NAS

Third Gilbert W. Beebe Webinar

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Alina Brenner

SOLID CANCER INCIDENCE AMONG THE LIFE SPAN STUDY OF ATOMIC BOMB SURVIVORS: 1958–2009

WORKING GROUP

	Epidemiologists	*Statisticians*
RERF	Brenner A	Cologne J
	Grant E	Cullings H
	Ozasa K	French B
	Sadakane A	Misumi M
	Sakata R	Sposto R
	Sugiyama H	Yamamura M
	Utada M	
NCI	Cahoon E	
	Mabuchi K	
Hirosoft		Preston D

SOLID CANCER INCIDENCE IN THE LIFE SPAN STUDY (LSS)

- Previous comprehensive reports - established significant linear dose response with dependence on sex, attained age and age at exposure for all solid cancer and multiple sites
  - 1958-1987, Thompson et al. *Radiat Res* 1994
  - 1958-1998, Preston et al. *Radiat Res* 2007

- 1958-2009 update consists of a series of papers with common methods

1958-2009 CANCER INCIDENCE PAPER SERIES

All solid cancer	Grant et al. *Radiat Res* 2017;187:513-37
Site-specific cancer	
Upper Digestive Tract	Sakata R et al. *Radiat Res* 2019;192:331-44
Lower Digestive Tract	Sugiyama H et al. *Int J Cancer* 2020;146:635-45
Hepatobiliary System	Sadakane A et al. *Radiat Res* 2019;192:299-310
Respiratory tract	Cahoon EK et al. *Radiat Res* 2017;187:538-48
Breast	Brenner AV et al. *Radiat Res* 2018;190:433-44
Uterus	Utada M et al. *JNCI cancer spectrum* 2018;2(4):pky081
Brain/CNS	Brenner AV et al. *Eur J Epidemiol* 2020;35:591-600
Ovary	Utada M et al. *Radiat Res* 2020;in press
Prostate	Mabuchi K et al. *Radiat Res* 2020;in press
Urinary tract	Grant E et al. *Radiat Res* 2020;in press
Methods	
Solid cancer curvature	Cologne et al. *Radiat Res* 2019;192:388-98
Population density	French et al. *Am J Epidemiol* 2018;187:1623-29
Liver cancer misclassification	French et al. *Int J Cancer* 2020;147:1294-99
Summary	Brenner et al. in preparation

STUDY METHODS

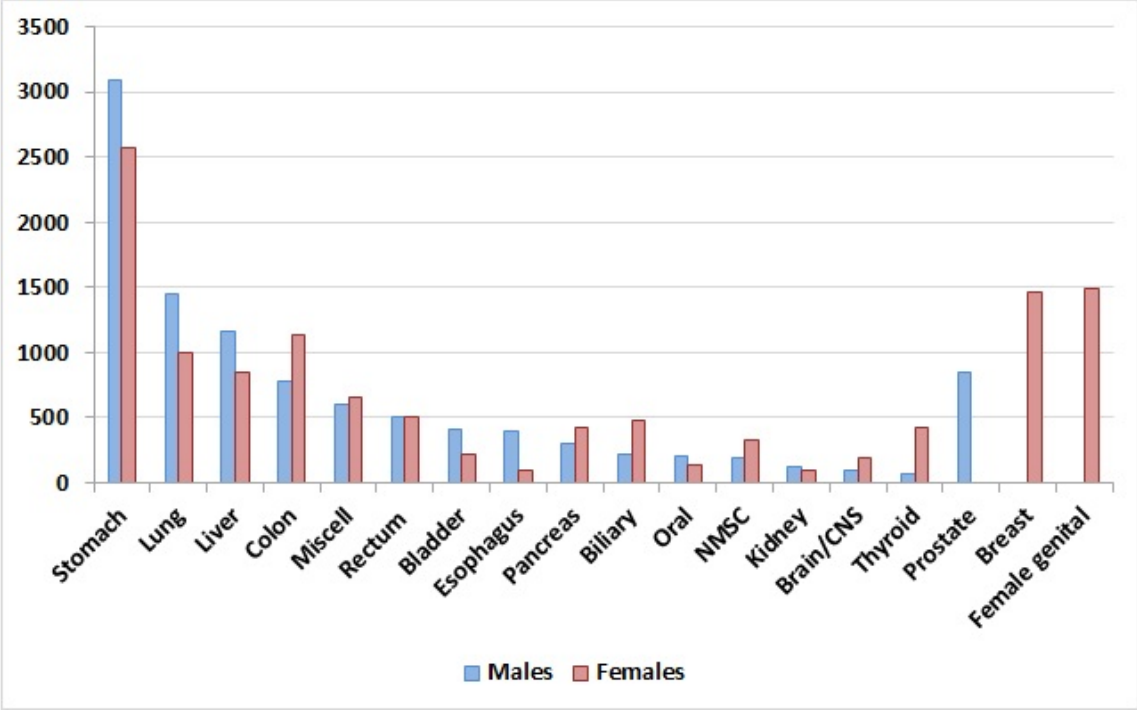
- Used improved organ-specific radiation doses, DS02R1
- Updated estimates of migration rates
- Excluded cancer cases identified at autopsy and not suspected clinically
- Used questionnaire data to adjust for relevant lifestyle factors
  - Smoking, body mass index, reproductive history
- Applied Poisson regression methods to model cancer rates and estimate excess radiation risk and effect modification

UPDATE SUMMARY

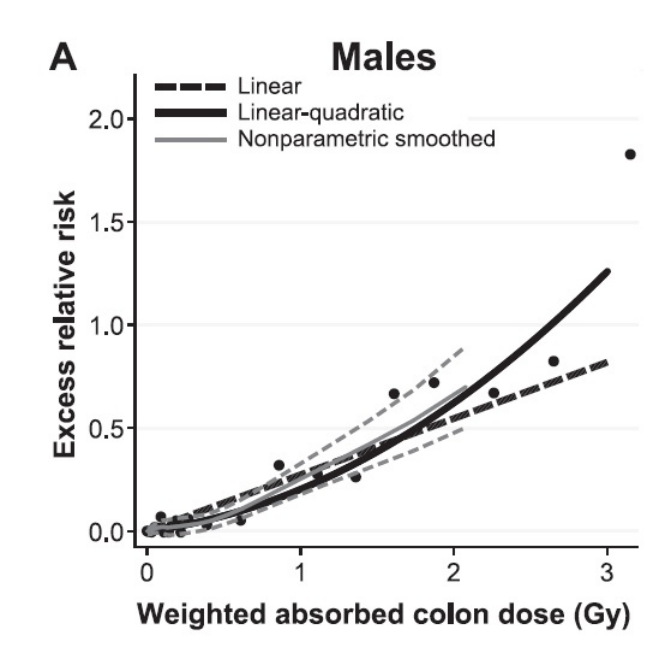
1958-2009 total: 3.1×10^6 PY and 22,538 cases

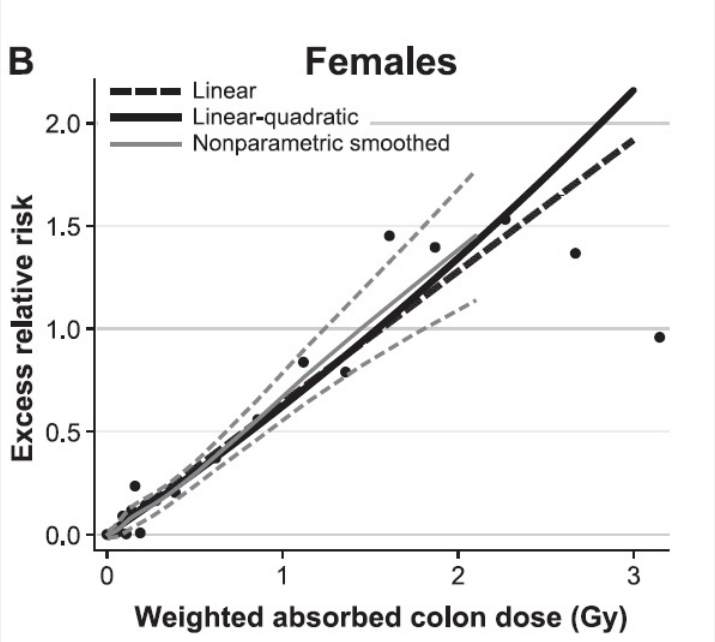
Added since 1998: 3.7×10^5 PY (14%) and 5,918 cases (35%)

- Doubled number of cases <20 years ATB



ALL SOLID CANCER INCIDENCE DOSE RESPONSE





P curvature = 0.002

ERR/Gy = 0.27 (0.19 to 0.37)
ERR at 1 Gy (LQ) = 0.20 (0.12 to 0.28)
ERR at 0.1 Gy (LQ) = 0.01 (-0.0003 to 0.02)

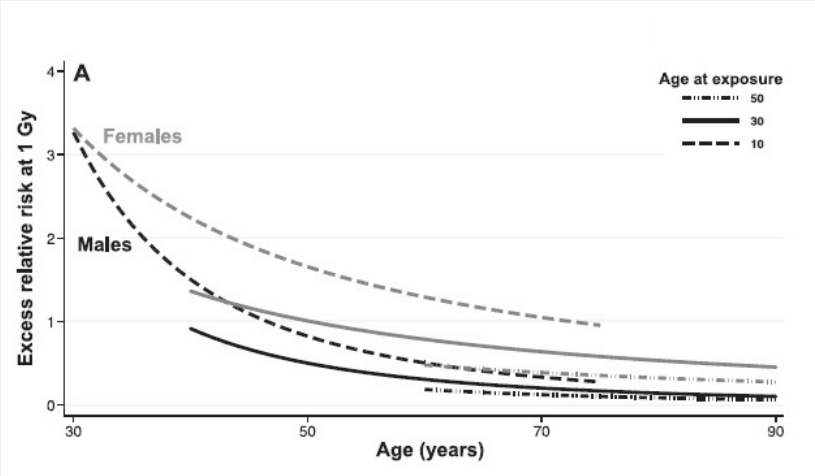
P curvature = 0.390

ERR/Gy = 0.64 (0.52 to 0.77)

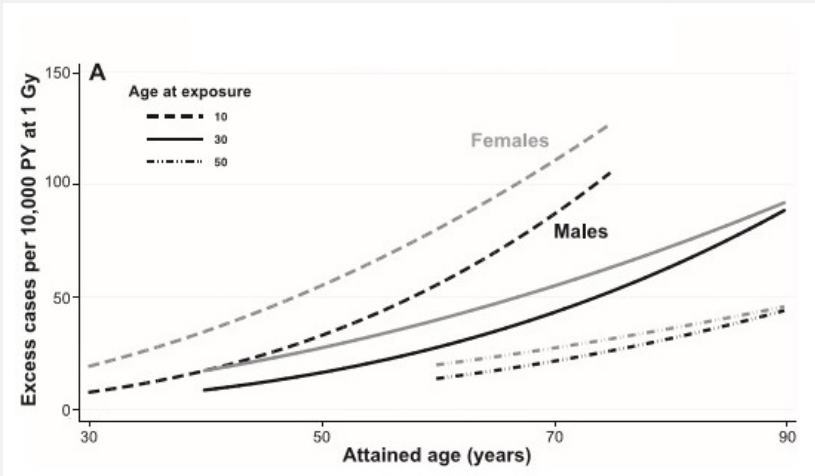
Grant et al. Radiat Res 2017

TEMPORAL PATTERNS OF RADIATION RISK BY SEX AND AGE AT EXPOSURE

EXCESS RELATIVE RISK



EXCESS ABSOLUTE RISK

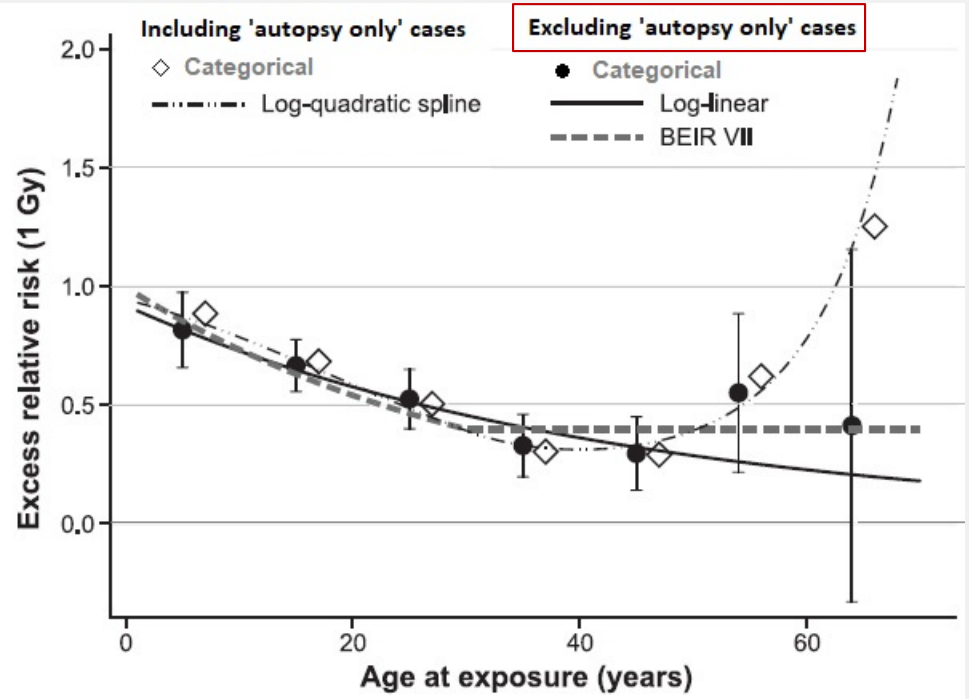


	Males	Females
Age, power	-2.7	-1.4
	(-3.6 to -1.8)	(-1.9 to -0.8)

	Males	Females
	2.9	2.1
	(2.1 to 3.7)	(1.6 to 2.5)

Grant et al. Radiat Res 2017

RADIATION RISK BY AGE AT EXPOSURE

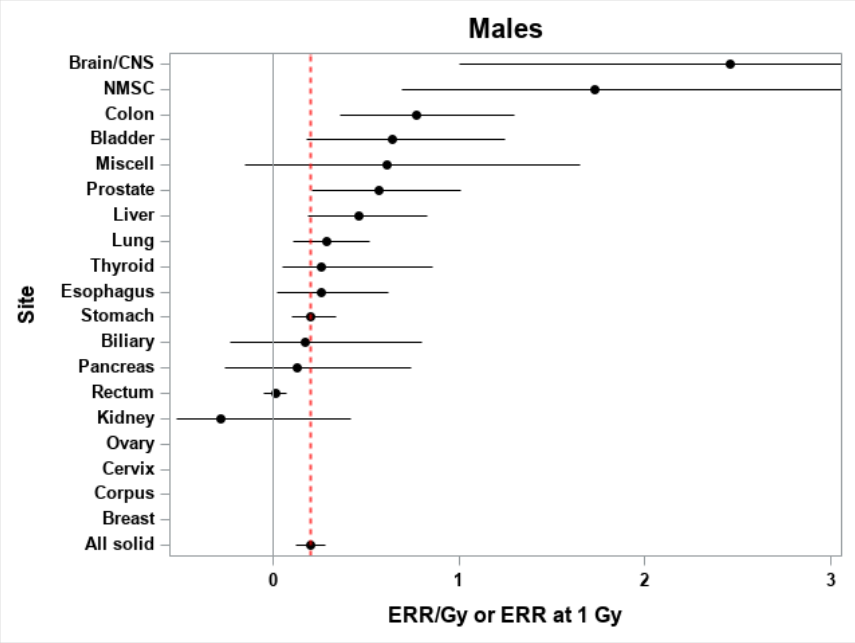


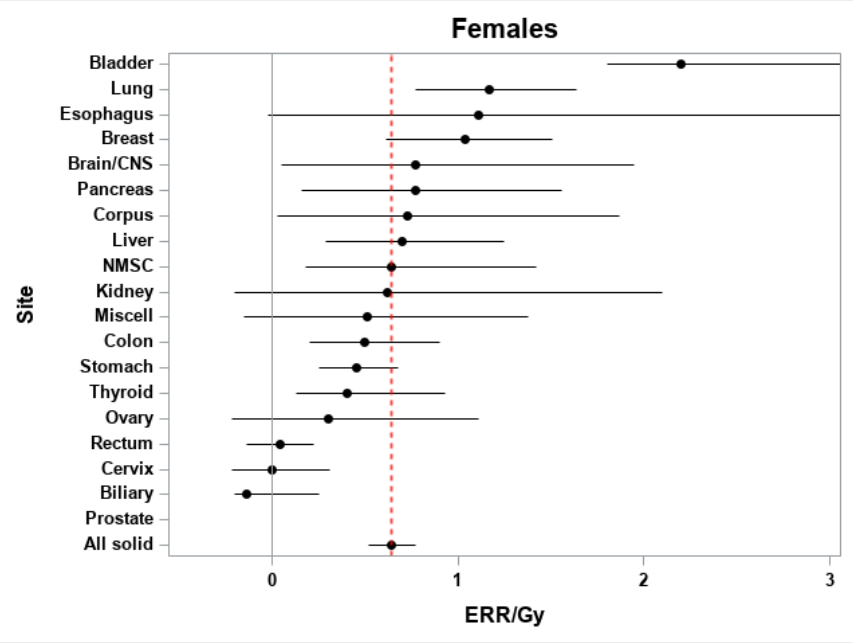
% change per decade

ERR	-22 (-30 to -13)
EAR	-30 (-37 to -22)

Grant et al. Radiat Res 2017

SITE-SPECIFIC ERR/GY



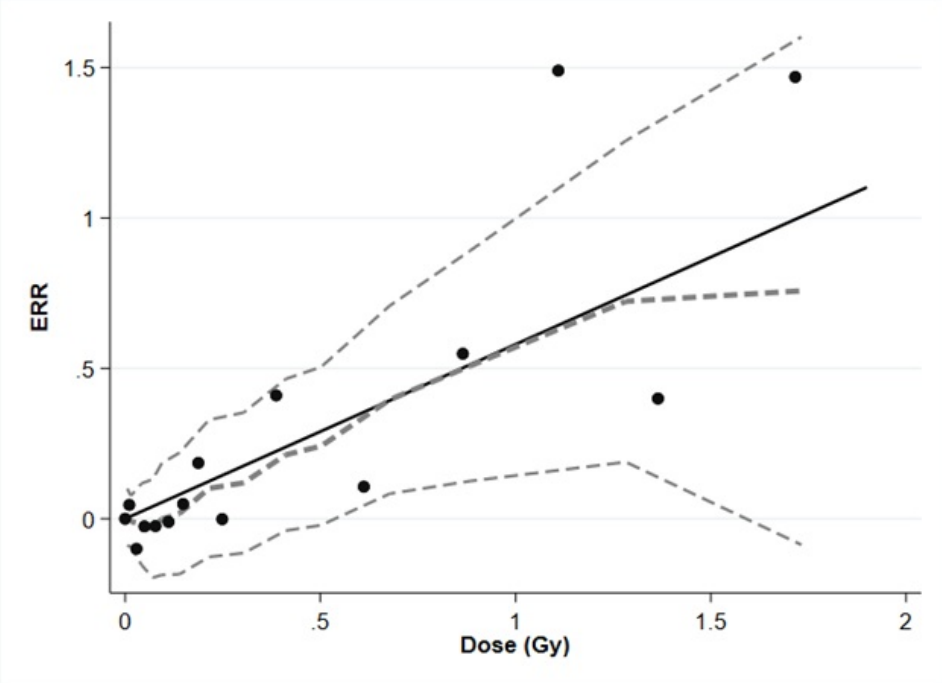


CHANGES IN ERR/GY SINCE LAST REPORT

- The ERR/Gy estimates are largely consistent with those in the previous report
  - Adjustment for lifestyle factors had little impact
- Number of sites without evidence of radiation dose response decreased
- New sites with significant dose response
  - Both sexes: brain/CNS
  - Females: pancreas, corpus uterus
  - Males: prostate
- Still no evidence of dose response
  - Both sexes: oral other than salivary, rectum, biliary
  - Males: pancreas
  - Females: cervix

PROSTATE CANCER SPOTLIGHT

- 1958-1998 - 387 cases
  - ERR/Gy = 0.21 (-0.20 to 0.80)
- 1958-2009 - 851 cases (↑120%)
- Strong age-period-cohort effect
  - PSA testing in AHS >2004
- ERR/Gy = 0.57 (0.21 to 1.00)
  - AHS ERR/Gy ≤2004 = 0.77
  - AHS ERR/Gy >2004 = 0.86



Mabuchi K et al. Radiat Res 2020 (in press)

INFLUENCE OF INDIVIDUAL SITES ON ALL SOLID CANCER MALE CURVATURE

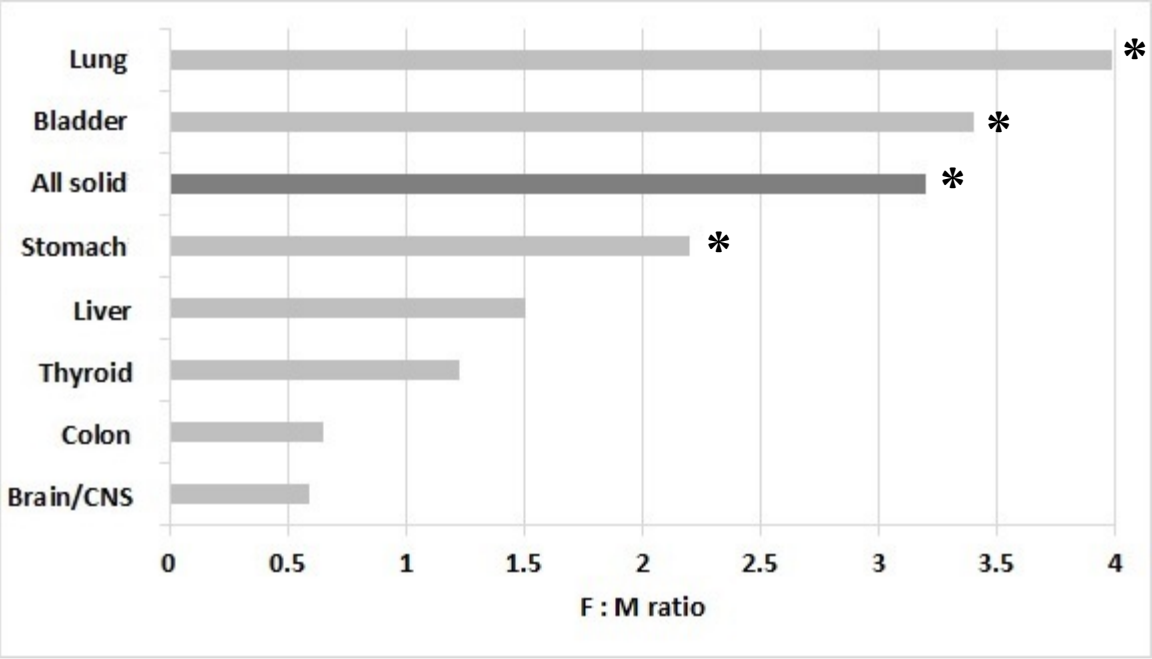
Estimated Curvature of Radiation Dose Response among Males with Exclusion of Selected Individual Cancer Sites

Site excluded by censoring	ERR curvature parameter among males			No. of cases excluded	
	Curvature estimate	95% confidence region[a]	*P* value	Male	Female
None	1.16	] −8.40, 0.18 [[a]	0.0024	0	0
Cancer sites with male cases					
Brain/CNS (including benign)	0.89	] −16.9, 0.11 [	0.0091	99	186
Esophagus	0.89	] −26.5, 0.12 [	0.0066	394	92
Thyroid	0.90	] −14.9, 0.12 [	0.0073	72	430
Bone/connective tissue	0.90	] −31.0, 0.12 [	0.0062	34	38
Non-melanoma skin cancer	0.96	] −8.90, 0.11 [	0.0090	195	321
Kidney	0.98	] −17.6, 0.15 [	0.0041	158	134

Cologne et al. Radiat Res 2019

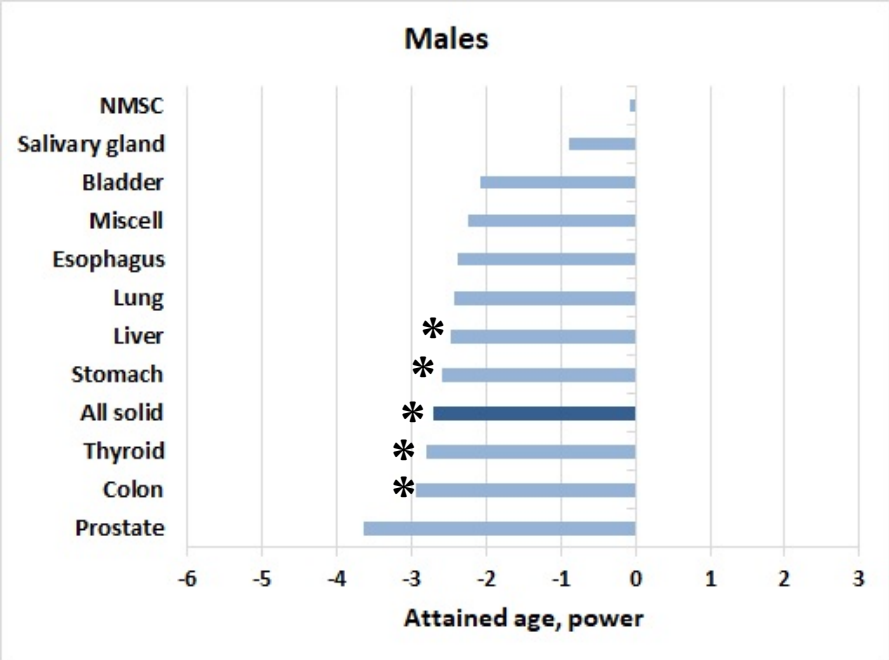
- Site-specific analyses suggest non-linearity in male dose response for NMSC, bone, esophageal, and kidney cancers
- Other sources of non-linearity are being investigated

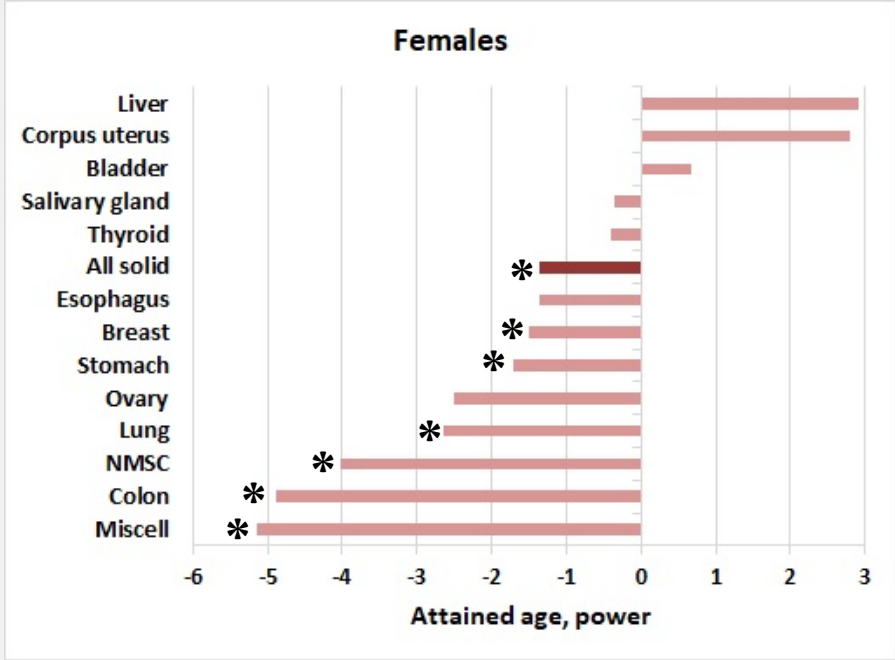
FEMALE TO MALE RATIO OF ERR/GY



*P<0.05

SEX-SPECIFIC ATTAINED AGE EFFECT (POWER OF AGE)

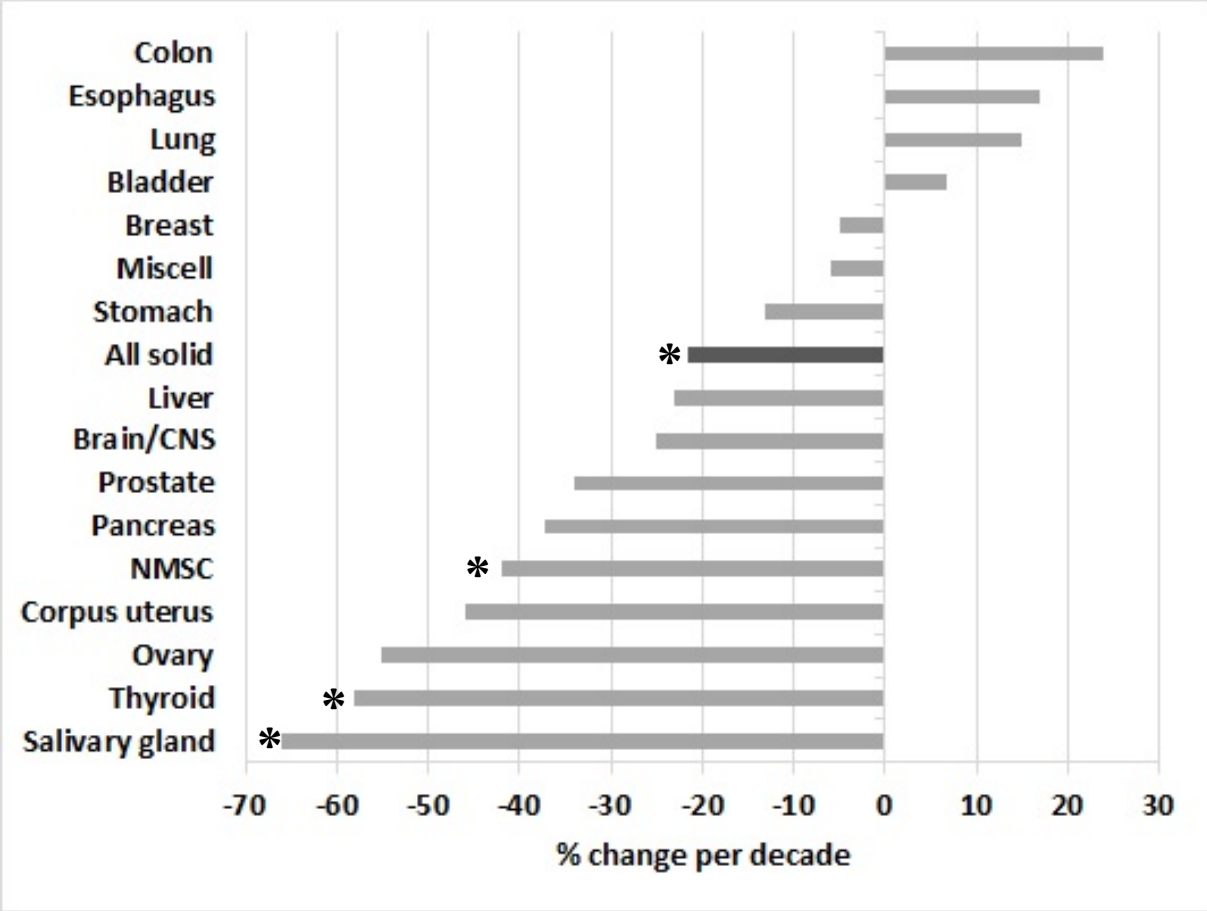




*P<0.05

Significant heterogeneity by sex: liver, NMSC, thyroid

AGE AT EXPOSURE EFFECT (LOGLINEAR TREND)

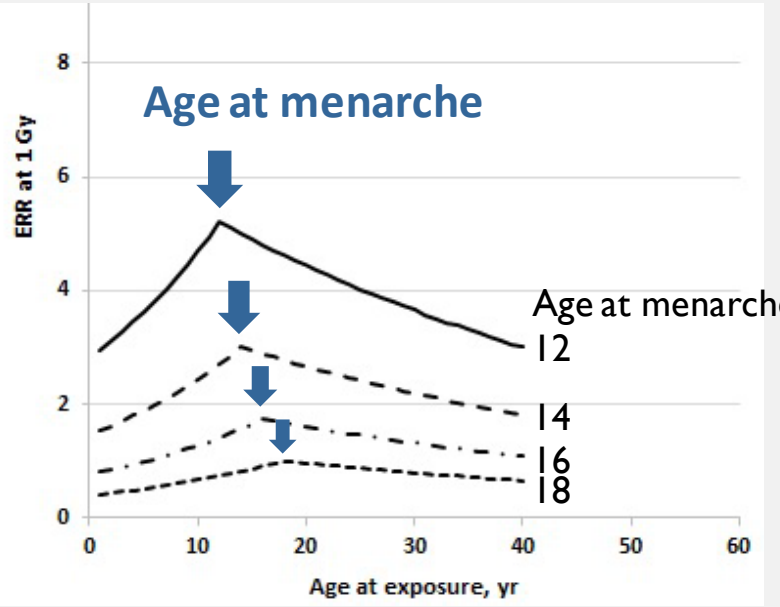


*P<0.05

NON-MONOTONIC AGE AT EXPOSURE

Breast cancer

Brenner et al. Radiat Res 2018

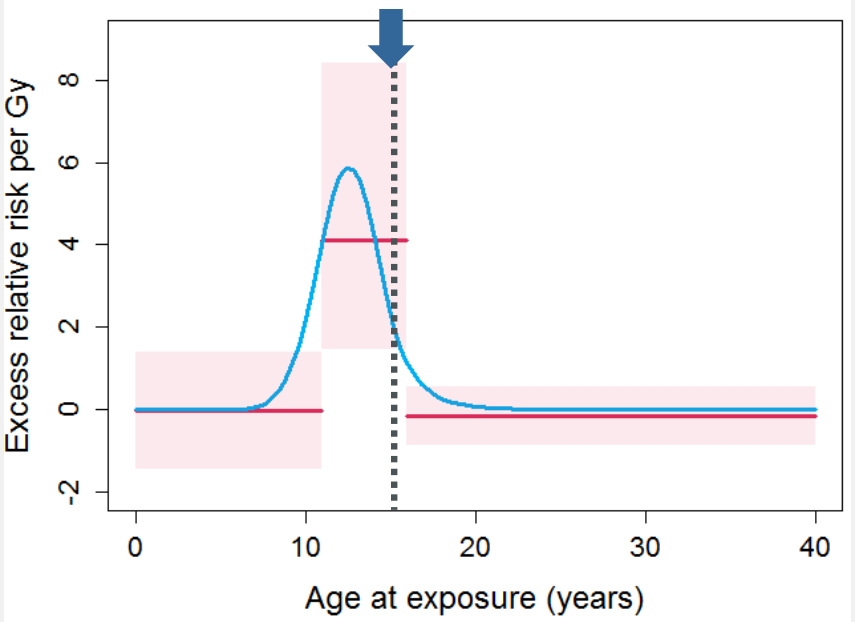


ERR/Gy by age at exposure for selected ages at menarche (at attained age 50)
Spline model with a knot at menarche age

Corpus cancer

Utada et al. JNCI Cancer Spectr 2019

Age at menarche (median=15 yr)



ERR/Gy by age at exposure (no effect modification by attained age or age at menarche)
Quadratic spline model with a knot at 15 years

Period of heightened radiation susceptibility appears to correspond to period of increased stem cell proliferation

OVERALL SUMMARY

- Atomic bomb radiation exposure resulted in increased rates for almost all solid cancers among both males and females of all ages at exposure. These increased rates seem likely to persist to the end of life

- Large number of new cancers and improved methods provided more precise estimates of radiation risks and patterns

- New findings
  - Upward male curvature in all solid cancer dose response and faster ERR decrease with age among males than females
  - Significant dose response for prostate cancer in males, pancreatic and uterine corpus cancers in females, and brain/CNS tumors in both sexes
  - Highest ERR/Gy for female breast and uterine corpus cancers following exposure in puberty

REMAINING CHALLENGES

- To refine understanding of dose response curvature and patterns of radiation risk
  - Peak of excess radiation cancers is expected in 2015-2020
  - Young survivors will become more influential – 73% remain alive
- To better understand heterogeneity of site-specific radiation effects
  - Improved statistical methods to account for heterogeneity in background rates, statistical variability, etc.
- To improve understanding of radiation carcinogenesis
  - Nested molecular studies of radiation-related cancers and integration of epidemiological and molecular data

Gilbert W. Beebe

March 24, 1988
Ceremony to Commemorate
the 40th Anniversary of
US-Japan Joint Studies
of Late A-bomb Effects,
Isemiya Kaikan, Nagasaki