Workshop – Individual Response to Ionizing Radiation

Sex-related Variation in Radiogenic Cancer Risk

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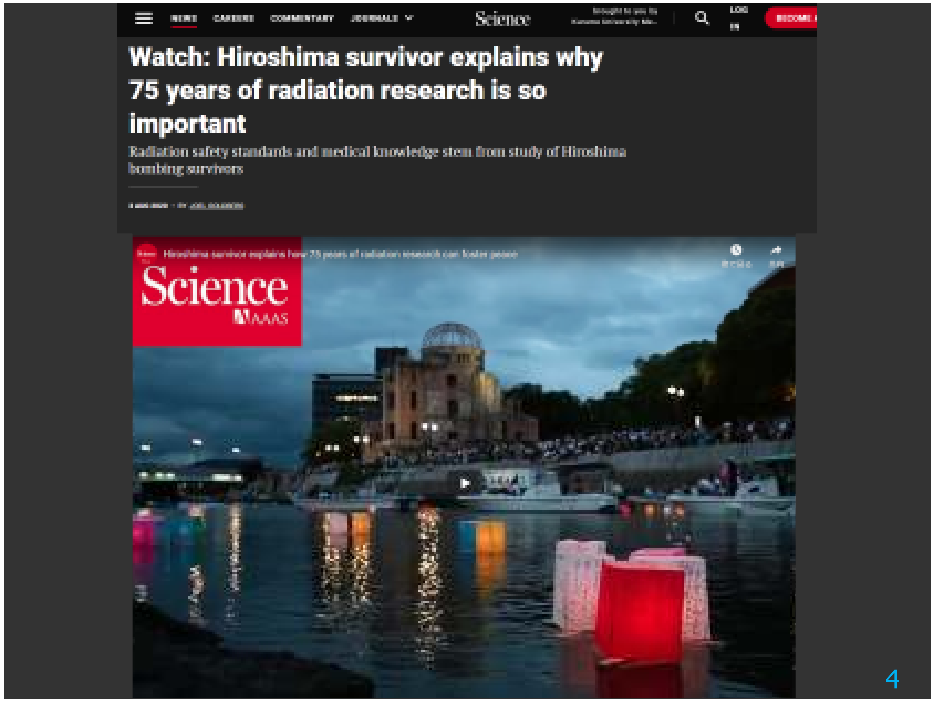
Introduction

- Sex has a crucial role in the incidence, prognosis and mortality in a variety of cancers.
  - For all sites combined, the cancer incidence rate was 20% higher in men than in women and the mortality rate was 40% higher in the US (Shiegel et al., 2017)
  - … probably reflecting the sex differences in exposure to cancer-causing environmental/biologic factors, endogenous hormones, immune functions ...
- Radiation-associated cancer risks are also likely sex-specific.
  - Overall lethality risk for women might be by ≈ 35% greater than that for men (ICRP Publication 103, 2007)
- However, few studies to date have systematically analysed possible sex-specific differences in sensitivity to ionising radiation.
  - How consistent is available evidence for the sex difference across studies ?

Aim of this talk

- To summarize currently available knowledge regarding the sex-related variations in radiation-associated cancer risks.

  - Life Span Study of Japanese Atomic-bomb survivors
  - Other Epidemiological Studies
  - Animal Studies



Life Span Study (LSS)

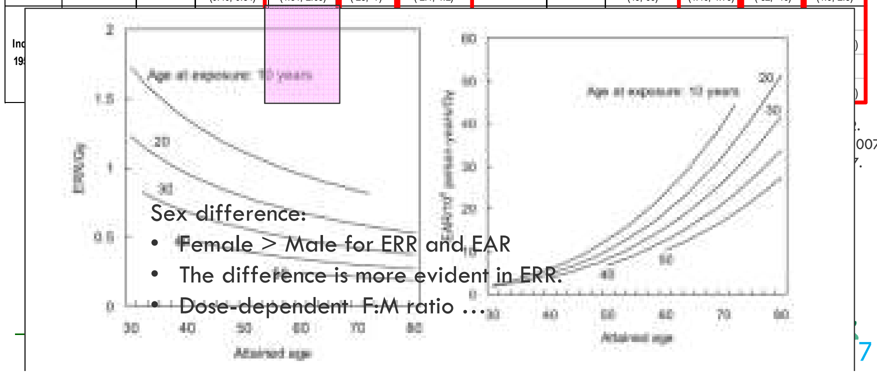
- A general population (n≈120,000) of all ages, both sexes
- Low-LET external, whole body exposure at 0-4Gy
  → Risk evaluation of any specific cancer site
- Followed up for mortality (1950~) and cancer incidence (1958~)
- Contains a clinical sub-cohort (AHS; Adult Health Study, n≈20,000) invited to biennial examinations (1958~)
- ≈27% alive in the end of 2015 (average: 80.3 years old)

LSS Cancer Studies

Data and period	cancer	Adjustment + modifying factors	
Mortality 1950-2003	all solid and 17 sites	Standard risk model (sex, age, agex)	Ozasa et al., Radiat Res 2012
Incidence 1958-1998	all solid and 19 sites	Standard risk model (sex, age, agex)	Preston et al., Radiat Res 2007
Incidence 1958-2009	all solid	Standard risk model (sex, age, agex) + smoking	Grant et al., Radiat Res 2017.
	lung	+ smoking	Cahoon et al., Radiat Res 2017.
	stomach, esophagus	+ smoking, drinking	Sakata et al., Radiat Res 2019.
	colon, rectum	+ smoking, drinking, BMI, meat consumption	Sugiyama et al., Int J Cancer 2020.
	liver, pancreas	+ smoking, drinking, BMI	Sadakane et al., Radiat Res, 2019.
	breast	+ smoking, BMI, age at menarche, pregnancy, childbirth	Brenner et al., Radiat Res, 2018
	uterine, cervical	+ smoking, age at menopause	Utada et al., JNCI Cancer Spect 2019
	urinary, bladder	+ smoking	Grant et al., Radiat Res 2021
	prostate		Mabuchi et al., Radiat Res 2021
	brain CNS		Brenner et al, Eur J Epidemiol 2020
1958-2005	thyroid	+AHS participation (screening effect)	Furukawa et al., Int J Cancer 2013
1958-2001	Urothelial carcinoma	+ smoking, drinking, fruits, vegetables, level of education	Grant et al., Radiat Res 2012

All Solid Cancer

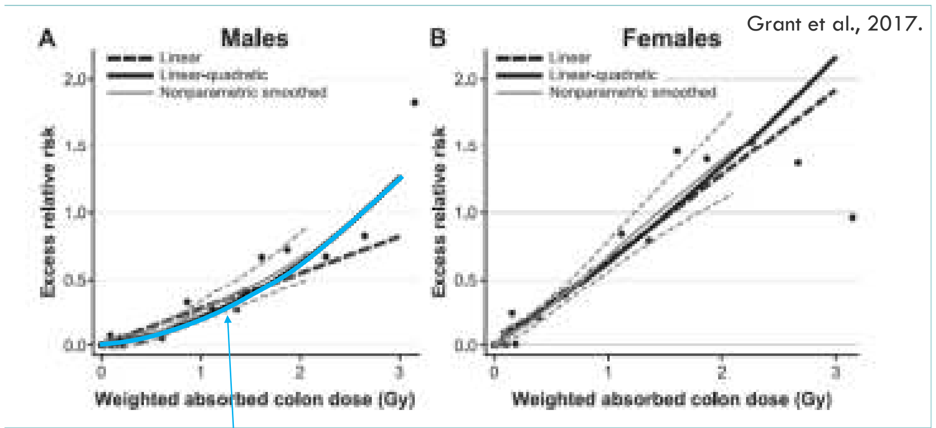
	ERR model						EAR model					
	ERR per Gy			female:male ratio	age at exposure	attained age (power)	EAR per 10,000 person-years-Gy			female:male ratio	age at exposure	attained age (power)
	Male	female	sex-averaged				Male	female	sex-averaged			
Mortality 1950-2003	0.27	0.57	0.42 (0.32,0.53)	2.1 (1.4, 3.1)	-29% (-41, -17)	-0.86 (-1.60,-0.06)	25.1	27.7	26.4 (20.3, 32.8)	1.10 (0.80, 1.74)	-19% (-31, -7)	3.40 (2.7, 4.1)
Incidence 1958-1998	0.36	0.58	0.47 (0.40, 0.54)	1.6 (1.31, 2.09)	-17% (-25, -7)	-1.65 (-2.1,-1.2)	43	61	52 (43, 60)	1.40 (1.10, 1.79)	-24% (-32, -16)	2.38 (1.9, 2.8)



Sex difference:
- Female > Male for ERR and EAR
- The difference is more evident in ERR.
- Dose-dependent F:M ratio …

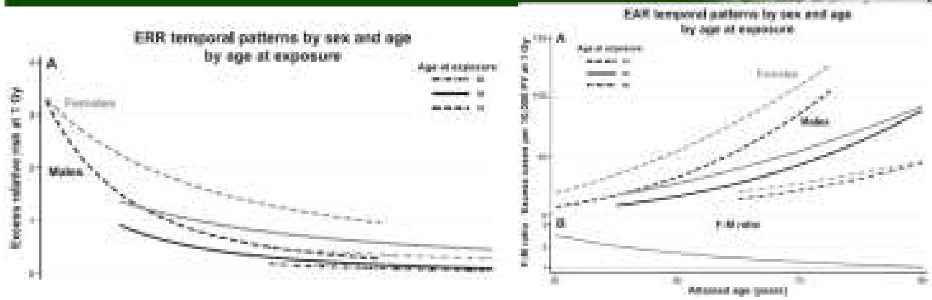
Sex difference in dose response

Grant et al., 2017.



Significant curvature observed in males only.

Sex difference in age effects



Grant et al., 2017.

The excess risk tends to be changing with age more quickly in males than in females

	ERR		EAR	
	Male	Female	Male	Female
Age effects (power)	-2.7	-1.4	2.9	2.1
	(-3.6, -1.8)	(-1.9, -0.8)	(2.1, 3.7)	(1.6, 2.5)
F:M ratio trend	increasing		decreasing	

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Further analyses on all solid cancer dose response

- Interpretation of the observed sex difference in "all solid cancers" dose response is not straightforward …
  - A sex difference in distributions of the cancer sites (of different dose response)
  - Curvature of males disappears after excluding a few sites (Cologne et al, 2019)
- Upward curvature in all solid cancer dose response was observed in mortality data (Brenner et al. 2022)
  - Upward curvature was suggested for solid cancer mortality among both males and females with no significant sex difference, while the curvature was significant only among males with a significant sex difference for solid cancer incidence.
  - The strength of evidence for the upward curvature likely depend on the composition of sites for all solid cancer, age at exposure or calendar period.

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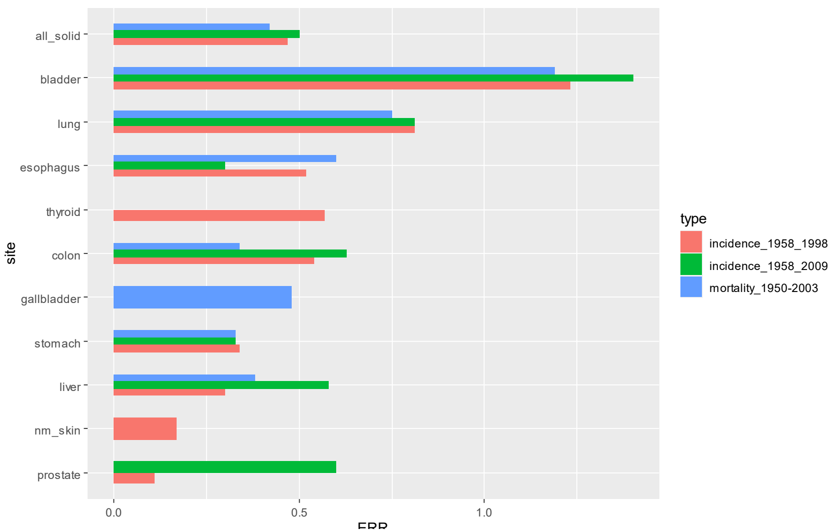
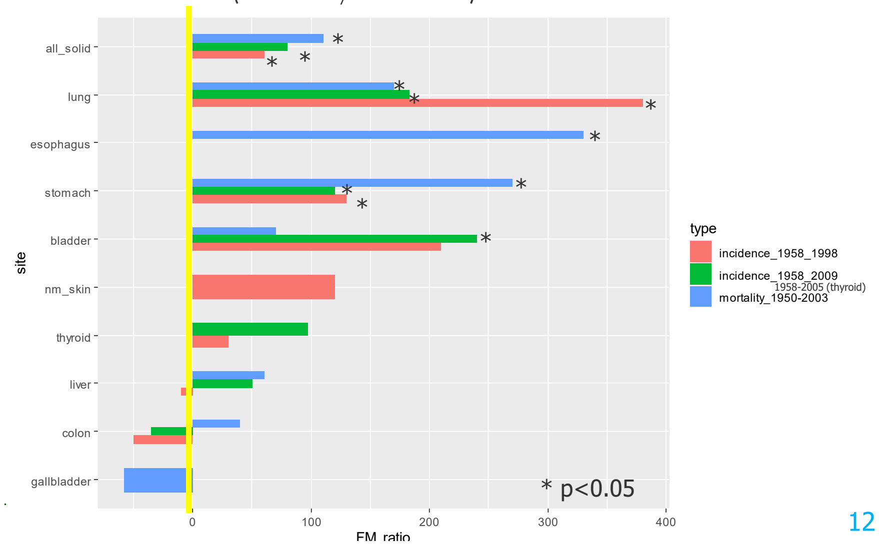
Site-specific cancer ERR/Gy in LSS

Sex-averaged ERR/Gy at age 70 after exposure at 30



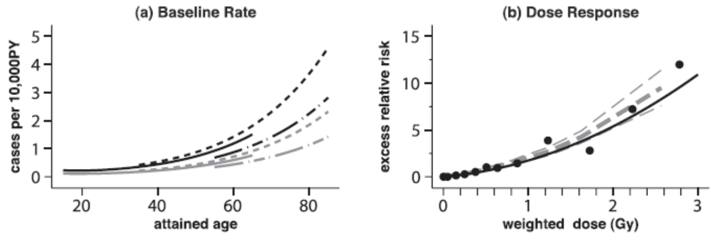
Sex difference by site

(FemaleERR/MaleERR – 1)x100



Leukemia in LSS

- All leukemia incidence other than CLL or ATL (Hsu et al., 2013)
  - Linear-quadratic ERR dose response was dependent on age at exposure and time since exposure but not on sex (p=0.3).
  - Linear-quadratic EAR is suggestively higher in men than in women (F:M=0.66, P=0.08)



- Multiple myeloma mortality: ERR/Gy for females was nearly eight times that for males (0.86 vs 0.11). (Ozasa et al., 2012)

Thyroid cancer in LSS

- The earliest solid cancer site that showed a risk increase in the LSS.
- The age-adjusted thyroid cancer rates for females in Japan are over 3-fold the rates for males.
- Thyroid cancer incidence ERR in LSS did not differ significantly by sex (P=0.3) but female EAR > male EAR, in particular among those exposed as children
  - Fitted excess cases: 35.5 (female) vs 5.6 (male) for exposure at age < 20 yrs.

Table 1. Observed and fitted cases of thyroid cancer incidence in the LSS (1958–2005) by categories of dose and other variables

	Age at exposure < 20 years							Age at exposure >= 20 years						
				Fitted values							Fitted values			
	n	Case	Rate[1]	Back-ground	Fitted excess	AF[2] (%)	95%CI	n	Case	Rate[1]	Back-ground	Fitted excess	AF[2] (%)	95%CI
Total														
	45,738	191	12.2	153.5	41.1	36*	(22–46)	59,663	180	12.5	173.2	3.3	4*	(1–17)
Sex														
Male	21,571	40	5.6	33.7	5.6	14	(0–27)	21,319	21	5.0	21.6	0.2	1	(0–6)
Female	24,167	151	17.5	119.7	35.5	23	(13–32)	38,344	159	15.5	151.6	3.1	2	(0–9)

Furukawa et al., Int J Cancer 2013

Lung cancer incidence in LSS

- One of the site that shows a relatively clear sex difference.
- Generalized radiation-smoking interaction model (Furukawa et al., Radiat Res 2010)

Radiation-ERR Smoking-ERR

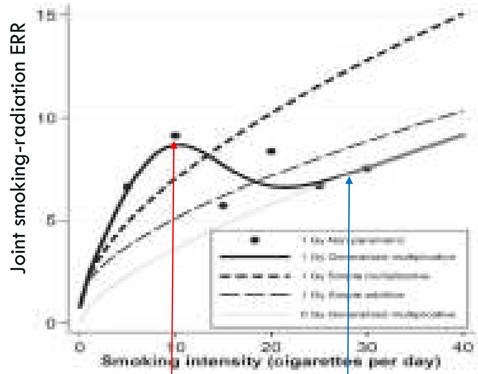
$$\lambda_d(a, smk, x) = \lambda_0(a, x)\{1 + \rho(d)\varepsilon(x, smk)\}\{1 + \phi(smk, x)\}$$

dose age smoking other factors sex, city, b-year, … smoking (total amount, intensity)

Lung cancer: Smoking and Radiation

- LSS Lung cancer incidence 1958-2009 (Cahoon et al., Radiat Res, 2017)

Smoking-radiation joint effects complicatedly depended on smoking behavior



Interaction

Light-moderate smokers: More than multiplicative

Heavier smokers: Little radiation-associated excess

Lung cancer: Smoking Effect by Sex

- LSS Lung cancer incidence by histological type 1958-1999

Smoking-ERR	All lung	Adeno	Squamous	Small cell
ERR* (Male)	3.6 (2.6, 5.1)	2.4 (1.4, 3.8)	12.7 (4.8, 51)	17.5 (4.6, 112)
ERR* (Female)	5.8 (4, 7.9)	3.4 (0.9, 7.3)	21.1 (9.7, 45)	41.4 (16.8, 107.9)
Birth year (%change/10yr ↓)	33 (15, 55)	6 (-25, 47)	45 (4, 104)	40 (-4, 104)
Years since quitting (power)	-0.47 (-0.8, -0.3)	-0.39 (-13, 0.2)	-0.37 (-0.7,-0.1)	-0.59 (-1.1,-0.3)

*Risk at age 70 for unexposed smokers with a pack/day for 50 years

Smoking risks are consistently significant and larger for females than for males.
The difference is more evident for squamous and small cell.

Furukawa et al., Rad Res 2010; Egawa et al., Rad Res 2012

Lung cancer: Radiation Effect by Sex

- LSS Lung cancer incidence by histological type 1958-1999

Radiation ERR	All lung	Adeno	Squamous	Small cell
ERR/Gy* (sex-averaged)	0.59 (0.3,1.0)	0.75 (0.3,1.3)	0.27 (0.0,1.5)	1.49 (0.1,4.6)
ERR/Gy* (male)	0.29 (0.1,0.6)	0.17 (0.0,0.8)	0.07 (0.0,0.7)	2.21 (0.2,7.6)
ERR/Gy* (female)	0.90 (0.5,1.5)	1.34 (0.6,2.3)	0.48 (0.0,2.6)	0.78 (0.0,3.3)
F/M ratio	3.12 (1.5,7.4)	7.94 (1.8,Inf)	6.89 (1.6,Inf)	0.35 (0.0,2.3)
Attained age (power)	-2.78 (-4.9,-0.7)	-2.34 (-5.3,0.8)	-8.91 (-25.9,-0.7)	-2.63 (-9.7,4.6)

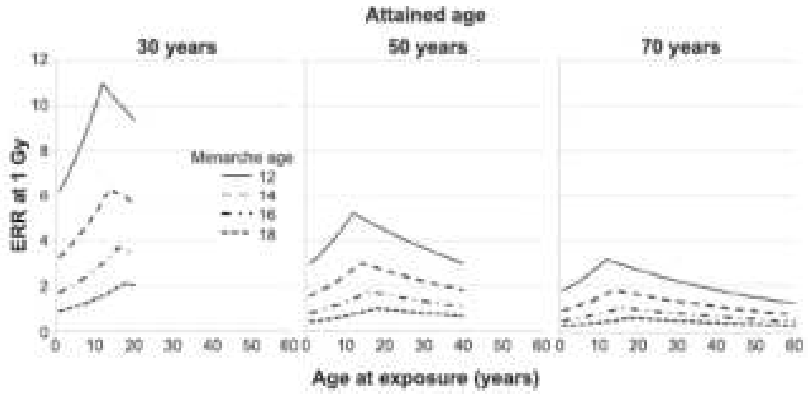
Strength of sex difference vary across lung cancer subtypes.

*Risk at age 70 after exposure at age 30 among never-smokers

Furukawa et al., Rad Res 2010; Egawa et al., Rad Res 2012

Variation by Reproductive History

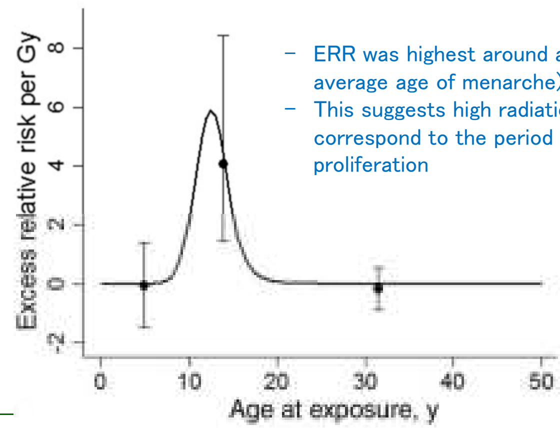
Breast cancer incidence 1958-2009 (Brenner et al., Radiat Res 2018)



ERR and EAR ↑ with age at menarche ↓
Age at exposure effects are highest around menarche
→ Highest breast sensitivity during puberty

Variation by Reproductive History

Uterine corpus cancer incidence 1958-2009 (Utada et al., JNCI Spect 2019)



- ERR was highest around age 15 (about the average age of menarche).
- This suggests high radiation susceptibility correspond to the period of increased stem cell proliferation

Summary of Sex-related variation in LSS

- For all solid cancers combined, the radiation-associated risk varied by sex (in addition to age at exposure and attained age).
- A significant sex-difference in dose response curvature was observed in incidence data (but not in mortality data).
- In site-specific analyses, ERR estimates were mostly higher in women than in men, but not significantly for many of them.
- Significant sex differences observed:
  - ERR: Female>male : all solid, lung, stomach, bladder (incidence), esophagus (mortality)
  - ERR/Gy was significant only in women for pancreas incidence (Sadakane et al., 2019) and rectum mortality (Ozasa et al., 2012)
  - Different dose response shapes were found on esophagus (incidence) (Sakata et al., 2019) and renal parenchyma cancer (incidence) (Grant et al., 2021)

Outline

- Life Span Study
- Other Epidemiological Studies
- Animal Studies

Evidence for Sex variations

- Increasing amount of evidence has been available from studies of exposed populations, mainly from medical, occupational and environmental exposures.
- However, regarding sex variations, most of them provide only sex-averaged risk estimates, or otherwise null or conflicting results.
- Only a few results report a significant sex variation in the risk.

Evidence for sex-difference

- Lung cancer mortality ERR
  - LSS: F>M (F:M=2-3) for ERR.
  - Mayak workers: F>M for ERR (plutonium intake): F:M≈4 --- (Gilbert et al., 2013, Gillies et al., 2013) --- Interpretation is challenging due to several reasons including dosimetry uncertainty and smoking adjustment
  - Patients with Hodgkin's disease: M>F, F:M≈1/4 for patients with dose > 5Gy (Gilbert et al., 2003)
  - Most of other studies of workers or patients (mostly, low LET, low dose rate exposed) reported no significant risk increase or otherwise no clear sex variation (Boice et al., IJRB 2018).

Evidence for sex-difference

- Non melanoma skin cancer incidence ERR
  - LSS: F >M for ERR (0.23 vs 0.10, P=0.3)
  - Mayak workers: ERR was significantly >0 in males only (Azizova et al., 2018)
- Thyroid cancer incidence
  - LSS: F>M for EAR, F:M=2 (P=0.3) for ERR
  - Chernobyl UkrAm: ERR F:M ≈2 (P=0.4)   (Brenner et al., 2011)
  - Pooled analysis : ERR F:M ≈2   (N.S.)   (Ron et al., 1995),
    "similar by sex (P=0.35)"   (Lubin et al, 2017)

Outline

- Life Span Study
- Other Epidemiological Studies
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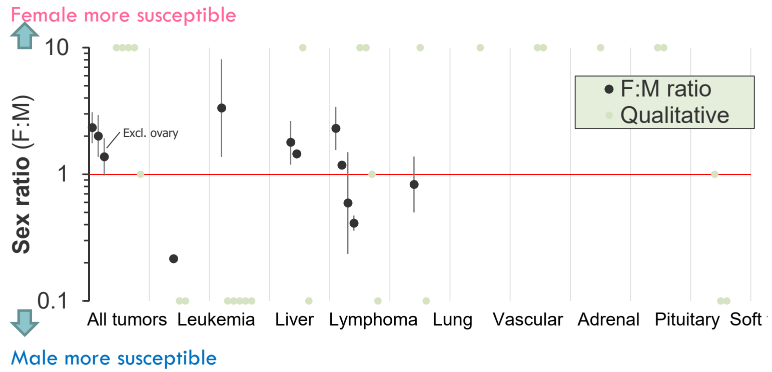
Sex variation evidence

Studies in animals have shown some sex-differences in radiation effects.

Radiation	Animal	Outcome	Measure	Modification (M vs. F)	Reference
γ rays	Mouse	Solid cancer Lymphoma	Sex ratio (95% CI)	M:F = 0.50 (0.34, 0.73) M:F = 0.56 (0.38, 0.84)	Chernyavskiy et al. 2017
$^{238}PuO_2$	Dog	Lung Bone Liver	Sex ratio (95% CI)	M:F = 1.34 (0.74, 2.42) M:F = 1.02 (0.67, 1.57) M:F = 0.78 (0.34, 1.78)	Muggenburg et al. 1996
γ rays	Mouse	Tumours excl. ovary Lymphoreticular Vascular Lung Liver Harderian	EAR (10^{-4} mouse-days Gy^{-1})	6.27 ± 0.84 vs. 8.60 ± 0.94 7.36 ± 1.08 vs. 3.65 ± 1.13 6.67 ± 1.21 vs. 5.54 ± 1.03 5.35 ± 0.87 vs. 12.30 ± 1.43 2.24 ± 0.96 vs. 7.46 ± 1.11 8.24 ± 0.70 vs. 9.69 ± 0.88	Grahn et al. 1992
X rays	Mouse	Myeloid leukaemia Malignant lymphoma Harderian Life lost with tumour	Dose response coefficient (%/Gy or days/Gy)	28.7 ± 12.3 vs. no increase 4.91 ± 3.62 vs. no increase 9.23 ± 1.46 vs. 13.2 ± 2.63 24 ± 3 vs. 56 ± 4 (days/Gy)	Di Majo et al. 1996
X rays	Mouse	Lung tumours	Dose response coefficient (%/Gy^2)	10.15 ± 2.71 vs. 6.01 ± 2.34	Coggle 1988
γ rays	Mouse	Thymic lymphoma	Dose response	6.9%/Gy vs. 120%/Gy^2	Ullrich and

Sex variation in risks for animals



Reference (from left)
(only X and γ rays)

Di Majo et al. 1996
Chernyavskiy et al. 2017
Grahn et al. 1992
Tanaka et al. 2007
Gross et al. 1988
Gross and Dreyfuss 1979
Lao 1998
Anisimov and Osipova 1993

Ullrich and Storer 1979b
Di Majo et al. 1996
Yoshida et al. 1993

Grahn et al. 1992
Tanaka et al. 2007
Sasaki and Kasuga 1981
Takahashi et al. 1992
Sasaki et al. 1978a
Vesselinovitch et al. 1971

Chernyavskiy et al. 2017
Zander et al. 2020
Tanaka et al. 2007
Di Majo et al. 1996

Grahn et al. 1992
Suzuki et al. (in press)
Coggle 1988
Zander et al. 2020
Sasaki and Kasuga 1981
Miller et al. 2013
Vesselinovitch et al. 1971
Tanaka et al. 2007

Grahn et al. 1992
Sasaki and Kasuga 1981
Tanaka et al. 2007

Tanaka et al. 2007

Tanaka et al. 2007
Sasaki and Kasuga 1981

Tanaka et al. 2007

van der Houven van Oordt et al. 1997
van der Houven van Oordt et al. 1999

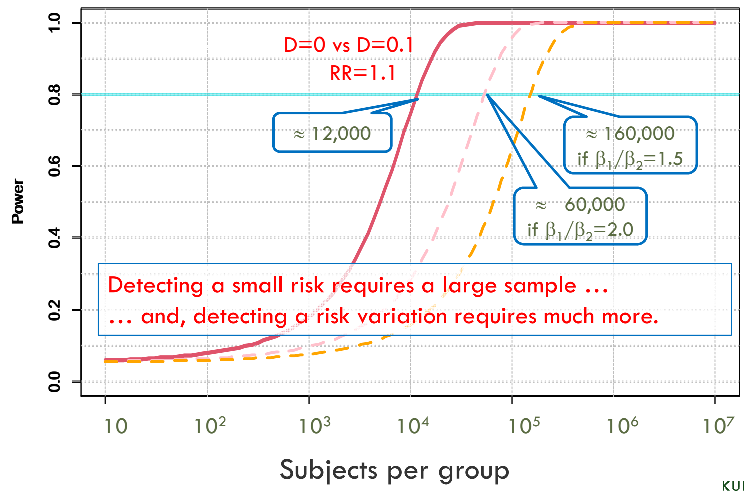
Morioka et al. 2014 (juvenile)
Morioka et al. 2014 (yound adult)
Trani et al. 2013

- Some indications of higher susceptibility of females to all solid tumors.
- For specific tumors data are limited or results are not consistent.

Concluding Remarks

- Epidemiological studies have provided some indications of possible sex-specific radiation sensitivity in humans.
- Most of the current evidence has been derived from the LSS, with qualitatively similar sex-specific variations observed for majority of cancer sites.
- Many other studies have provided evidence for radiation-associated increase of cancer risks but many of them failed to show possible sex differences in the risks.
  - Statistical power issues become even harder to estimate an effect modification.

A binary regression model: $p=0.1*(1+\beta_s D)$
Statistical power to reject $H_0: \beta_1=\beta_2$ when $\beta_1/\beta_2>1$



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- Many other studies have provided evidence for radiation-associated increase of cancer risks but many of them failed to show possible sex differences in the risk.
  - Statistical power issues become even harder to estimate an effect modification.
- Overall, further epidemiological and biological studies are needed to produce reliable evidence to fully elucidate the sex differences.
- The need for mechanistic and systematic studies on the effects of sex should be also emphasized.