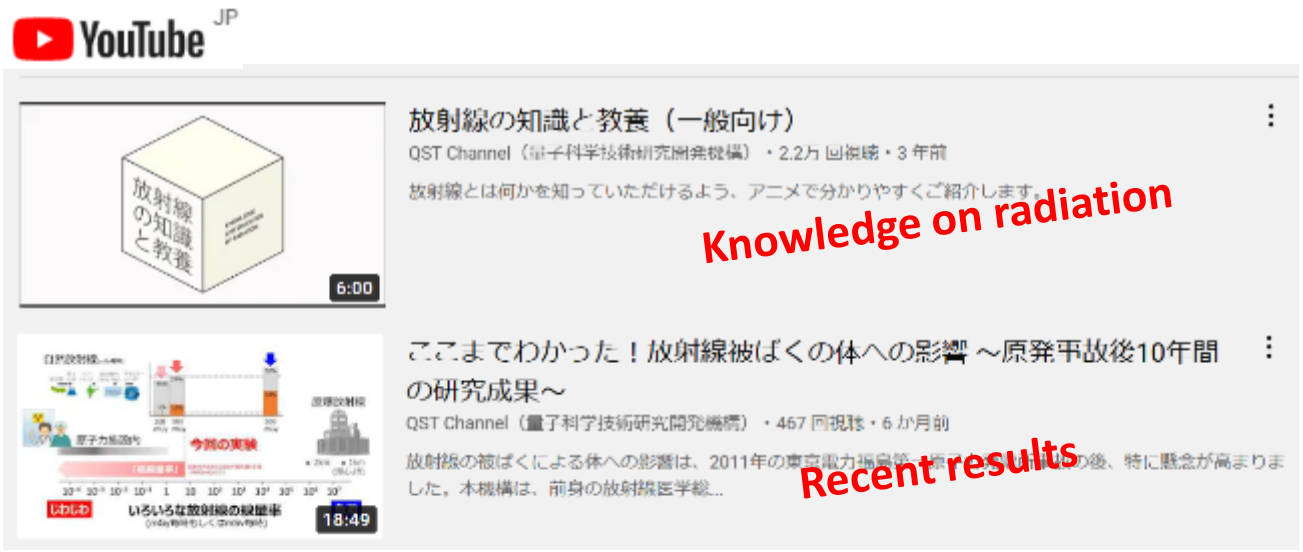
QST

Communication of research findings with expert and non-expert groups

Communication with non-experts

Open campus

- We usually perform exhibition of posters on research topics.
- Due to COVID-19, face-to-face events were held on a smaller scale in 2021.
- Instead, live sessions and on-demand videos on activities and recent results were published.

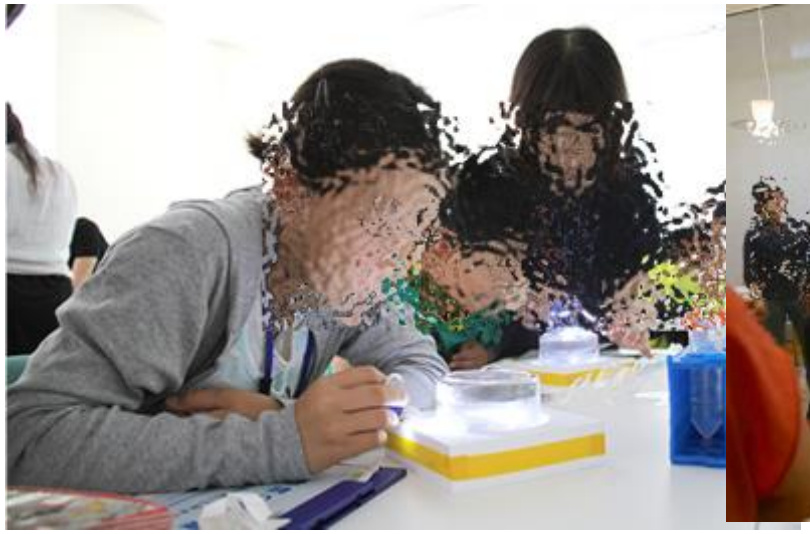


Notice on the ‘online’ open campus 2021

Communication with non-experts

Science camp of parents and children in Fukushima and Chiba

- The purpose of this event is for parents and children to learn basic knowledge about radiation together through hands-on events, and to deepen engagement between parents and children in Fukushima and Chiba beyond the region.



Fabrication of cloud chambers

Presentations

Learn clinical use of radiation

3-day course

Low-Dose Radiation Research at IES

Yoshiya Shimada

President

Institute for Environmental Science
Japan

Institute for Environmental Sciences (IES)

Established: 1990

Objective: Monitor the radioactive emissions released to the environment (by the Spent Nuclear Fuel Recycling Plant) and study its effect on the environment and human health

Funding: Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan through the Aomori Prefectural Government

Research Departments:

1. Radioecology
2. Radiobiology

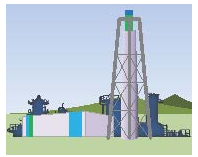
Research Priorities:

1. Environmental monitoring of radioactive materials
2. Low dose and low dose-rate exposures

IES

Radiation facilities and accessibility

Dose rates in irradiation facilities for animal experiments in comparison with human exposure scenarios



Estimated exposure from Rokkasho NFRP emission

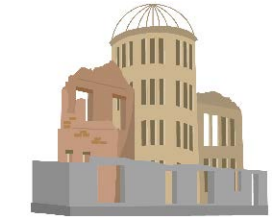
Public dose limit: 1 mSv/yr

Natural radiation: 2 mSv/yr

Average radiation exposure in Japan: 6 mSv/yr

Evacuation order in Fukushima;
Occupational dose limit: 20 mSv/yr

Dose-rate of A-bomb radiation



Low dose-rate

High dose-rate

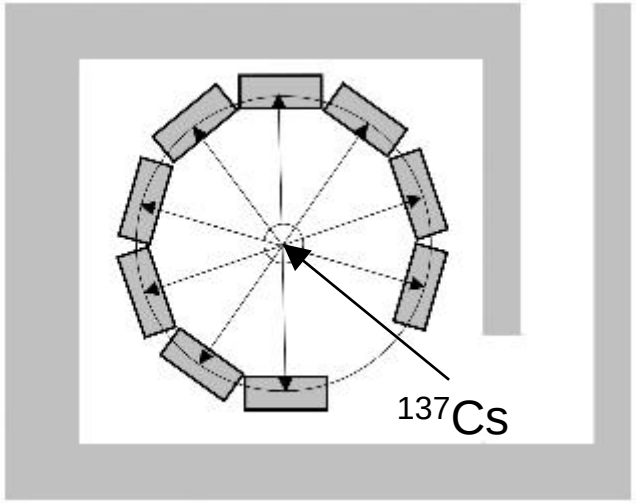
0.00001 | 0.01 | 10 | 10,000 | 10,000,000 | 10,000,000,000

Dose-rate (mGy/day)

IES, Japan, 1995
0.05, 1, 20 mGy/day

MICADO, IRSN, France, 2017
Kyoto Univ., Japan, 1996
CNL, Canada, 1994
QST-NIRS, Japan, 2003
Hiroshima Univ., Japan, 1984
SCK-CEN, Belgium, 1980s
CRIEPI, Japan, 2000
FIGARO, NMBU, Norway, 2003
Argonne, USA（closed in 1992）

Irradiation rooms in IES (1)



Floor Plan

Fixed dose-rates: 0.05, 1, 20, 400 mGy/day

Irradiation rooms in IES (2)

Variable dose-rates: 0.4 – 2000 mGy/day (for cultured cells)
20 – 13000 mGy/day (for mice)

IES

Overview of low-dose radiation research, with emphasis on cutting-edge technologies

Life span of mice exposed to low dose-rate gamma-rays

Animal ：SPF B6C3F1 (C57BL/6J x C3H/He) mouse, 8 weeks of age

No. of mouse examined：500/sex/group

Non-irradiated

Kept until the animals die a natural death

Irradiated (male 500 and female 500 each)

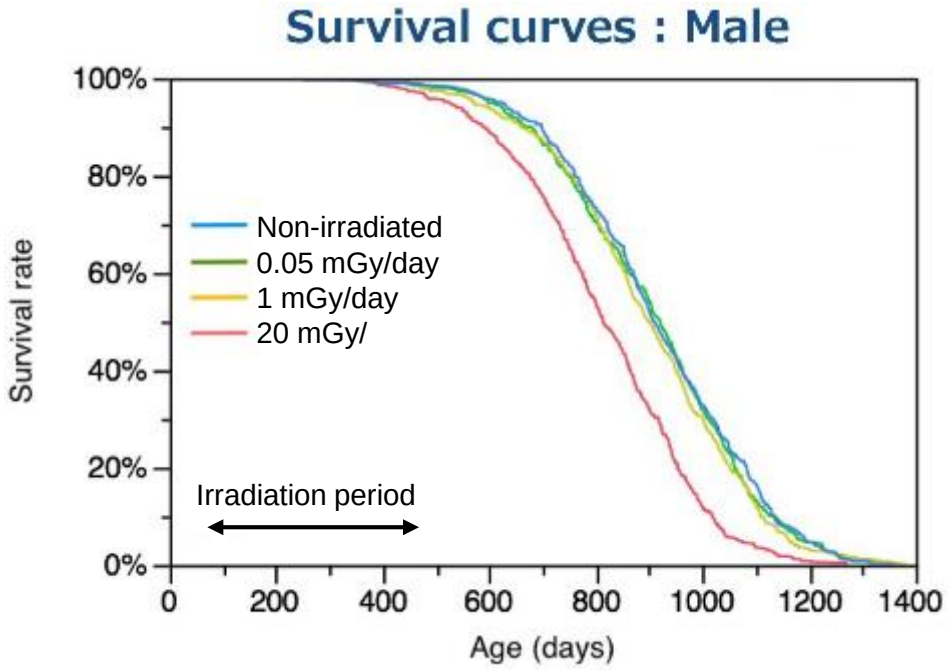
^{137}Cs gamma-ray

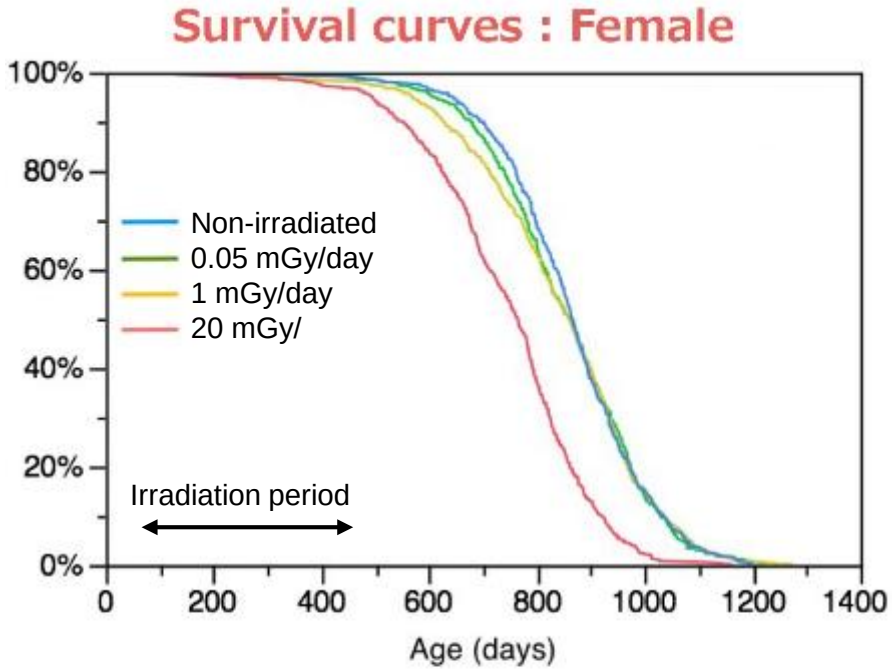
0.05	mGy/day	×400 days =	20 mGy
1	mGy/day	×400 days =	400 mGy
20	mGy/day	×400 days =	8000 mGy

Irradiation

Kept until the animals die a natural death

Life span of mice exposed to low dose-rate gamma-rays



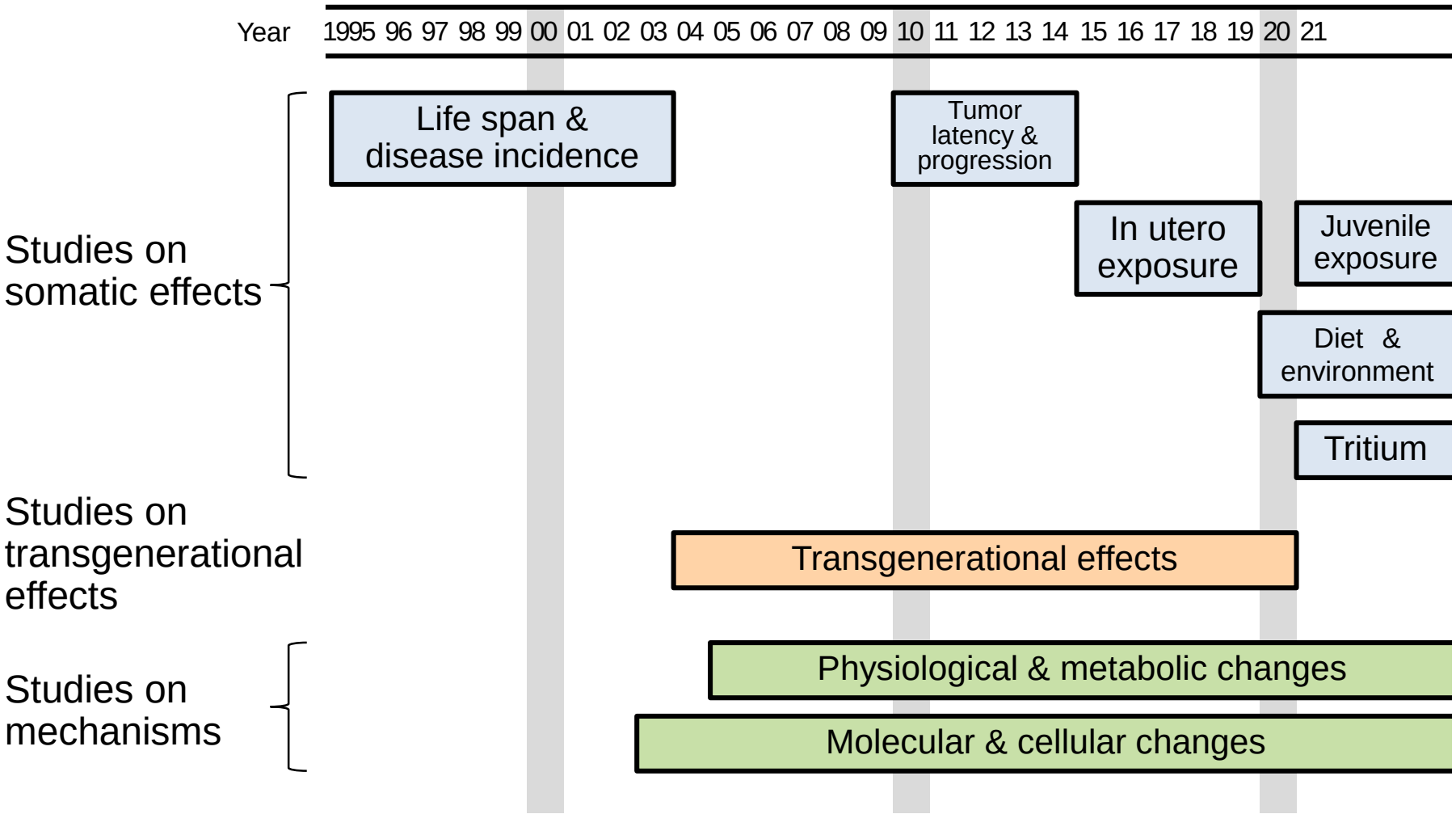


	Average	SE	P
Non-irradiated	912.7	8.2	
0.05 mGy/day (20 mGy)	905.8	8.3	0.901
1 mGy/day (400 mGy)	895.2	8.2	0.143
20 mGy/day (8000 mGy)	812.0	7.6	0.001

	Average	SE	P
Non-irradiated	860.5	6.3	
0.05 mGy/day (20 mGy)	851.8	6.7	0.694
1 mGy/day (400 mGy)	839.8	7.5	0.035
20 mGy/day (8000 mGy)	740.9	6.8	0.001

Shortening of life span was obvious at 20 mGy/day (total dose: 8000 mGy).
Shortening of life span was significant only in females at 1 mGy/day (total dose: 400 mGy).
Detection of significant effects was difficult at 0.05 mGy/day (total dose: 20 mGy).

Studies on low dose-rate radiation effects performed in IES



Summary of biological effects of long-term (400 days) low dose-rate irradiation of mice at IES

( ): Preliminary results

Endpoint \ Dose-rate (Total dose)	0.05 mGy/day (20 mGy)	1 mGy/day (400 mGy)	20 mGy/day (8000 mGy)
Somatic effects			
Life span	Not detected	Shortened in females	Shortened
Neoplasm incidence	(Increased in males)	(Increased in males)	Increased
Anti-tumor immune activity	Not determined	Not determined	Decreased
Oocyte number	Not determined	Decreased	Decreased
Chromosome aberration	(Not detected)	Increased	Increased
Gene expression	(Altered)	(Altered)	Altered
Transgenerational effects (effects on F1 mice, when male F0 mice were irradiated)			
Life span	Not detected	Not detected	Shortened in males
Mutation (CNV)	(Not detected)	(Not detected)	Increased

Summary of biological effects of long-term (400 days) low dose-rate irradiation of mice at IES

( ): Preliminary results

Endpoint \ Dose-rate (Total dose)	0.05 mGy/day (20 mGy)	1 mGy/day (400 mGy)	20 mGy/day (8000 mGy)
Somatic effects			
Life span	Not detected	Shortened in females	Shortened
Neoplasm incidence	(Increased in males)	(Increased in males)	Increased
Anti-tumor immune activity	Not determined	Not determined	Decreased
Oocyte number	Not determined	Decreased	Decreased
Chromosome aberration	(Not detected)	Increased	Increased
Gene expression	(Altered)	(Altered)	Altered
Transgenerational effects (effects on F1 mice, when male F0 mice were irradiated)			
Life span	Not detected	Not detected	Shortened in males
Mutation (CNV)	(Not detected)	(Not detected)	Increased

Effects difficult to detect consistently

Effects detected in specific endpoints

Large effects detected in various endpoints

Ongoing projects and future perspectives in IES

- Dose-rate effect: comparison with high dose-rates
- Individual radiosensitivity
  - Sex/gender
  - Age dependency (juvenile exposure)
  - Diet, environment
  - Genetic background
- Epigenetic changes
- Tritium internal exposure
- Neurobiological changes - behavior and pathology
- Developing archives
- Adapting the Adverse Outcome Pathway (AOP)

IES

Communication of research findings with expert and non-expert groups

Communication with non-experts

Environmental Science Seminars

- Open irregular seminars for citizens
- Familiar topics on health, environment, etc. are talked by an external speaker.
- Recent research topics are presented by IES researchers.

Open campus

- The facilities are open to the public for hands-on science events and exhibits.
- Cancelled in 2021 due to COVID-19.

Communication with non-experts and young experts

IES Local Communication Seminar

Seminar for local citizens

- A topic familiar to everyday life and related to radiation is talked by an external speaker
- An easy commentary on research at IES is attached to the application form.

Seminar for young researchers

- A plenary lecture by an external speaker
- Presentations by young researchers in Japan (IES, Hirosaki Univ, Fukushima Univ, and Kyoto Pref Univ in 2021)

Thank you for your attention