Introduction to the Radiation Effects Research Foundation: 75 Years of Studying the Health Effects of the Atomic Bombs

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Study History of Health Effects of Atomic Bomb Radiation

1945 1947 1948 1975 2000

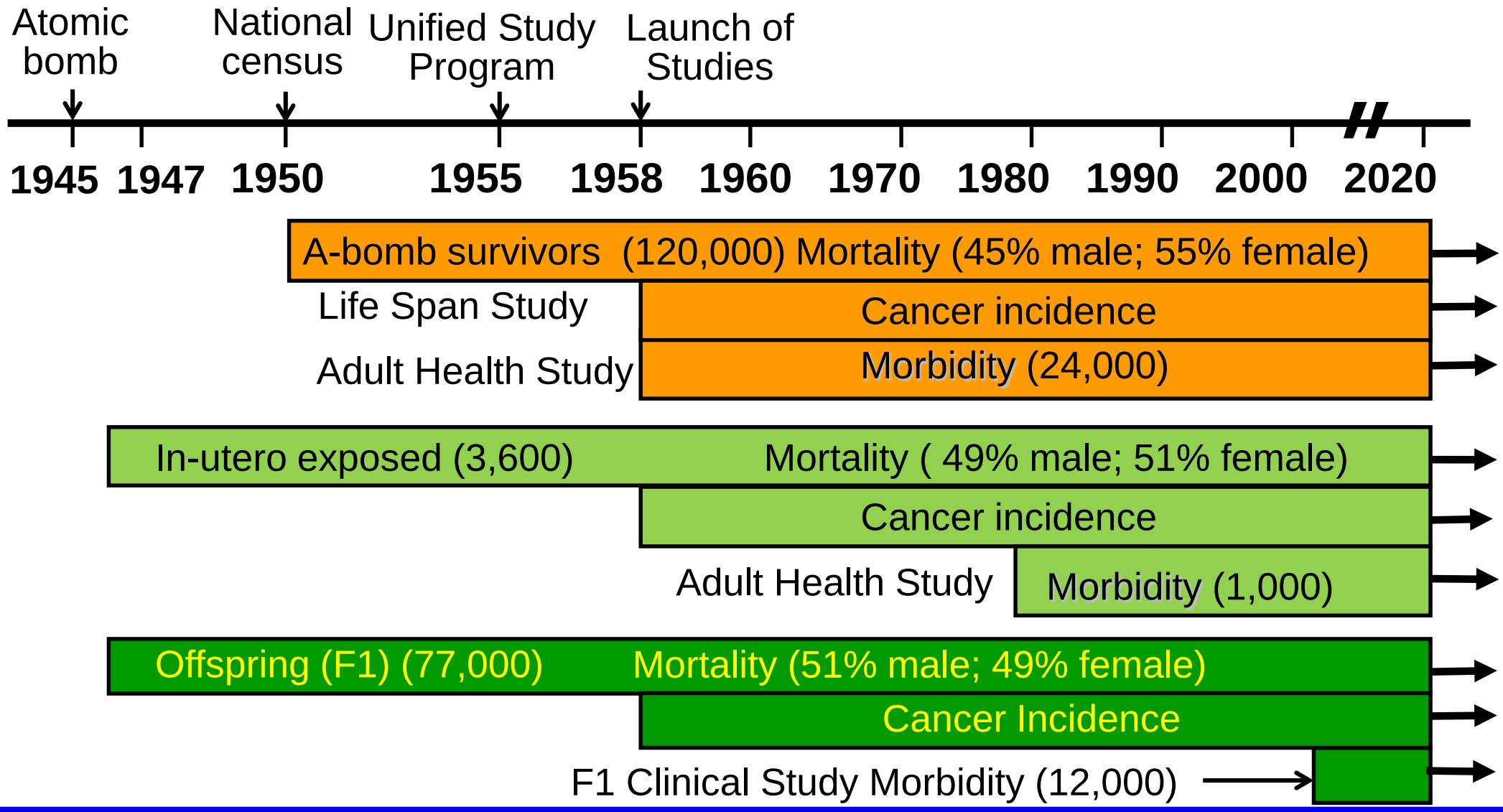
08/06 1945
08/09 1945

Atomic Bomb Casualty Commission (ABCC)

Japanese National Institute of Health

Radiation Effects Research Foundation (RERF)
Binational/Joint Funding
DOE/MHLW

Epidemiological/ Clinical Data & Biosamples



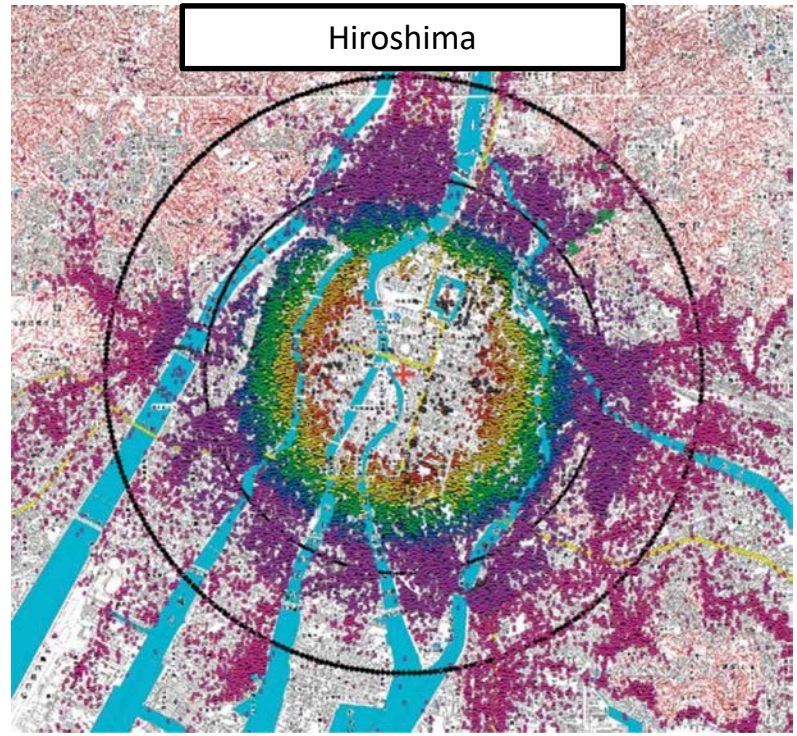
Accumulation of a large amount of epidemiological data/longitudinal clinical data and biosamples
LSS: Serum(1969);Plasma and blood cells(1990)/FOCS(2002)/Trios(1985)/LSS Pathology (autopsy/surgical)

Cohort Status As of 2017

- **LSS/AHS: 25% (29,801 of 120,321)**
  - **Average Age: 81**
- **F1/FOCS: 87% (67,061/76,814)**
  - **Average Age: 60**

Advantages of Study

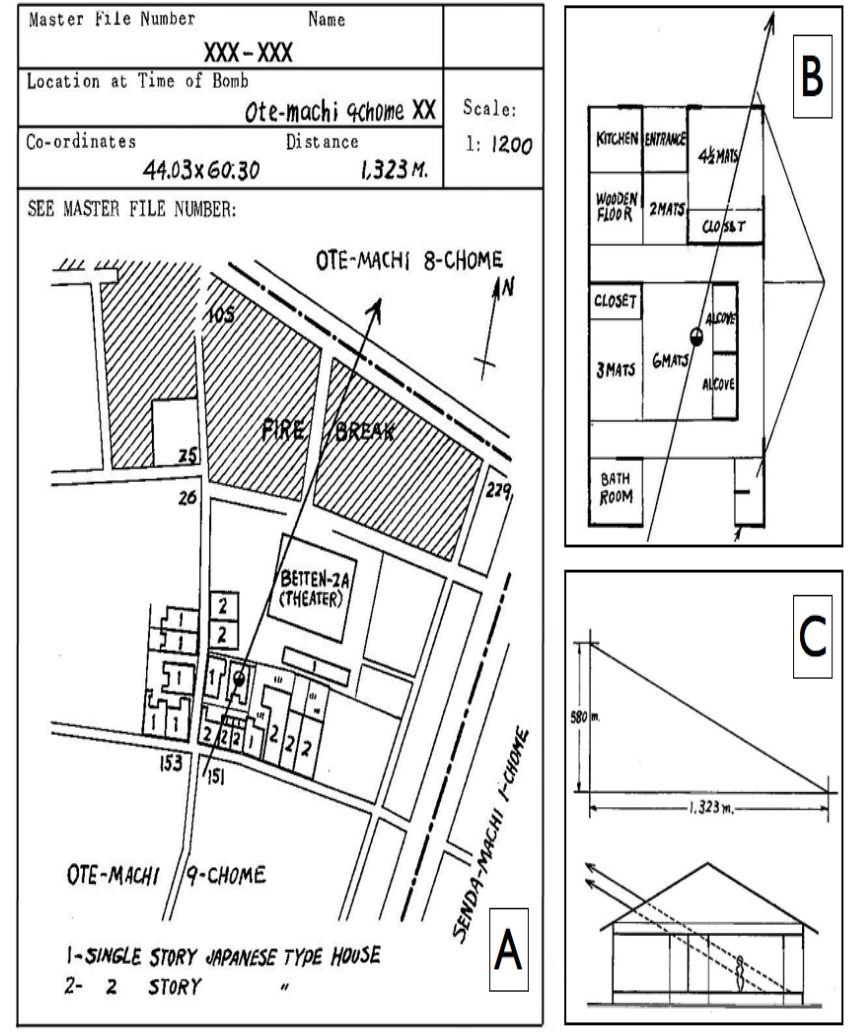
- **Well-defined doses**
- **Non-selectively exposed population with rapidly decreasing doses by distance**
- **Little chance for bias or confounding by major cancer risk factors**
- **Highly significant risks by dose for all solid cancers in aggregate**



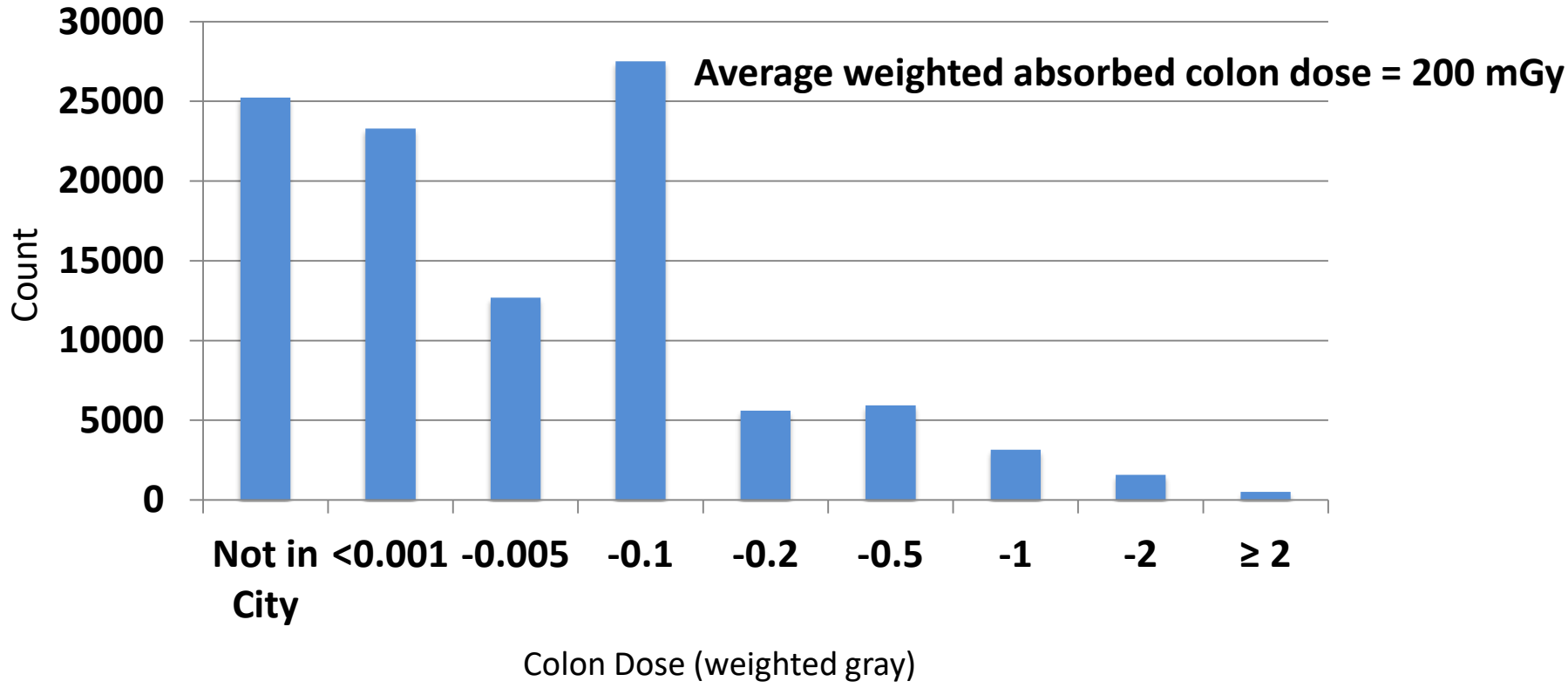
Cullings, et al. *Health Physics*, 2017;112:46-97

Dosimetry

- Survivors were interviewed for shielding conditions at the time of the bombing
- Doses calculated from source term, distance to the survivor, terrain shielding, local shielding (may be an average), self (body) shielding
- 15 organ doses calculated



Life Span Study Dose Distribution n=120,321



Dose Error

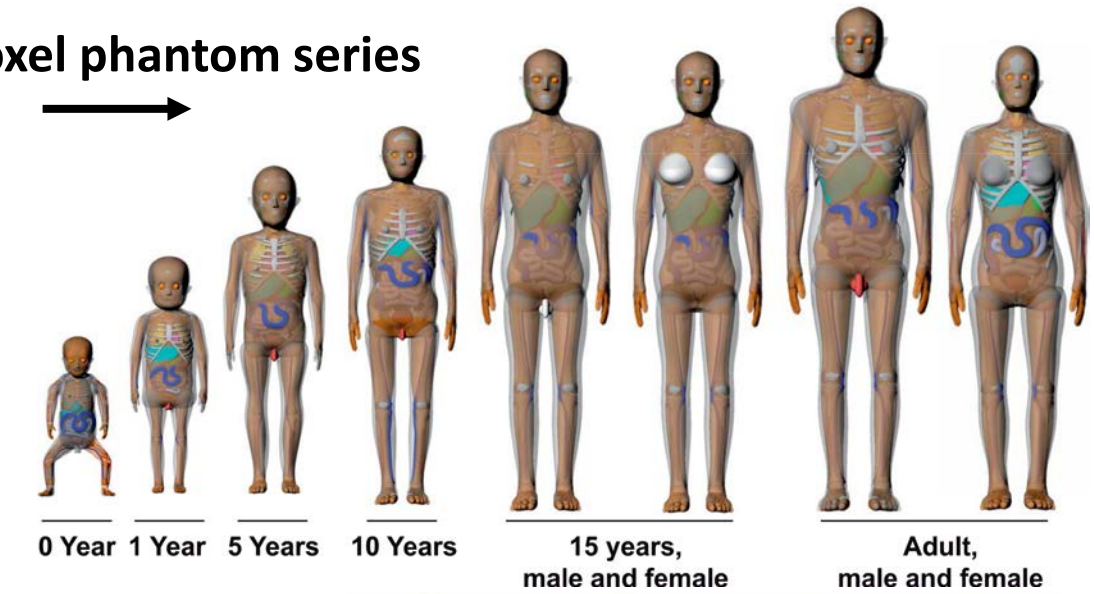
- **We have plans to implement dose error correction. However, how we implement this in the future will likely be different from what we have been doing.**

- **The current dose error adjustments are based only on a classical dose error model – e.g., errors due to misspecification of the location of the subject – but do not consider additional so-called Berkson type error – i.e, differences based on categories of shielding**

Phantoms

J45 pediatric and adult voxel phantom series

Griffen et al Rad Res 191,369-379 (2019)



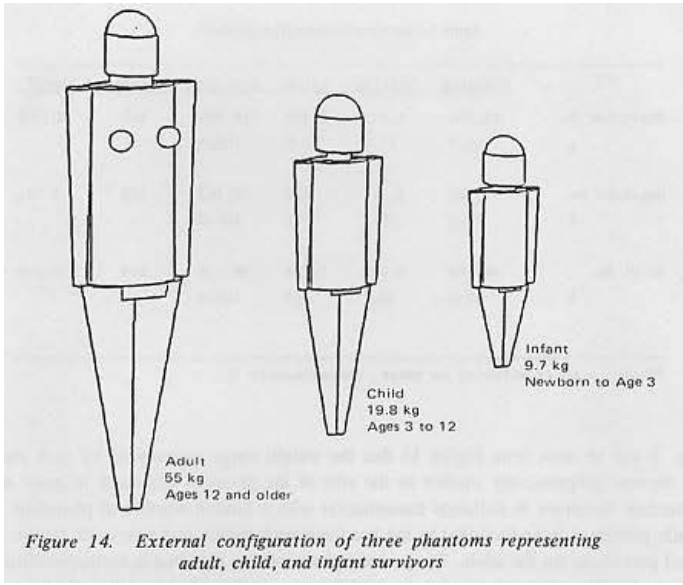
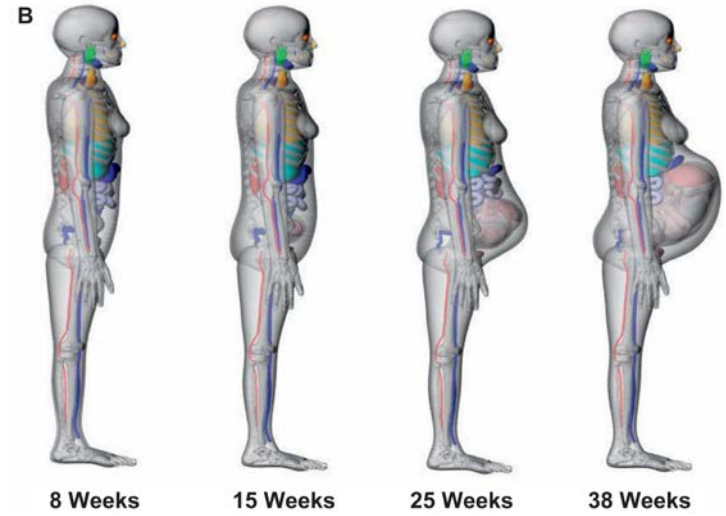


Figure 14. External configuration of three phantoms representing adult, child, and infant survivors

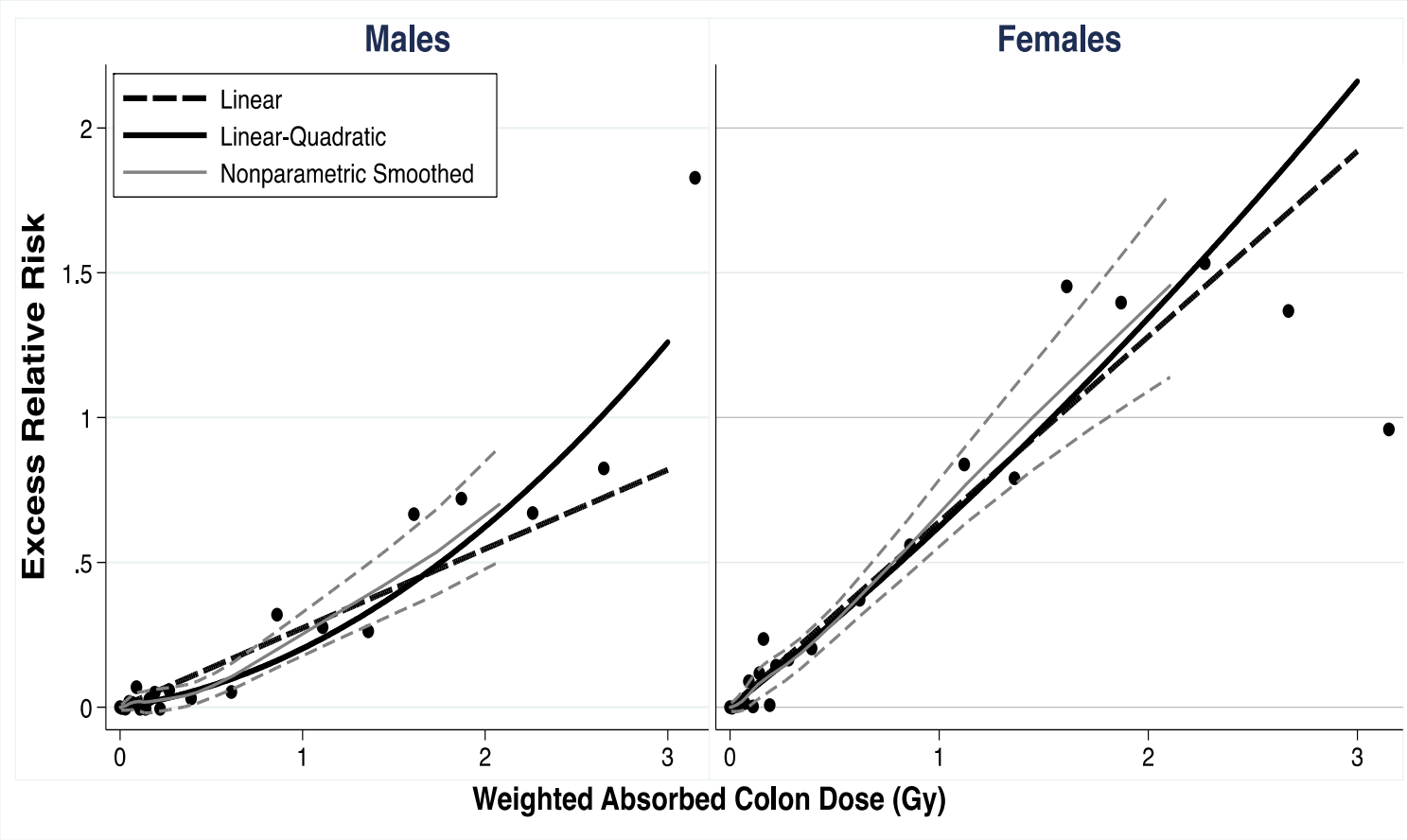
DS86/DS02 stylized phantoms
15 organs

J45 pregnant female and fetus voxel phantom series

Paulbeck et al. Rad Res 192, 538-561 (2019)



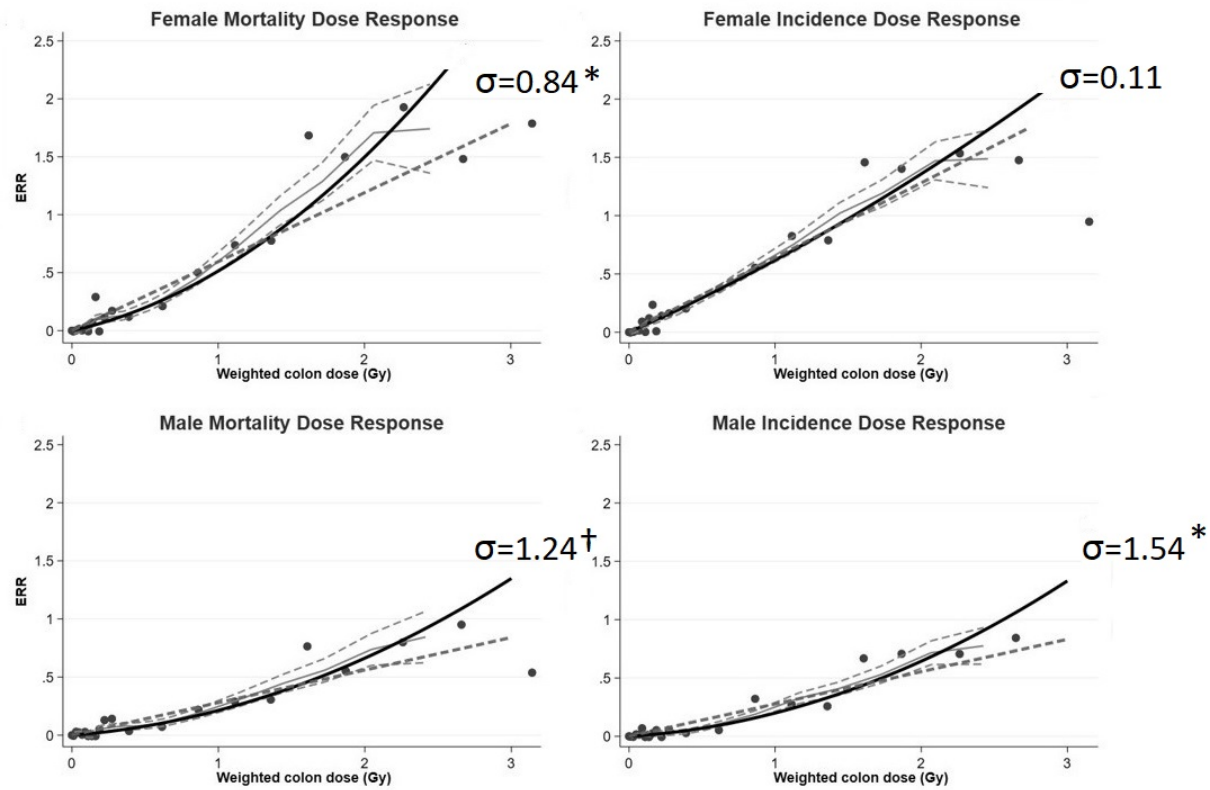
Solid Cancer Incidence
1958-2009



- **No threshold dose observed**
- **Lowest range of a significant dose response was 0-100 mGy**

Grant et al., Radiation Res 2017

All Solid Cancer Dose Response 1958-2009



σ, curvature; *P < 0.05; †P = 0.06

Brenner et al. Radiation Research, in press

Solid Cancer Radiation Risks: 1958-2009

- A single acute exposure increases solid cancer risks for life
- Shape of dose response more curvilinear
- Significantly elevated risks still evident in low dose range (0-100 mGy)

Radiation Risk of Cancer Incidence for Major Sites, LSS, 1958-2009

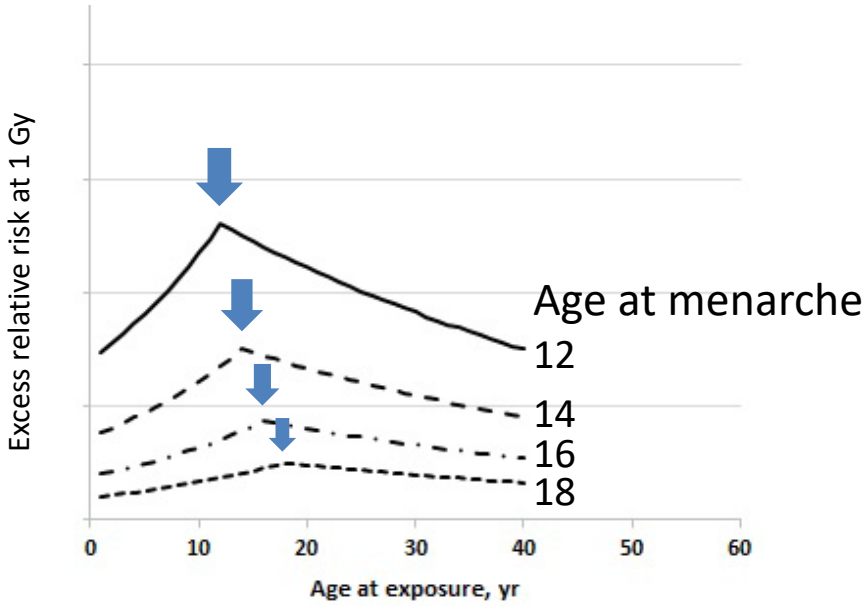
Site	Incidence cases (m; f)	Sex-averaged **ERR** at 1Gy（95%CI）	Effect modification by ATB, AA	Adjusted lifestyle and other factors	Publication
All solid	10,473; 12,065	0.47 (0.39, 0.55)	30,70 *	Smoking	Grant EJ, et al. *Radiat Res*, 2017
Esophagus	394; 92	0.30 (0.06, 0.66)	30, —	Smoking, drinking	Sakata R, et al. *Radiat Res*, 2019
Stomach	3,090; 2,571	0.33 (0.20, 0.47)	—, 70	Smoking	As above
Colon	782; 1,132	0.63 (0.34, 0.98)	30, 70	Smoking, drinking, meat intake, BMI	Sugiyama H, et al. *Int J Cancer*, 2020
Rectum	518; 528	0.025 (-0.087, 0.14)	30, 70	As above	As above
Liver	1,166; 850	0.58 (0.27, 0.95)	30, 70	Smoking, drinking, BMI	Sadakane A, et al. *Radiat Res*, 2019
Pancreas	306; 417	0.45 (0.07, 0.92)	30, 70	Smoking, drinking, BMI	As above
Lung	1,445; 1,001	0.81 (0.51, 1.18)	30, 70	Smoking	Cahoon EK, et al. *Radiat Res*, 2017
Female Breast	1,470	1.12 (0.73, 1.59)	30, 70	Smoking, BMI, menarche, menopause, pregnancy-delivery	Brenner AV, e al. *Radiat Res*, 2018
Uterine Corpus	224	0.73 (0.03, 1.87)	—, —	Smoking, first-pregnancy, menopause	Utada M, et al. *JNCI Cancer Spect*, 2019
Uterine Cervix	982	0.00 (-0.22, 0.31)	—, —	BMI, pregnancy-delivery, menopause	As above
Urinary Tract, Bladder	493; 297	1.4 (0.82, 2.1)	30, 70	Smoking	Grant EJ, et al. *Radiat Res*, 2021
Ovary	288	0.30 (-0.22, 1.11)	—, —	None of lifestyle or reproductive factors	Utada M, et al. *Radiat Res*, 2021
Prostate	851	0.57 (0.21, 1.00)	—, —	None	Mabuchi K, et al. *Radiat Res*, 2021
Central Nervous System	99; 186	1.40 (0.61, 2.57)	—, —	None	Brenner AV, et al. *Eur J Epidemiol*, 2020

ATB: age at bombing, AA: attained age, * Risk estimates for ATB of 30 years and AA of 70,
—: No effect modification by ATB or AA

Effect of Age at Exposure

Breast cancer

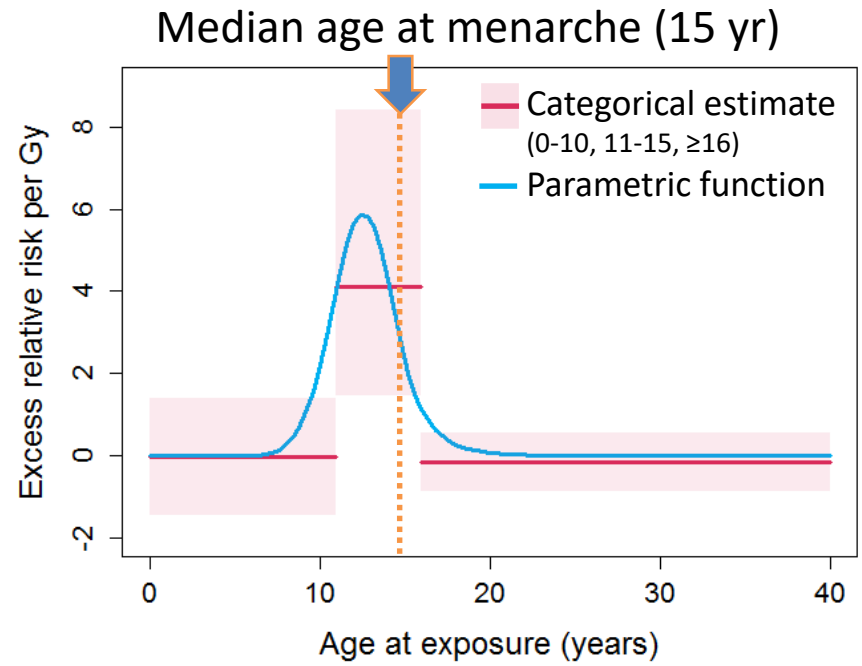
Around menarche
(Brenner et al., Rad Res, 2018)



ERR/Gy by age at exposure for several ages at menarche at attained age 50.
Linear spline model with a knot age at menarche.

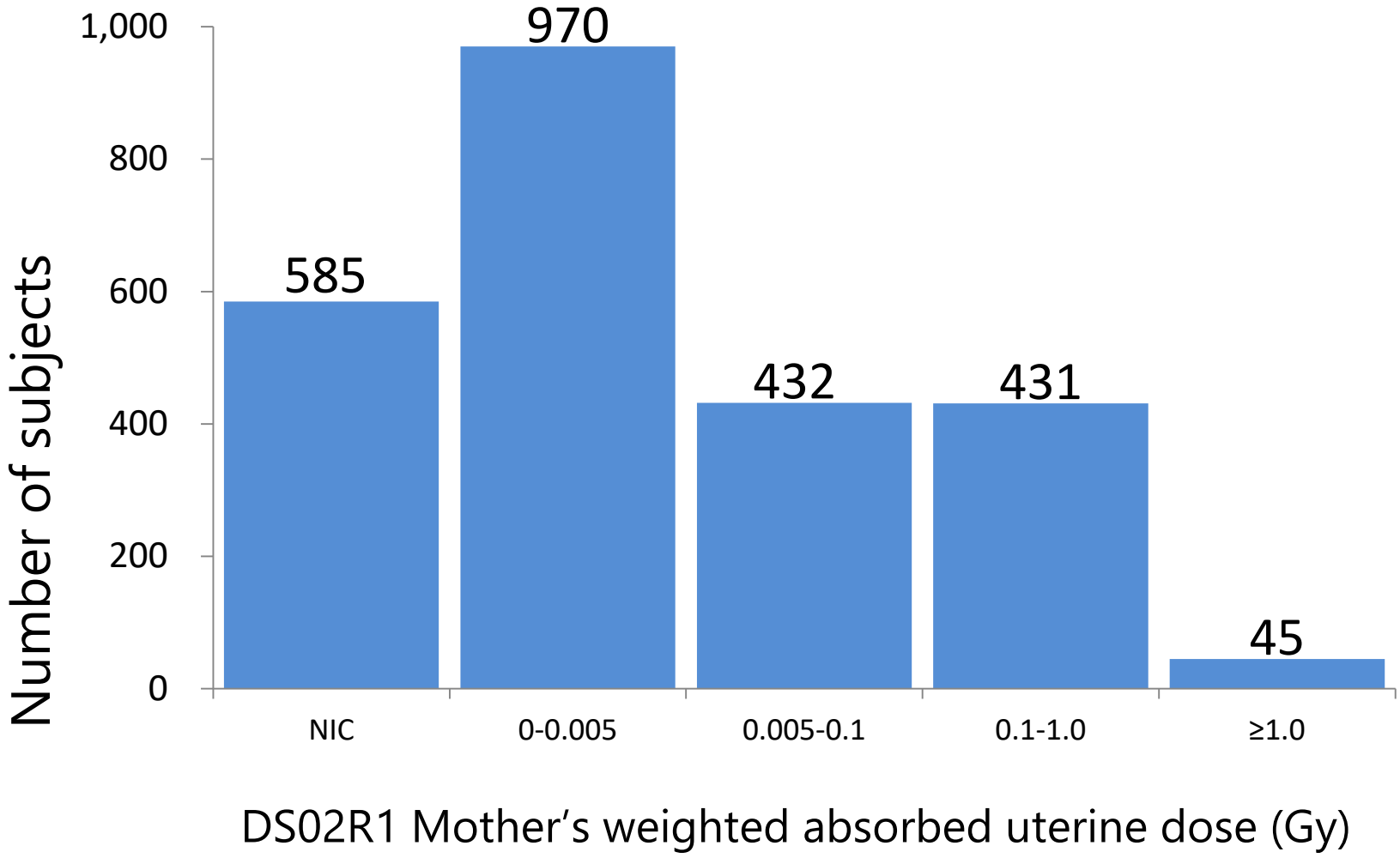
Uterine corpus cancer

Before menarche
(Utada et al., JNCI-CS, 2019)



ERR/Gy by age at exposure without effect modification by attained age or age at menarche.
Quadratic spline model with a knot at age 15.

In Utero:
Distribution of Radiation Dose



In Utero: Results

- **339 deaths from 1950 to 2012**
  - **Solid cancer (n=137) including childhood cancer (n=1)**
  - **Lymphohematopoietic cancer (n=8)**
  - **Non cancer disease (n=134)**
  - **External cause (n=56)**
  - **Unknown cause (n=4)**
- **Radiation-associated ERR/Gy**
  - **Solid cancer deaths: ERR/Gy was increased in females (2.5).**
  - **Non-cancer disease deaths: ERRs/Gy were increased in both males and females (1.2/2.86).**

F1 Study--Background

- Prior to the atomic bombings, plant and animal experiments had shown that ionizing radiation caused mutations that were passed to progeny
- Hereditary effects after radiation exposure among humans was unknown–and was a major concern
- Therefore, one of ABCC's first major studies was to investigate genetic effects among the children of the survivors (F1 Cohort)

F1 Studies To Date

Untoward Pregnancy Outcome	77,000 （1948－1954）
Sex ratio	140,000 (1948－1966)*
Chromosome Aberrations	16,000 （1967－1985)*
Protein electro-mobility	23,000 （1975－1984)*
Mortality	80,000 （1947 – ongoing)
Clinical	12,000 （2002-ongoing)

* No Significant Effect Observed

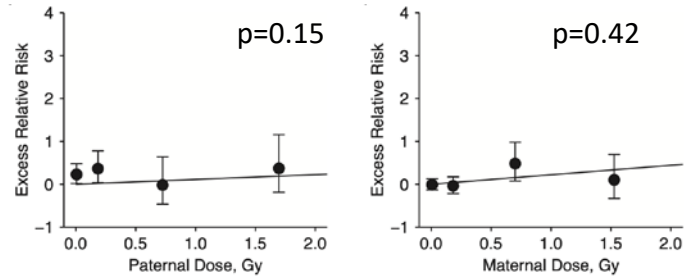
Reappraisal of Congenital Malformations and Perinatal Deaths among Children of Atomic Bomb Survivors: 1948-1954 (n=71,603 births)

Major Malformations

p=0.28 p=0.24

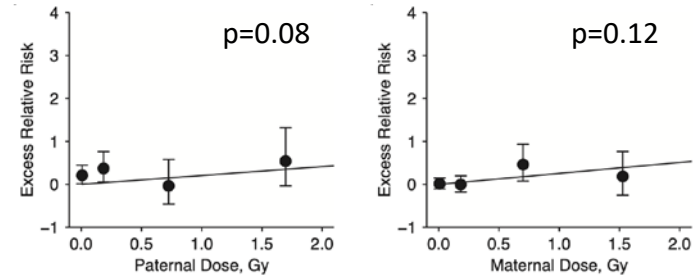
ERR/Gy$_{conjoint}$ = 0.35 (p=0.08)

Perinatal Deaths (≤7 Days)



ERR/Gy$_{conjoint}$ = 0.14 (p=0.18)

Perinatal Deaths (≤14 Days)

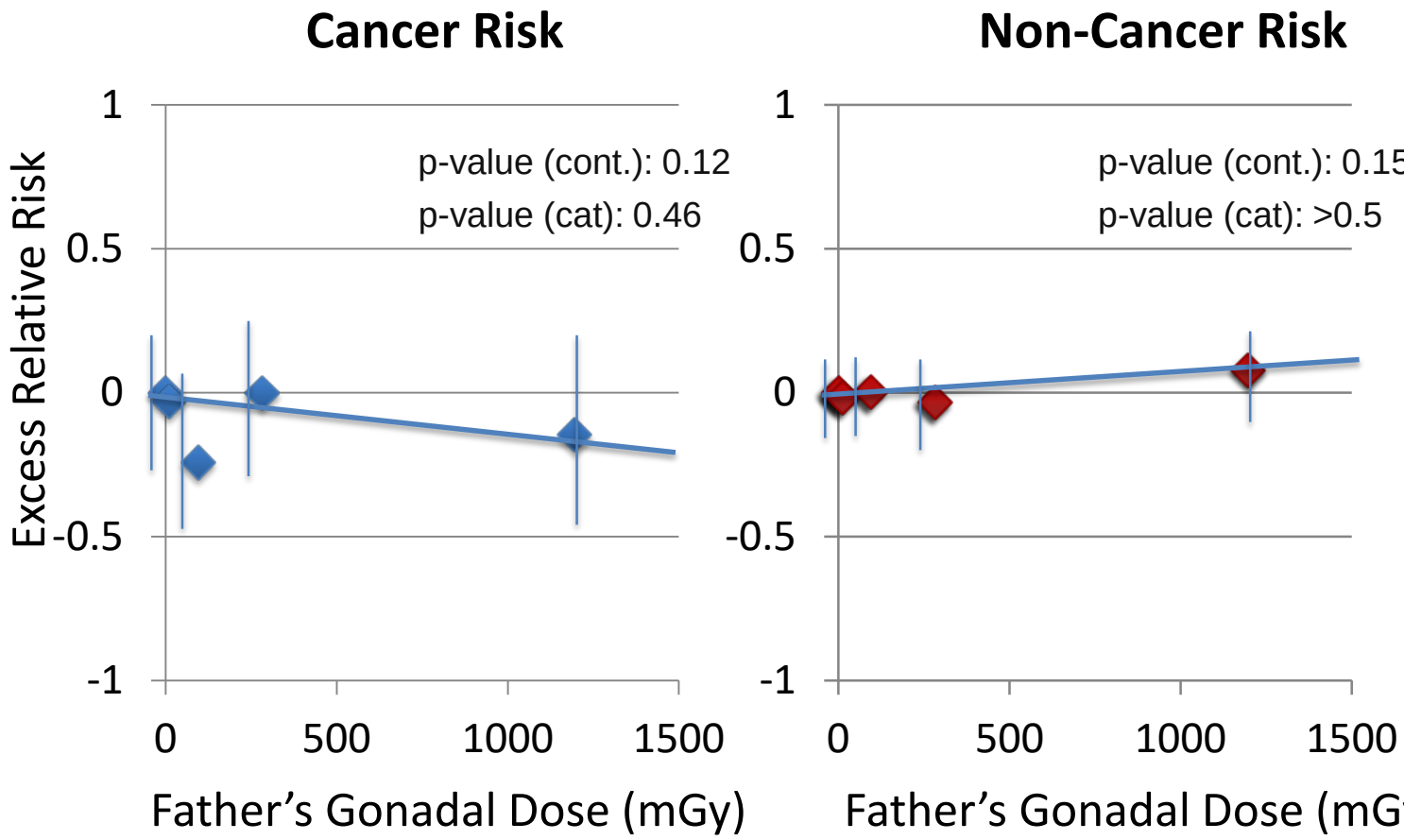


ERR/Gy$_{conjoint}$ = 0.21 (p=0.03)

p-value: 2-sided, 95% confidence interval

Yamada et al. *AJE*. 2021;190(11)2323-2333

Radiation Risk By Fathers Gonadal Dose
(260 mGy)

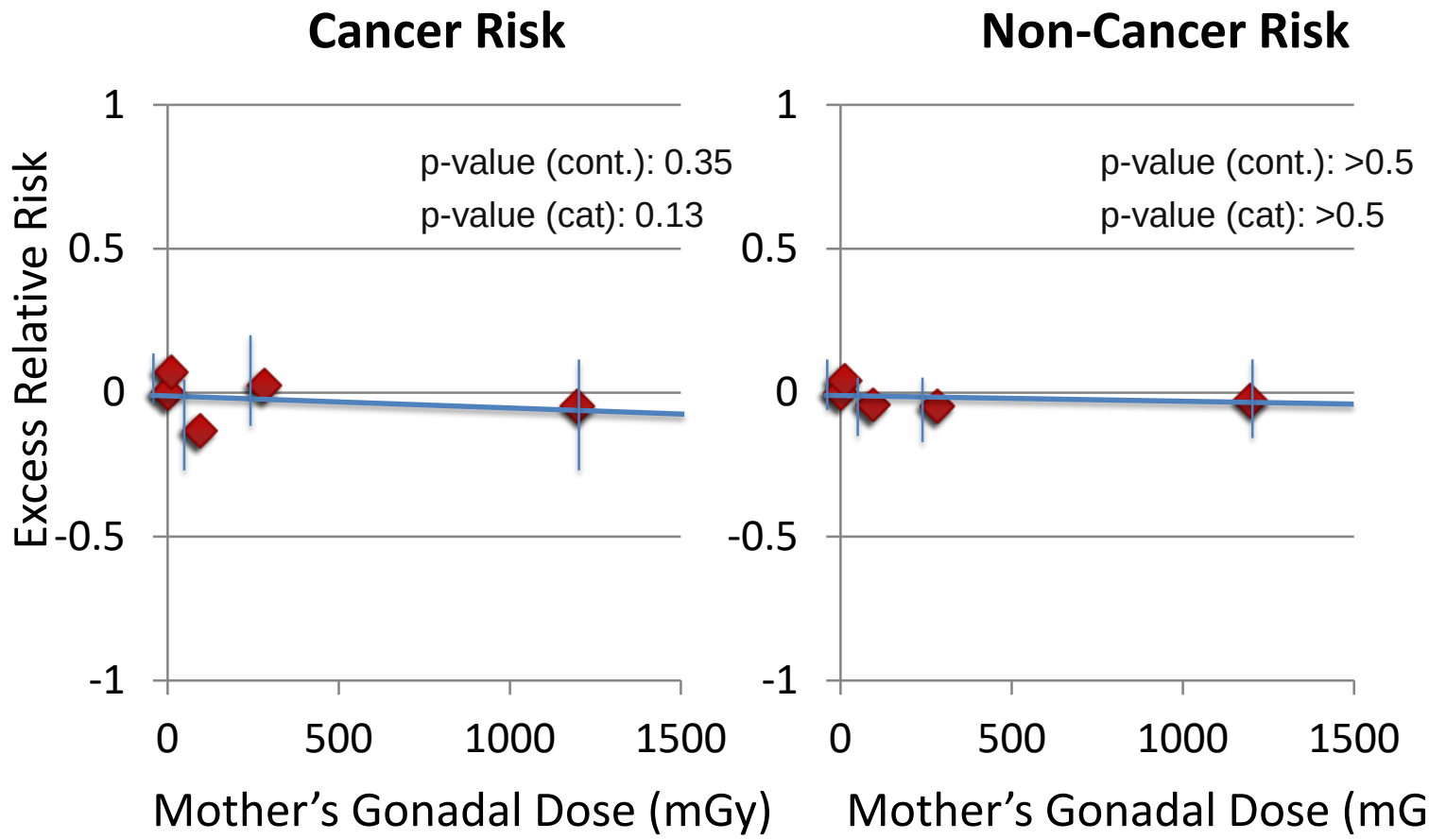


Grant, et al. *Lancet Oncology*, 2015

Adjusted for: city, sex, birth year, (birth year)^2, birth weight, mother's age at delivery, follow-up phase

Radiation Risk By Mother's Gonadal Dose

(260 mGy)



Grant, et al. *Lancet Oncology*, 2015

Adjusted for: city, sex, birth year, (birth year)^2, birth weight, mother's age at delivery, follow-up phase

Dose Distribution and Numbers of Trios for WGS Study

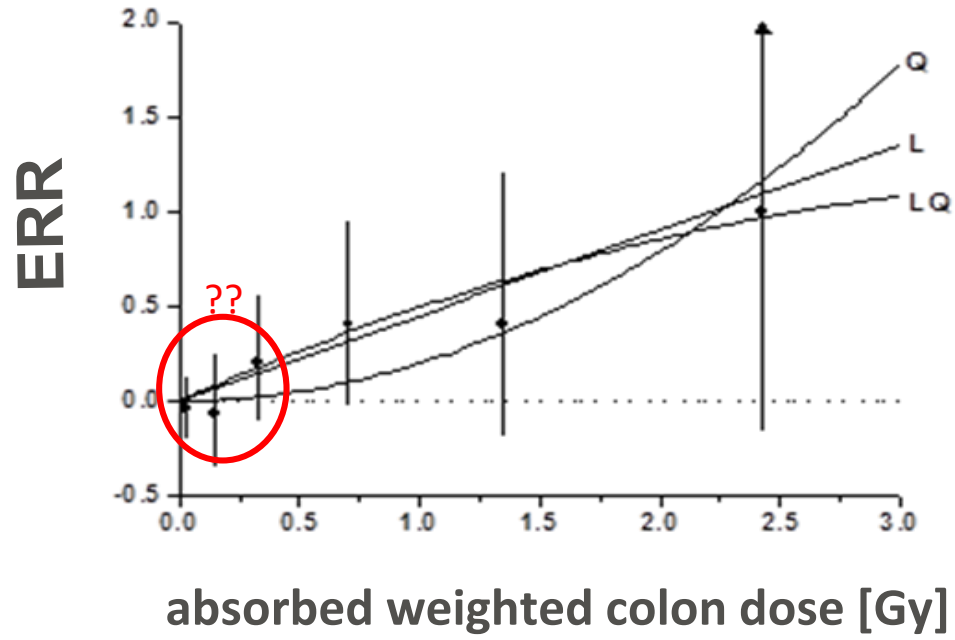
Children (F1)		Mother DS02R1 weighted dose (Gy)				
		NIC & < 0.01	0.01+	1.0+	2.0+	Total
Father DS02R1 weighted dose (Gy)	NIC & < 0.01	618	320	94	9	1041
	0.01+	239	57	5	2	303
	1.0+	96	16	4	0	116
	2.0+	58	4	2	0	64
	Total	1011	397	105	11	1524

Non-Cancer Effects Currently Under Study
Risks, Characterization, and Mechanisms

- Cardiovascular Disease
- Stroke
- Diabetes
- Chronic Kidney Disease
- Cataracts

Cardiovascular Disease Dose Response LSS (1950-2008)

Shimizu et al, BMJ, 2010.
Takahashi et al.Rad Res, 2017



Recently Published Data on Atherosclerotic Pathologies Suggest a Linear Response in the Low Dose Range

Nakamizo et al., European J of Epidemiology 36:401-414, 2021

Future Plans and Opportunities for Collaborations

Heritable Effects

- **The capability to study such a large well-defined population is unique in the world**
  - **WGS (2022-2025)**
  - **Bulk and single cell whole genome, transcriptome, epigenome sequencing and high dimensionality immunophenotypic and clinical phenotypic analyses**
- **Assets**
  - **(a) leukocytes collected from > 1000 trios with parental exposure over a range of well-defined doses; (b) clinical histories**
- **Candidate radiation-associated changes will be assessed mechanistically in laboratory models.**

WGS Collaborators: Chanock and Berrington, US NCI; Nakagawa, RIKEN

Large Scale Associations

2023-ongoing

- **Large-scale omic analyses of DNA, RNA, proteins, lipids, and metabolites from blood biosamples from AHS participants will identify candidate radiation associated genomic or epigenomic features that differ between exposed and unexposed individuals.**

Tissue-Based Analyses

2022-ongoing

- **The characterization of radiation-associated tumors and other diseases is particularly amenable to research at RERF.**
  - **A large number of formalin-fixed paraffin-embedded (FFPE) samples exist and will continue to become available for a range of diseases with well-defined radiation dose-response relationships with radiation exposure/disease.**
  - **Characterized using bulk and single cell omic and imaging approaches to identify candidate radiation associated genomic, epigenomic and microenvironmental features.**

Stakeholders and Community

- **Stake Holders Committee**
- **Stakeholders (Survivors; F1; Community)**
- **Public Involvement**
- **Media**

Future Contributions to Low Dose Program

- Data and Sample Sharing
  - Accesibility/Security
  - Integration
  - Cloud environment
  - Research Resource Center
  - Complications
    - New Japanese regulations for epidemiological data
- Collaborative Studies
- Timelines

Research Priorities

- **Integration of Epidemiology and Cutting Edge Basic Science Using Biosamples as a First Priority**
  - **Essential to address low statistical power of epidemiological studies at low doses (<100mGy) and develop and mechanistic hypotheses**
- **Use *Carefully Selected Relevant* Laboratory Models to Conduct Mechanistic Studies (Based On Hypotheses From Molecular Epidemiological Studies)**
  - **Directly measuring effects at low doses with epidemiology alone is not possible and dependa on mechanistic understandings**

Recommendations

- **Focus on Collaborative Multidisciplinary Programs Rather Than Single Investigator Grants**
- **Training**
  - **Multi-Institutional**
  - **Foster New Talented Research Scientists**
  - **Funding For Short-Term Fellowships (Both Junior and Senior Scientists)**
- **Funding Infrastructure ?**

Hiroshima Today