Cancer Risks from Low-dose Ionizing Radiation: The JNCI Monograph

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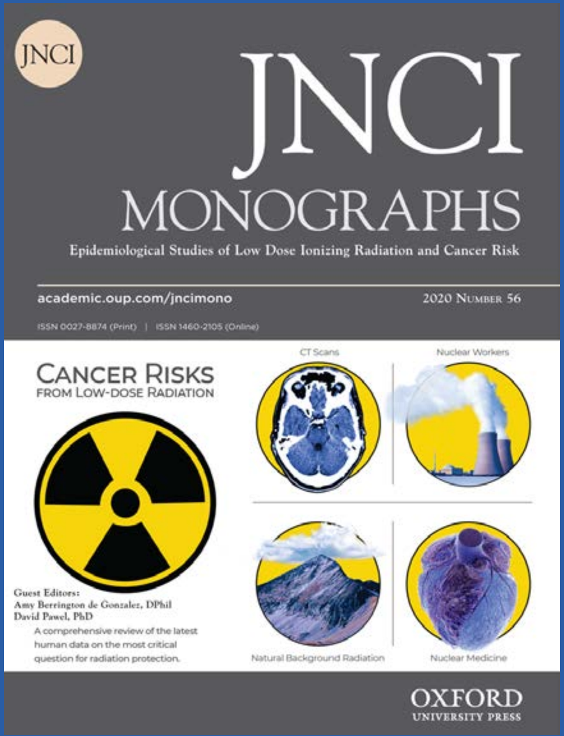

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NAS BEIR VII 2006 report on low-dose radiation and cancer……“*the available scientific evidence is consistent with a linear dose-response relationship between ionizing radiation and the development of cancer in humans…. the smallest dose has the potential to cause a small increase in risk to humans*”.

Pooled Analyses

Highly Susceptible Populations

New Era of Low-Dose Studies

Electronic Record Linkage

New Exposures

Aims of the Review

Aim 1

- Summarize findings of epidemiological studies published since NAS BEIR VII

Aim 2

- Systematically assess impact of potential biases & conduct meta-analysis

Study Eligibility

- Cancer risks in humans published 2006-17
- Mean ionizing radiation dose <100mGy
- Risk estimates for dose-response

Environmental Exposures

- 8 eligible studies
- 4 natural background & 4 accidental

Medical Exposures

- 4 eligible studies
- 3 pediatric imaging/therapy & 1 adult cardiac imaging

Occupational Exposures

- 14 eligible studies
- 11 nuclear workers, 1 medical & 2 clean-up workers

Summary Study Characteristics

Primary outcomes: 91,000 solid cancers & 13,000 leukemias

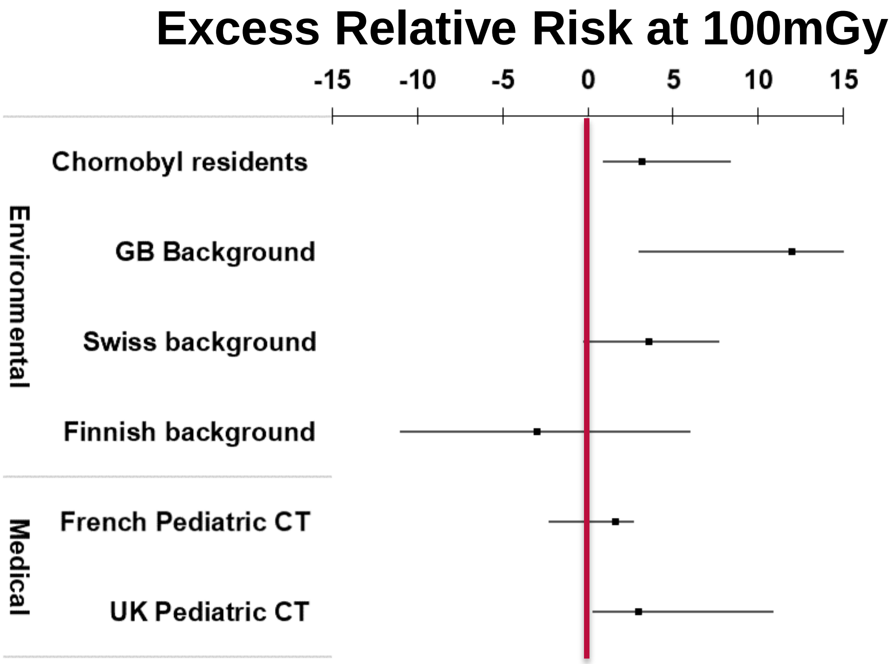
Mean dose range: 0.1mSv (Three Mile Island) to 82mSv (Chernobyl liquidators)

Most study participants exposed to <100mSv

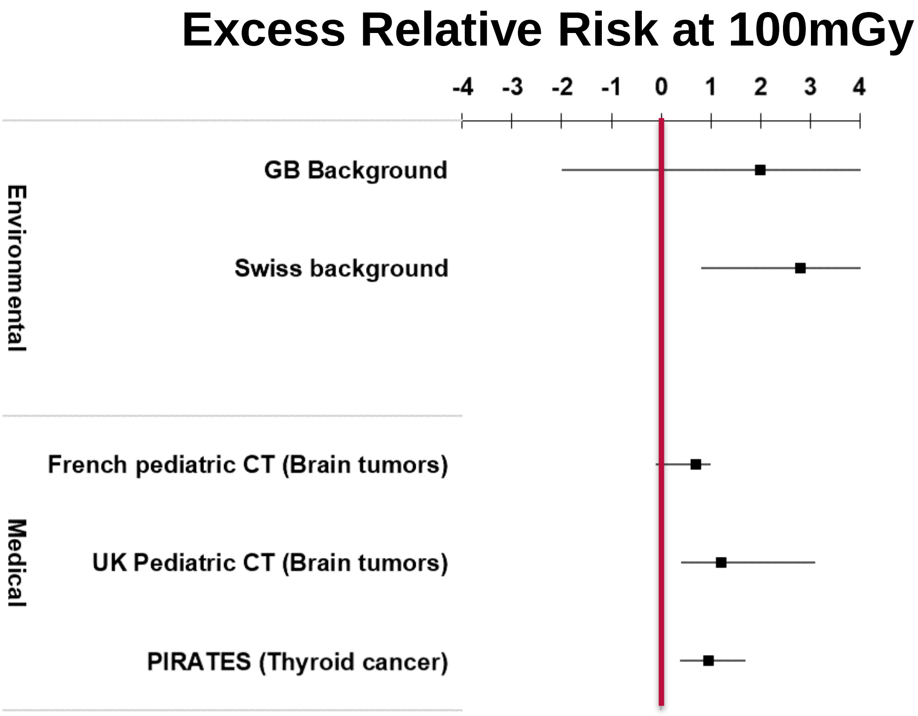
(21 studies <10% had doses >100mSv)

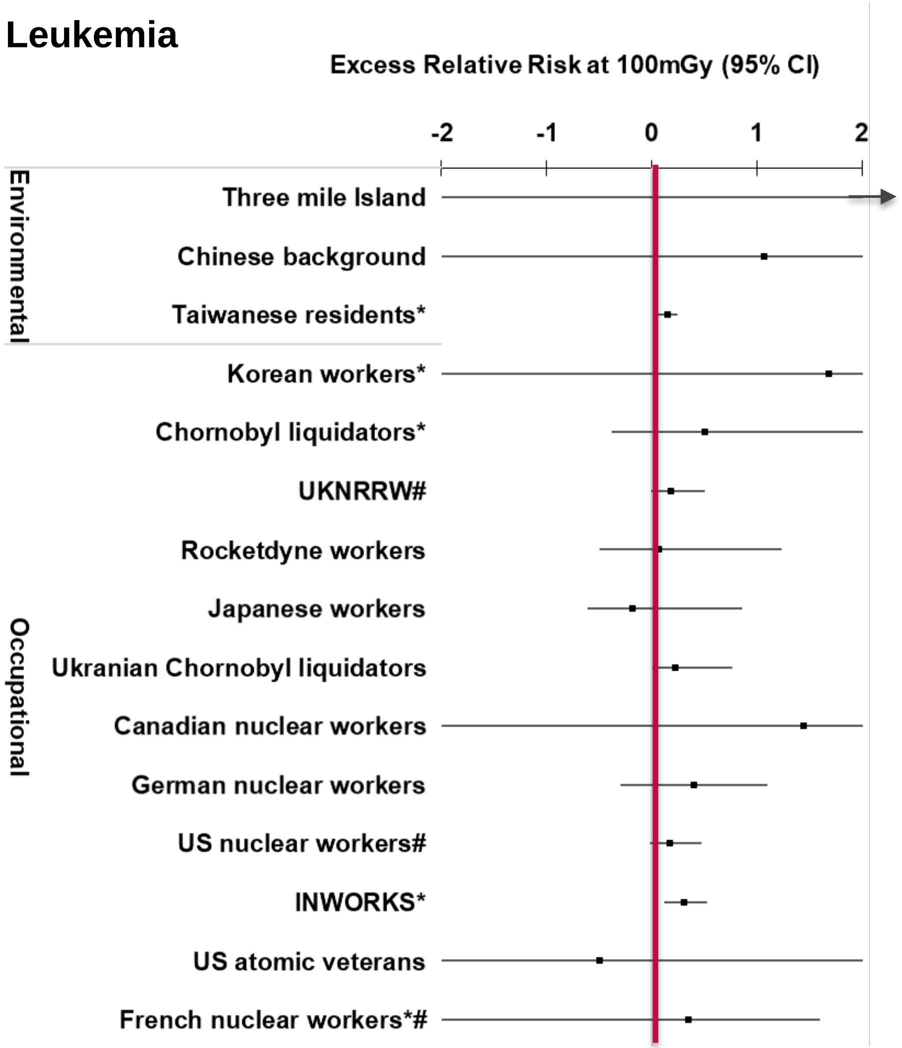
Cancer Risk Following Low-Dose Exposure in Childhood

Leukemia

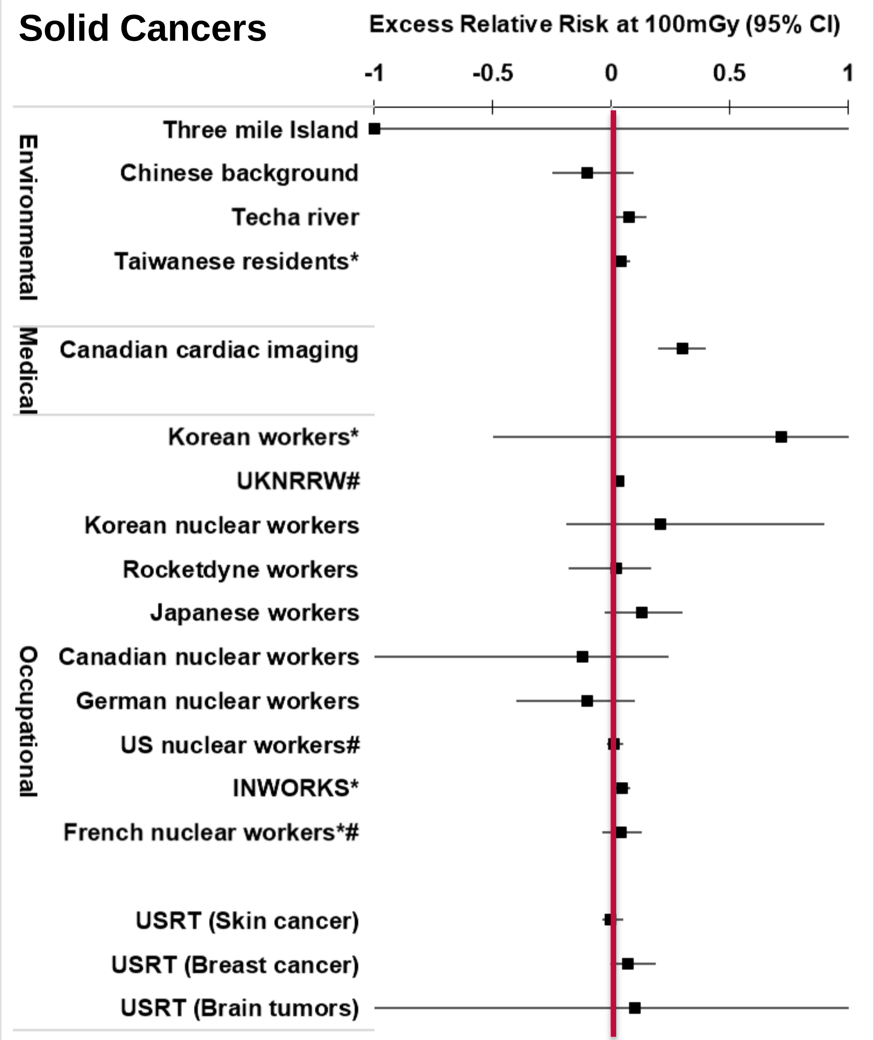


Solid Cancers





Leukemia
Excess Relative Risk at 100mGy (95% CI)
-2
-1
0
1
2
Environmental
Three mile Island
Chinese background
Taiwanese residents*
Occupational
Korean workers*
Chornobyl liquidators*
UKNRRW#
Rocketdyne workers
Japanese workers
Ukranian Chornobyl liquidators
Canadian nuclear workers
German nuclear workers
US nuclear workers#
INWORKS*
US atomic veterans
French nuclear workers*#



Solid Cancers
Excess Relative Risk at 100mGy (95% CI)
-1
-0.5
0
0.5
1
Environmental
Three mile Island
Chinese background
Techa river
Taiwanese residents*
Medical
Canadian cardiac imaging
Occupational
Korean workers*
UKNRRW#
Korean nuclear workers
Rocketdyne workers
Japanese workers
Canadian nuclear workers
German nuclear workers
US nuclear workers#
INWORKS*
French nuclear workers*#
USRT (Skin cancer)
USRT (Breast cancer)
USRT (Brain tumors)

Ineligible Studies: Failed on 1 Criterion (n=14)

Population	Author	Year	Reason for exclusion	Finding
US scoliosis (thyroid)	Ronckers	2008	Mean dose = 120mGy	+ (ns)
Kerala background	Nair	2009	Mean dose = 161mGy	- (ns)
Chornobyl clean-up	Kesminiene	2012	Mean dose =100-200mGy	+ (s)
Techa river (leukemia)	Krestinina	2013	Mean dose = 410mGy	+ (s)
Mayak workers	Solkinokov	2015	Mean dose = 354mGy	+ (s)
Chornobyl clean-up	Kashcheev	2015	Mean dose = 132mGy	+ (s)
Chinese medical workers	Sun	2016	Mean badge dose = 250mGy	+ (s)
US Shipyard workers	Matanoski	2008	Categorical risk estimates	+ (ns)
Australian nuclear test	Gun	2008	Categorical risk estimates	+/- (ns)
French biology researchers	Guseva	2008	Categorical risk estimates	+ (s)
Finnish reindeer herders	Kurttio	2010	Categorical risk estimates	+ (s)
Childhood X-rays	Hammer	2009	Categorical risk estimates	+/- (ns)
French background	Demoury	2017	Risk for dose rate not cumulative dose	+/- (ns)
German background	Spix	2017	Risk for dose rate not cumulative dose	+ (ns)

s – statistically significant ($p<0.05$)

ns – not statistically significant ($p\geq0.05$)

Summary Study Findings

Solid cancers: 16 of 22 studies positive ERR

Leukemia: 17 of 20 studies positive ERR

Ineligible (1 criterion): 10 of 14 studies positive

Bias Assessment Framework

Assess whether there is potential bias from each of the following sources.

- Dose error?
- Confounding?
- Selection bias?
- Outcome ascertainment?

Assess the likely direction of the bias from each source.

- Towards null?
- Away from null?*
- Uncertain?*

If possible, estimate the magnitude of the bias.

- Is bias large enough to explain the result (ie bias correction would move ERR/Gy to 0)?

Berrington et al (JNCI Monograph 2020)

Distinctiveness of Bias Assessment Approach

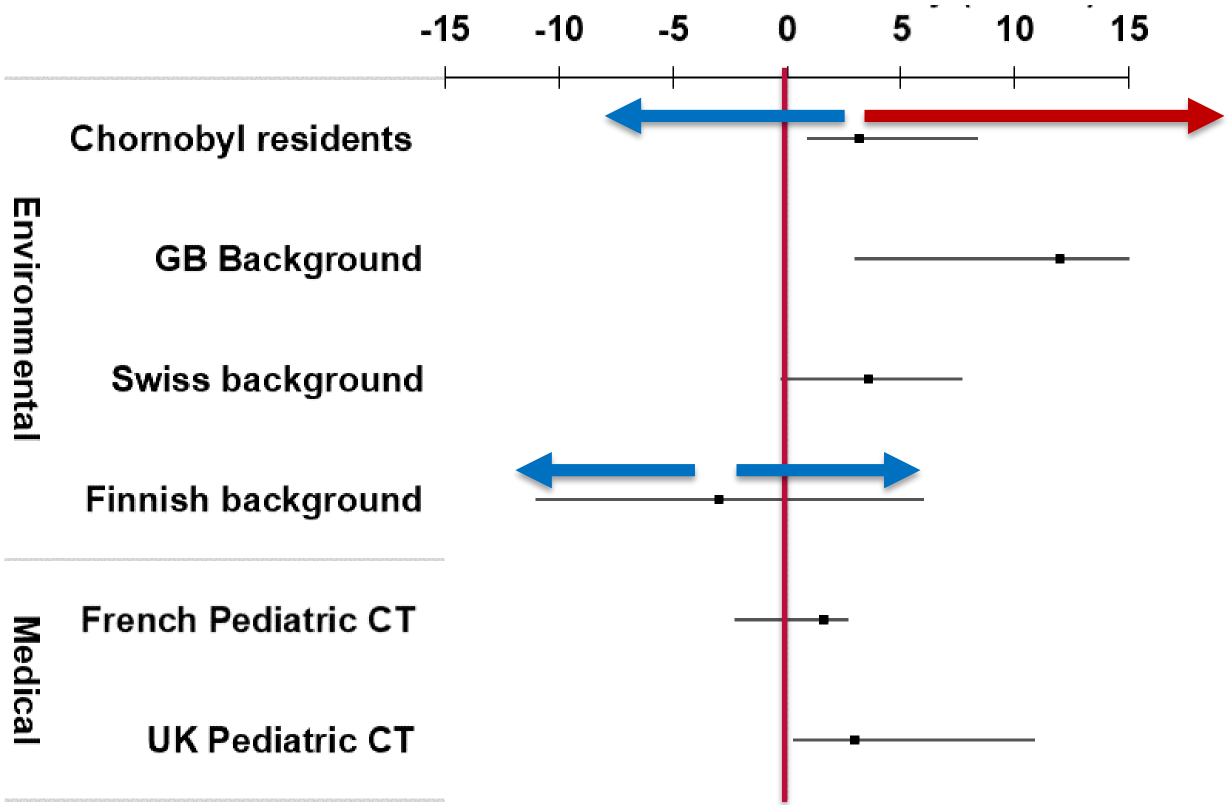
Study Quality?

- No adjustment for smoking
- Low quality dosimetry

Bias?

- Direction & strength of confounding?
- Impact of dose error on risk coefficient?

Excess Relative Risk at 100mGy



Our priority is to identify +ve studies with potential bias away from null

Potential Biases…Common misconceptions

No unexposed comparison group

- Exposed vs unexposed more likely to be biased (eg confounding, selection bias) than a dose-response in exposed subjects

Retrospective cohort study

- Equally valid as a prospective study if using passive data collection (no recall bias)

Dr Schubauer-Berigan

Bias impact assessment

Assess whether there is potential bias from each of the following sources.

- Dose error?
- Confounding?
- Selection bias?
- Outcome ascertainment?

Bias impact assessment: radiation dose error

Dosimetry quality assessed for each study, emphasizing potential to lead to spurious dose-response findings

18/24 studies had minimal dosimetry error, which would not be expected to cause substantial bias

- Bias toward null association from non-differential dose error likely for most studies
- 3 case-control studies potentially biased away from null

Daniels et al (JNCI Monograph 2020)

Bias impact assessment: confounding & selection bias

For each study, assessed methods used to control for confounding and selection bias in design & analysis

- Identified confounders of concern for environmental, medical, and occupational exposure studies

Evaluated direct and indirect evidence demonstrating likely impact of confounding

Where no data were available, used theoretical worst-case assessment of confounding impact

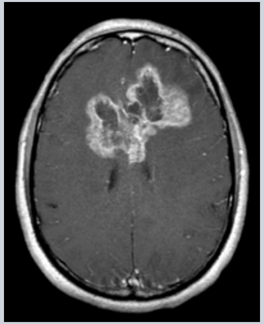
Confounders of concern by exposure type

Environmental

- Lifestyle-related factors

Medical

- Confounding by indication (children)
- Lifestyle-related factors (adults)



Occupational

- Lifestyle-related factors
- Other occupational carcinogens
- Healthy worker effect & healthy worker survivor bias (HWSB)

Schubauer-Berigan et al (JNCI Monograph 2020)

Direct & indirect evidence of confounding

Environmental

- Lifestyle-related factors
  - Most studies controlled for age, sex, birth cohort
  - Most studies controlled for lifestyle correlates [smoking, education, or socioeconomic status (SES)]
- Some studies adjusted for region of residence and natural background radiation

Medical

- Lifestyle-related factors
  - All studies adjusted for age, sex, calendar year
- Confounding by indication
  - Most studies excluded children with predisposing conditions [e.g., cancer susceptibility syndromes (CSS)]

Occupational

- Lifestyle-related factors & other occupational carcinogens
  - Most studies adjusted for age, sex, birth cohort & SES
- Healthy worker effect & HWSB
  - Most studies adjusted for employment duration

Direct & indirect evidence of confounding

Environmental

- Bias impact evaluation
  - Little evidence that potential confounders were actually related to radiation dose
  - Minimal impact of adjustment on dose-response estimates
- Main concern: potential selection bias in 1 study

Medical

- Bias impact evaluation
  - Most known risk factors for brain cancer & leukemia unlikely related to radiation dose
  - CSS generally very rare and were not strongly related to number of CT scans
  - Positive confounding unlikely by SES in studied countries
- Main concern: residual confounding by indication (lack of adjustment in 1 study; incomplete data for 1 study)

Occupational

- Bias impact evaluation
  - After adjusting for sex, age, birth cohort & SES, little indirect evidence of smoking confounding (e.g. COPD negatively or not associated with dose)
  - Benzene not likely a strong confounder; more potential for asbestos confounding
- Main concern: residual confounding by smoking, asbestos, & HWSB (no adjustment in 3 studies; partial in others)

Bias impact assessment: confounding & selection bias

Worst-case estimation of confounder disparity by dose group that would reduce point estimate to null

This evaluation was done for CSS in CT studies, and for tobacco and asbestos in nuclear worker studies

Example: low-dose radiation in International Nuclear Workers Study (INWORKS)

Bias impact assessment: confounding & selection bias

Assume no radiation-cancer association & calculate distribution of smoking required to explain the dose-response observed for all cancer mortality in INWORKS

- Overall smoking prevalence 50-70%, smoking-related all cancer RR=1.6: **calculated smoking prevalences in highest dose categories exceed 100%**: smoking differences cannot explain observed radiation risks
- Overall smoking prevalence=30%, a 3-fold difference in smoking prevalence across dose categories would be needed to explain observed radiation risks

Similar findings for asbestos exposure in occupational studies and CSS in medically exposed populations

Bias impact assessment: outcome assessment quality

Main concerns for all-cancers & leukemia excluding CLL

- Loss to follow-up (LTFU), over- or under-ascertainment, outcome misclassification, changing classifications over time, combining heterogeneous cancers that may differ in radiogenicity or latency

Most studies had acceptable outcome assessment quality, but with potential for non-differential misclassification

- Low LTFU; 4 studies had differential ascertainment by dose group; few studies had evidence of differential classification by dose group

Linet et al (JNCI Monograph 2020)

X- and γ-radiation are *known human carcinogens*

Sites with "*Sufficient*" evidence of human carcinogencity

- Oral cavity & digestive: salivary gland, oesophagus, stomach, colon
- Respiratory: lung
- Urinary tract: kidney, urinary bladder
- Other solid cancers: bone, basal cell of the skin, female breast, brain and CNS, thyroid
- Lymphatic & hematopoietic: leukaemia (excluding chronic lymphocytic)
- "In-utero exposure to X-radiation and γ-radiation causes cancer"

Sites with "*Limited*" evidence of human carcinogenicity

- Oral cavity & digestive: rectum, liver, pancreas
- Respiratory: --
- Urinary tract: --
- Other solid cancers: ovary, prostate
- Lymphatic & hematopoietic: non-Hodgkin lymphoma, multiple myeloma

Source: IARC Monogr. Eval. Carcinogen. Risks Hum. Vol. 100D (2012)

Bias impact assessment: analytical issues

Statistical power is low for most studies, if the ERR/Gy estimates from LSS are generalizable

- Adjusting for confounding is important, but over-adjustment should be avoided
- Pooling of compatible studies can help overcome limited power
- Estimates derive from Japanese Life Span Study (LSS)

Gilbert et al (JNCI Monograph 2020)

Bias impact assessment: analytical issues

Dose measurement error impact

- Most studies had high-quality dosimetry, although varying levels of individualization
- Errors most likely to be non-differential
  - Can further reduce power
  - Can lead to underestimation of risk per unit dose
  - Unlikely to cause spurious dose-response association

Summary: Systematic Bias Assessment for Leukemia

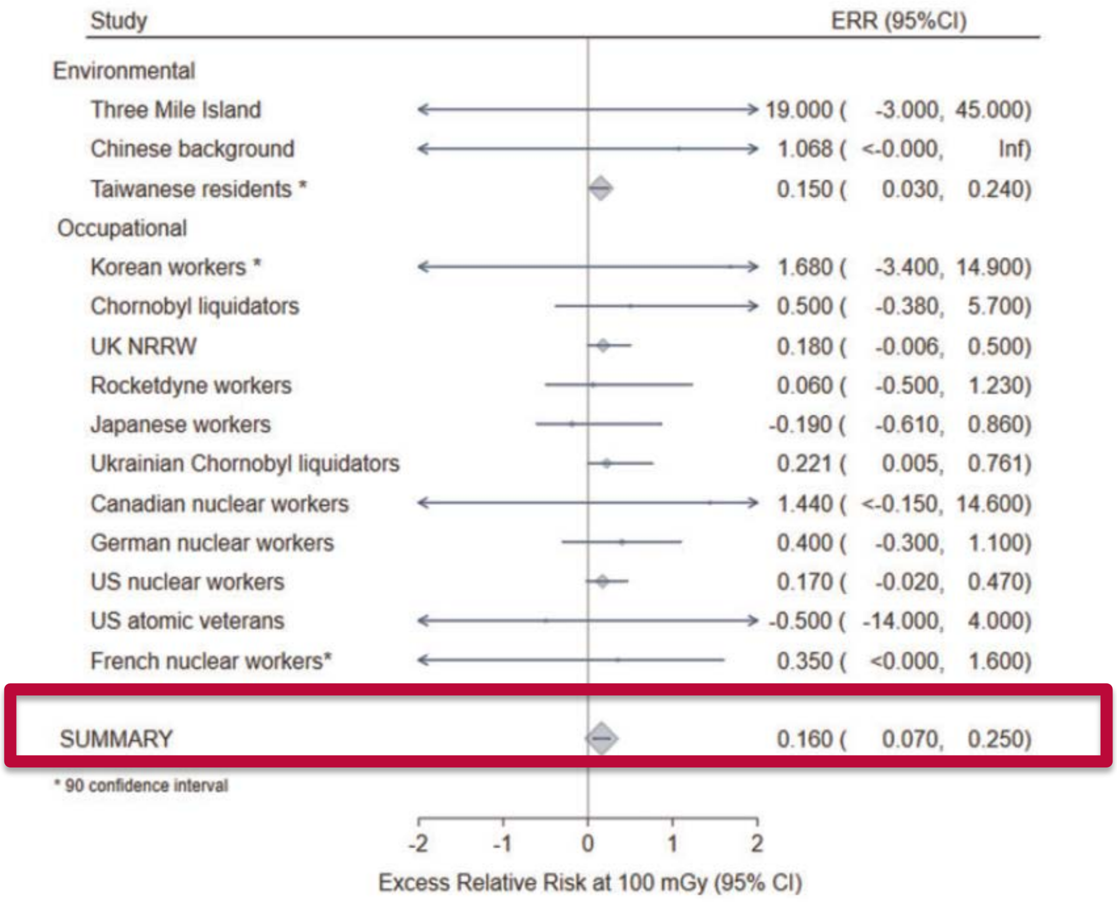
Study	ERR at 100 mGy	(95% CI)	Dose error	Confounding	Outcome misclassification	Could bias adjustment move ERR towards null?
Environmental						
Chernobyl residents	3.2	(0.9 to 8.4)	↑	↑		Yes. Exclusion of subgroup with potential recall bias reduced risk to null.
Three Mile Island	19	(−3 to 45)	↓			No. Adjustment would move ERR away from null.
Chinese background	1.07	(<0 to inf)			↕	Uncertain. Adjustment could move ERR towards or away from null.
GB background	12	(3.0 to 22.0)				
Swiss background	3.6	(−0.3 to 7.7)				
Finnish background	−3	(−11 to 6)				
Taiwanese residents	0.15	(0.03 to 0.24)				
Medical						
French Pediatric CT	1.6	(−2.3 to 2.7)				
UK Pediatric CT	3	(0.3 to 10.9)				
Occupational						
Korean workers	1.68	(−3.4 to 14.9)		↓	↑	Uncertain. Adjustment could move ERR towards or away from null.
Chernobyl liquidators 1	0.5	(−0.38 to 5.70)	↑			Yes. Adjustment possibly moves ERR to null.
UKNRRW	0.18	(0.02 to 0.44)				
Rocketdyne workers	0.06	(−0.50 to 1.23)				
Japanese workers	−0.19	(−0.61 to 0.86)		↓	↓	Yes. Adjustment possibly moves ERR towards null.
Chernobyl liquidators 2	0.22	(0.005 to 0.76)	↑			Yes. Adjustment possibly moves ERR towards null.
Canadian workers	1.44	(<−0.15 to 14.6)				
German workers	0.4	(−0.3 to 1.1)		↓		No. Adjustment would move ERR away from null.
US nuclear workers	0.17	(−0.02 to 0.47)				
INWORKS	0.3	(0.12 to 0.52)				
US atomic veterans	−0.5	(−14 to 4)				
French workers	0.35	(<0 to 1.6)		↓		No. Adjustment would move ERR away from null.

Leukemia: 17 of 20 studies reported + ERRs

Sign test median ERR=0 rejected (p=0.001)

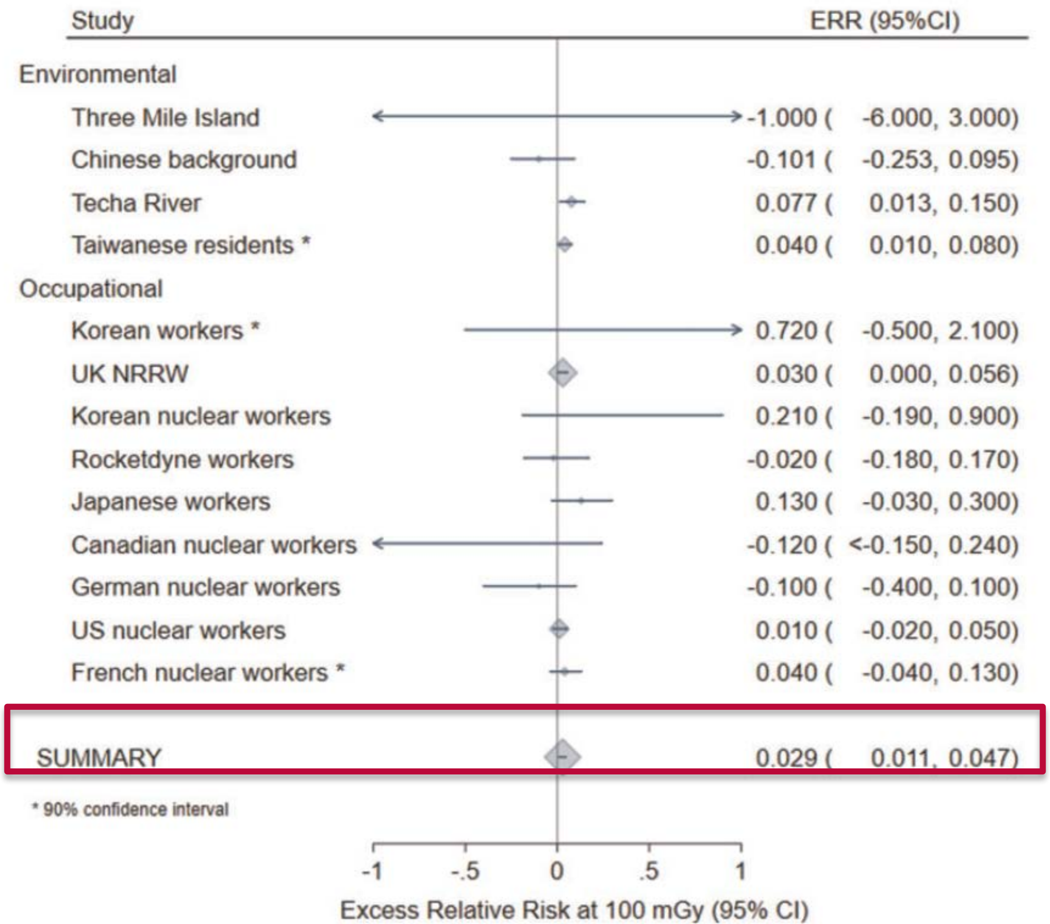
After exclusion of 5 + studies with potential for bias away from null (p=0.02)

Summary: Leukemia after adulthood exposure (ERR at 100mGy)



Consistent with LSS ERR/100mGy
0.08 (0.003-0.19)

Summary: Solid cancers after adulthood exposure



Solid cancers: 16 of 22 studies reported + ERRs

Sign test median ERR=0 rejected (p=0.03)

After exclusion of 4 + studies with potential for bias away from null (p=0.12)

Consistent with LSS ERR/100mGy 0.027 (males)

Overall Summary: Meta-analysis

Table 3. Meta-analysis of excess relative risks (ERR) at 100 mGy for all solid cancers and leukemia

Outcome	No. of studies	ERR at 100 mGy (95% CI)	*P*	Cochran Q (*P*)	I^2
Adult solid cancer	14*	0.055 (−0.0027, 0.112)	.03	37.25 (<.001)	0.65
Adult solid cancer excluding the Canadian cardiovascular imaging study due to heterogeneity	13*	0.029 (0.011, 0.047)	<.001	9.89 (.63)	NA
Adult leukemia	14†	0.160 (0.070 to 0.250)	<.001	4.12 (.99)	NA
Childhood leukemia	6	2.840 (0.370 to 5.320)	.01	6.40 (.27)	0.22

*Excluding INWORKS and site-specific results from US Radiologic Technologists.

†Excluding INWORKS.

Hauptmann et al (JNCI Monograph 2020)

Bradford Hill Criteria for Causality

Consistency	Has it been repeatedly observed by different persons, in different places & time?
Biological gradient	Is there a dose-response?
Biological plausibility	Is there a biological mechanism?
Strength	Strength of the association – although we must not be too ready to dismiss small risks.

Conclusions: systematic review of low-dose radiation epidemiology studies since BEIR VII

Most studies had low potential for bias that would cause spurious positive dose-response

- Non-differential dose error of relatively low magnitude
- Healthy worker survivor bias in occupational studies
- Non-differential outcome misclassification

Results of meta-analyses indicate risk per unit dose that is generally consistent with BEIR VII models

- Leukemia model results suggest that LSS models may underestimate low-dose effects in non-Japanese populations

Implications for dose and dose-rate assumptions

BEIR VII Bayesian analysis of DDREF, 2006

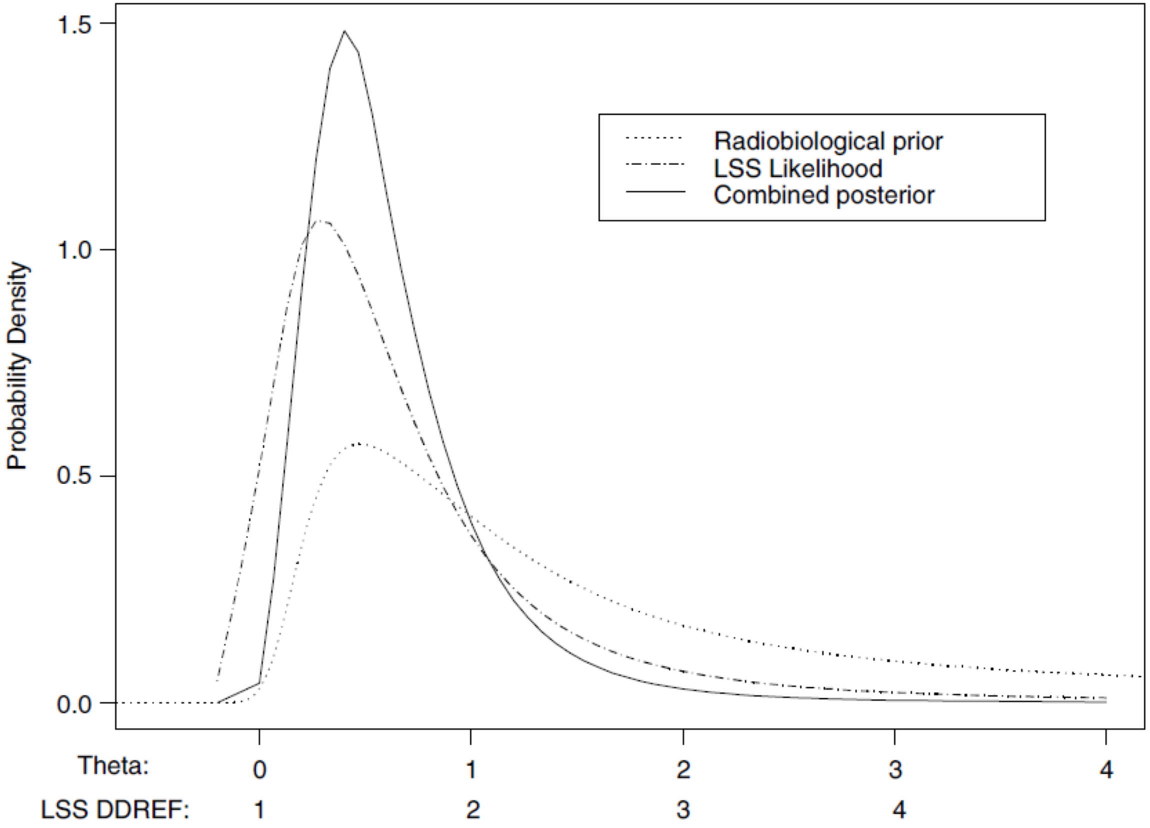


FIGURE 10-3 Results of a Bayesian statistical analysis of dose-response curvature and associated LSS DDREF values. The

Recommendations for Future Work

Quantification of Risk at Low-Doses

- Pooling projects to improve risk estimates
- Eg EPICT, INWORKs

Routine Bias Assessments

- In the original study manuscripts (preferably)
- As part of systematic reviews

Questions?