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INSTITUT DE RADIOPROTECTION ET DE SÛRETÉ NUCLÉAIRE

OVERVIEW OF RECENT EPIDEMIOLOGICAL FINDINGS IN THE FIELD OF LOW DOSES

D Laurier

IRPA 16 conference, Orlando (FL), USA
Refresher Course 2 - Tuesday 9 July 2024

IRPA 16

MEMBRE DE ETSON

Content

- **Radiation Epidemiology**
- Cancer risk
- Non-cancer diseases
- Conclusions and perspectives

Effects of exposure to ionising radiation

Radiobiology

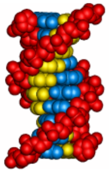
Radiotoxicology

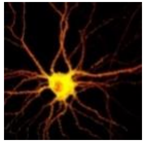
Experimentations in vitro, ex vivo, in vivo

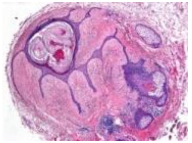
Epidemiology

Ecotoxicology

Molecule → Cell → Tissue → Organism → Population







Effects of exposure to ionising radiation

Deterministic effects
- seriousness is function of the dose
- high doses (> 500 mGy)
- early and specific effects
- threshold model

(rash, burns, modification of blood formula…)

→ Medical Case Reports/Series

Stochastic effects
- frequency is function of the dose
- low and moderate doses
- late and non-specific effects
- no threshold model

(cancers, hereditary effects…)

→ **Epidemiology**

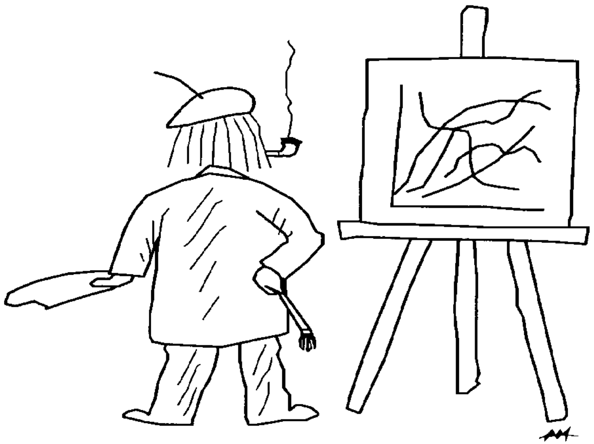
Objectives of epidemiology in the field of ionizing radiation

To identify the effects induced by radiation

To characterize the time sequence between exposure and effect

To quantify the dose-risk relationship

To determine the modifying factors of the relationship



"Which line do you like best ?"

Bands of radiation dose

Terminology for dose bands	*Range of absorbed dose for low-LET radiation*[a, b]	*Scenarios*
High	Greater than about 1 Gy	Typical dose (whole or partial body) to individuals after severe radiation accidents or from radiotherapy
Moderate	About 100 mGy to about 1 Gy	Doses to about 100,000 of the recovery operation workers after the Chernobyl accident (annex D [U14])
Low	About 10 to about 100 mGy[c]	Dose to an individual from multiple whole-body computerized tomography (CT) scans
Very low	Less than about 10 mGy	Dose to an individual dose from conventional radiology (i.e. without CT or fluoroscopy)

Bands (approximate ranges) of total absorbed dose (to the whole body or to a specific organ or tissue of an individual) received in addition to the total from normal background exposure to natural sources of radiation. The bands of radiation dose do not account for the rate at which the dose is delivered.

[UNSCEAR 2012, Annex A, p23, tab 1]

History of epidemiological studies of ionizing radiation

1950	Radiologists (1900-30)
1950	Radium dial painters (1910-30)
1950	Medical exposures for non malignant illnesses, diagnostic exposures (1920-40)
1950	Hiroshima-Nagasaki A-Bomb survivors “Life Span Study (LSS)” (1945)
1960	Miners (uranium) (1940-90)
1970	Population exposed to fallout from atmospheric nuclear weapons (1950-60)
1970	Nuclear workers (1950-)
1980	Population exposed to natural background radiation
1990	Population exposed to releases from the Chernobyl accident (1986)
2000	Children with CT-scan examination (1985)
2011	Population exposed to releases from the Fukushima accident (2011)

Content

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- **Cancer risk**
- Non-cancer diseases
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Study of Hiroshima and Nagasaki A-bomb survivors

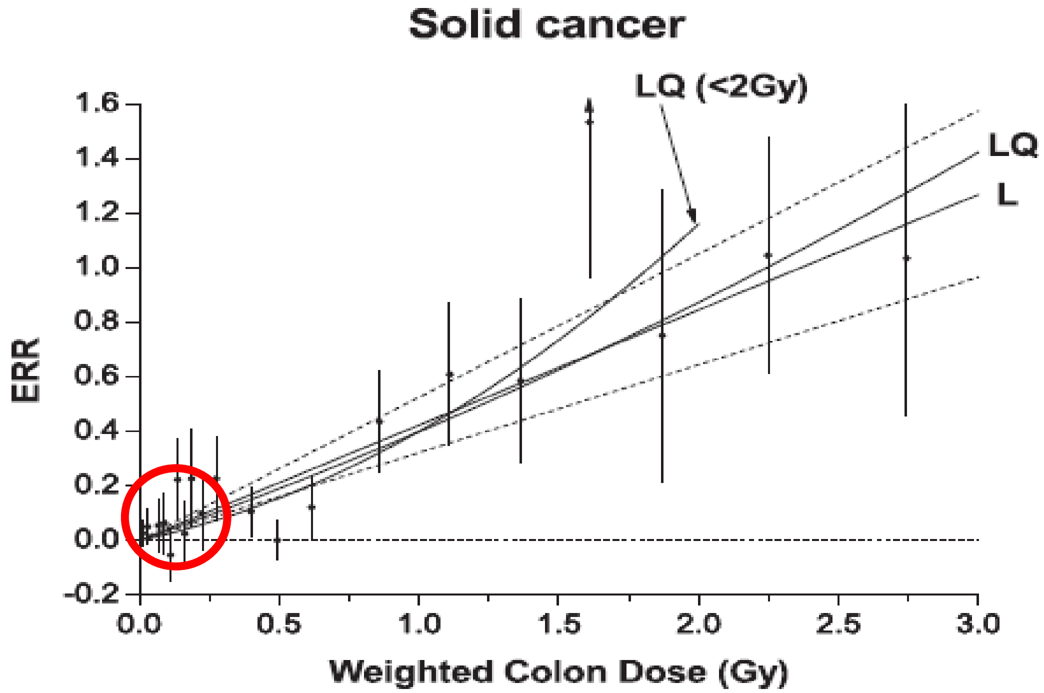
The Life Span Cohort Study (LSS)

- 120 000 individuals alive in 1950
- 86 611 individuals with reconstructed dose
- External irradiation (gamma + neutron) at high dose rate
- 80% of doses lower than 100 mGy
- both sexes - all ages (and *in utero*)
- mortality follow-up from 1950 to 2009
- incidence follow-up from 1958 to 2009

→

radiation induced cancers
estimates of the dose-risk relationship
latency between exposure and increased risk
effect of age
non cancer diseases

Excess relative risk of solid cancer mortality in A-bomb survivors



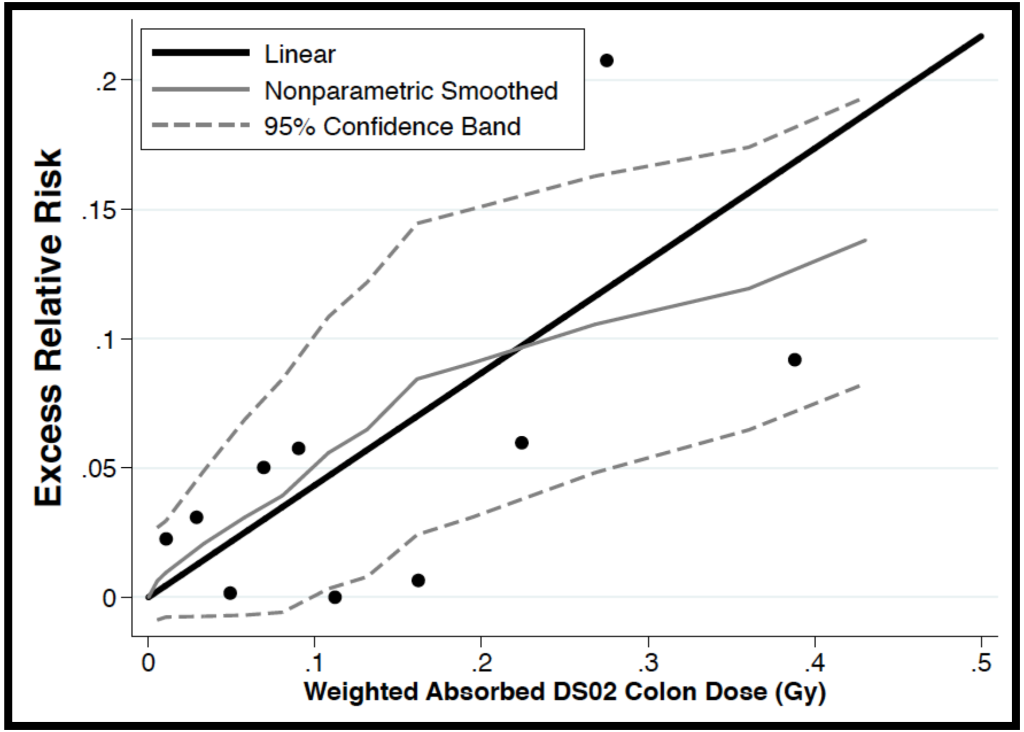
Linear: $\beta(d) = 0.42$

Linear-Quadratic < 2Gy:
$\beta(d) = 0.22$
$\beta(d^2) = 0.18$

Mortality
Follow-up 1950-2003

[Ozasa et al. Rad Res 2012]

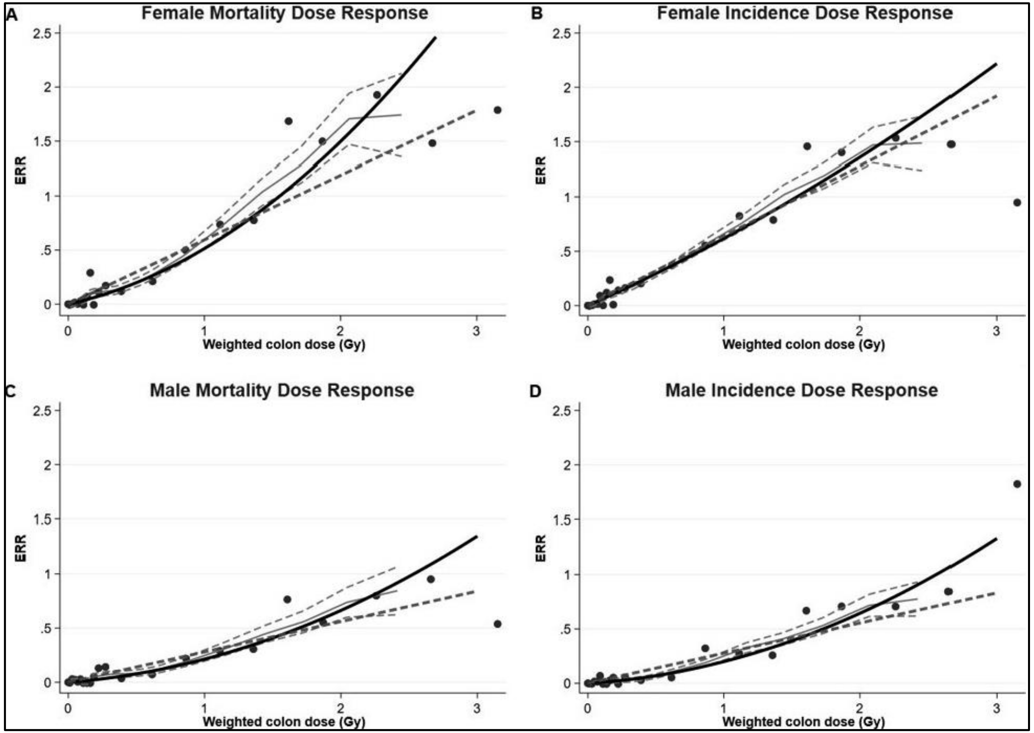
Excess relative risk of solid cancer mortality in A-bomb survivors



[NCRP Commentary No. 27, 2018]

Excess relative risk of solid cancer incidence and mortality in A-bomb survivors

[Brenner et al., Radiat Res 2022]



- 105,444 LSS individuals, follow-up 1958-2009
- > 3 million Person-Years
- 22,538 incident solid cancers
- 15,419 solid cancer deaths

Differences in the shape of the dose-risk relationship when considering all solid cancers aggregated together

The shape of the dose-response depends on the composition of sites comprising the solid cancer group which may differ with dose, age at exposure, and time since exposure.

Underscores the importance of examining shape of dose-response for individual cancer sites.

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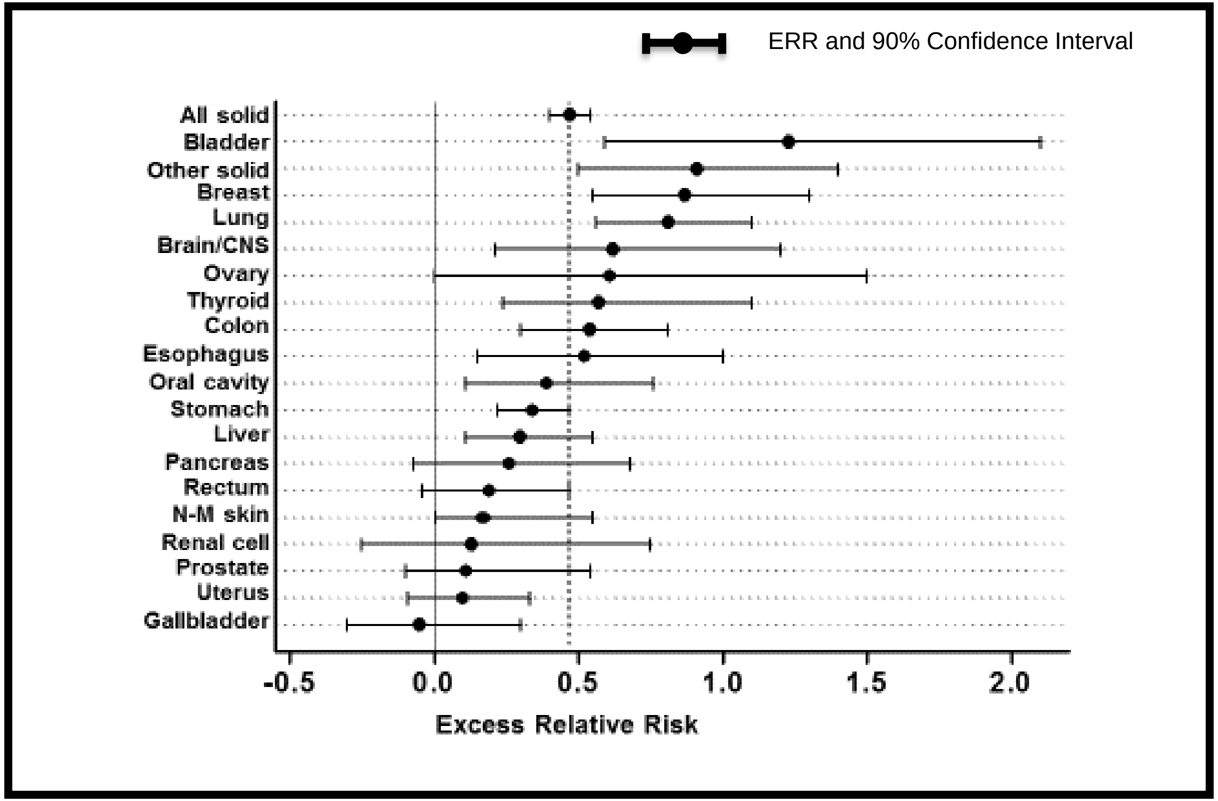
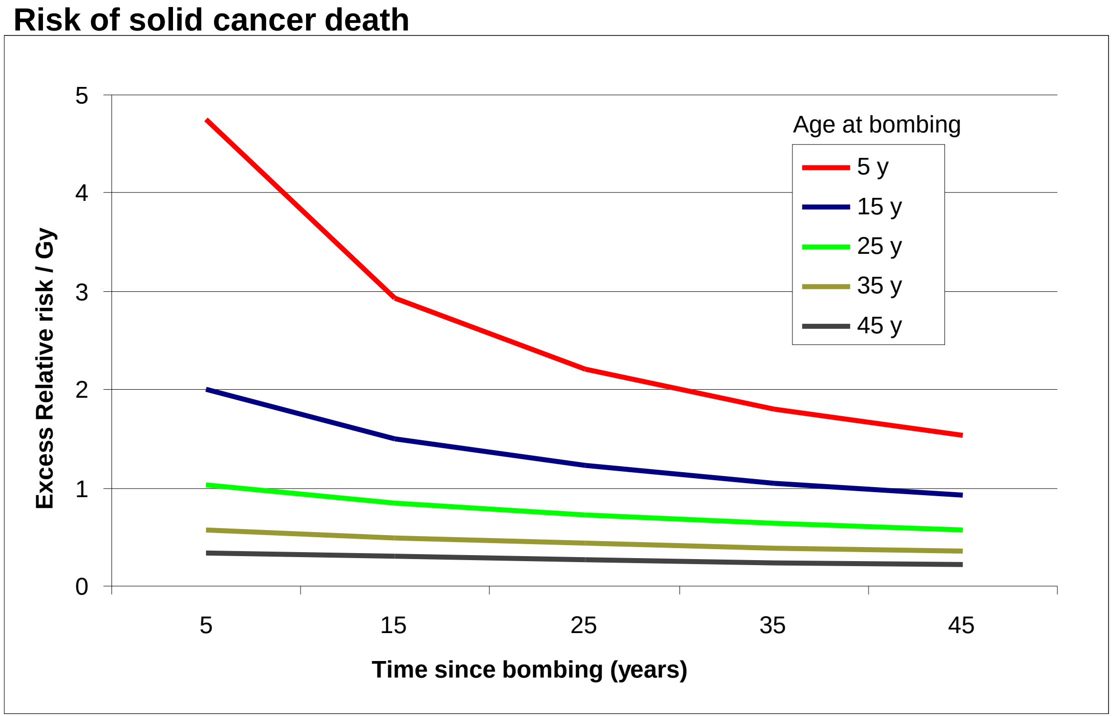
Excess relative risk of specific solid cancers incidence in A-bomb survivors



Incidence
Follow-up 1958-1998
[data from Preston et al. Rad Res 2007; graph from Kamiya et al. Lancet 2015]

Modifying effect of age on solid cancer risk in A-bomb survivors



[from Preston et al. 2003]

Life Span Study – Summary of results

- Still new results 70 years after bombings
- Demonstrated radiation induced risk for many specific cancer sites: leukemia, breast, lung, thyroid, colon cancer…
- The risk of solid cancer et leukemia increases with the dose
- Excess relative risk per unit dose decreases with age at exposure for leukemia and most solid cancers (window of sensitivity during puberty for female breast cancer)
- Latency of a few years (leukemia) to several decades (solid cancer)
- Dose-risk relationship for solid cancer still significant after exclusion of highly exposed individuals
- No element to support the existence of a dose threshold for cancer
- Indications of variation of dose-risk relationship between incidence and mortality, with sex, and with cancer type

- Association with dose for the risk of Heart Disease and Stroke

Studies of nuclear workers

- Well defined populations, since mid 40s
- Large size
- Stable work history and good quality of follow-up
- Individual monitoring of external radiation exposure
- Although some early workers may have received high cumulative doses (some doses ~1 Sv), the pattern is many small doses accumulated at low dose-rates

➡ **Very good capacity to quantify the shape of the dose-risk relationship associated with low dose protracted exposure**

➡ **Epidemiological cohorts first implemented in the 60s**

INWORKS: study population

National cohort
n = 60 697

UK NRRW
n = 147 872

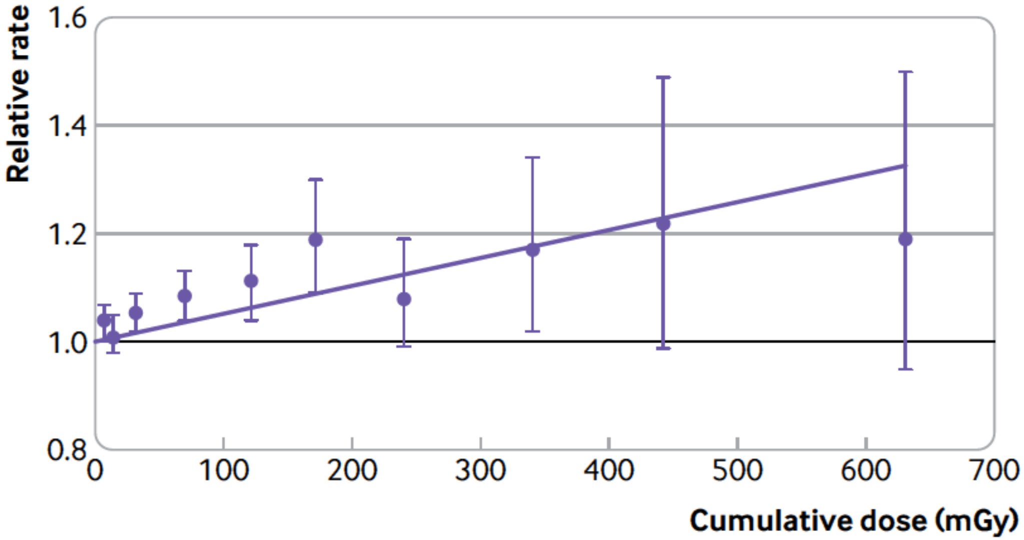
US combined cohort
n = 101 363

309 932 workers employed at least 1 year
and monitored for external exposure to ionizing radiation

Mean duration of employment (y)	15
Mean age at last observation (y)	66
Mean duration of follow-up (y)	34
Total person years (million)	10.7
Mean cumulative whole body dose (Hp10, mSv, exposed)	20
Number of deaths	103 553
solid cancers	28 089
leukaemia (excluding chronic lymphatic leukaemia)	771

INWORKS: Results

Relative rate of mortality due to solid cancer by categories of cumulative colon dose



Bars indicate 90% confidence intervals, and purple line depicts fitted linear model for change in excess relative rate of solid cancer mortality with dose; 10-year lag; * Strata: country, age, sex, birth cohort, socioeconomic status, duration employed, neutron monitoring status

ERR/Gy = 0.52 (90%CI: 0.27; 0.77)
(n=28089)

Indication (not significant) of downward curvature of the dose-risk relationship

[Richardson et al. BMJ 2023]

INWORKS: Results

Restricted dose ranges

Estimates of excess relative rate (ERR) per Gy for death due to solid cancer

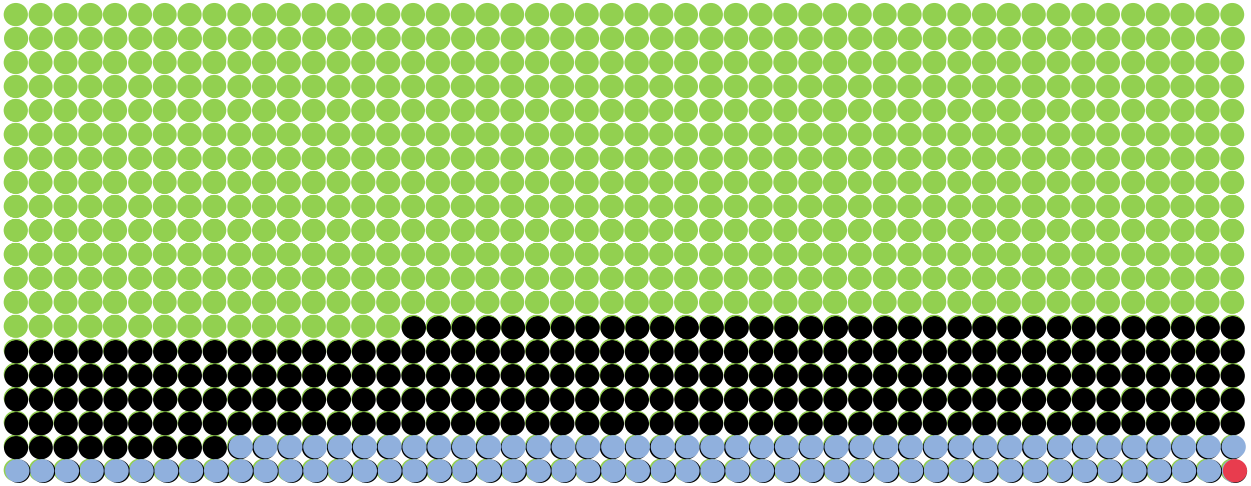
Restricted dose range	Deaths	ERR per Gy†	90% CI	LRT	p
No restriction	28,089	0.52	0.27, 0.77	13.28	<0.001
<400 mGy	27,960	0.63	0.34, 0.92	13.49	<0.001
<200 mGy	27,429	0.97	0.55, 1.39	15.69	<0.001
<100 mGy	26,283	1.12	0.45, 1.80	7.82	0.005
<50 mGy	24,518	1.38	0.20, 2.60	3.74	0.05
<20 mGy	21,293	1.30	-1.33, 4.06	0.66	0.42

10-year lag; *P*: p-value for the reported likelihood ratio test (LRT); †strata: country, age, sex, birth cohort, socioeconomic status, duration employed, neutron monitoring status

[Richardson et al. BMJ 2023]

INWORKS: Calculation of attributable risk

Among 1000 « INWORKS workers »



334 deaths

Out of which 91 by solid cancer

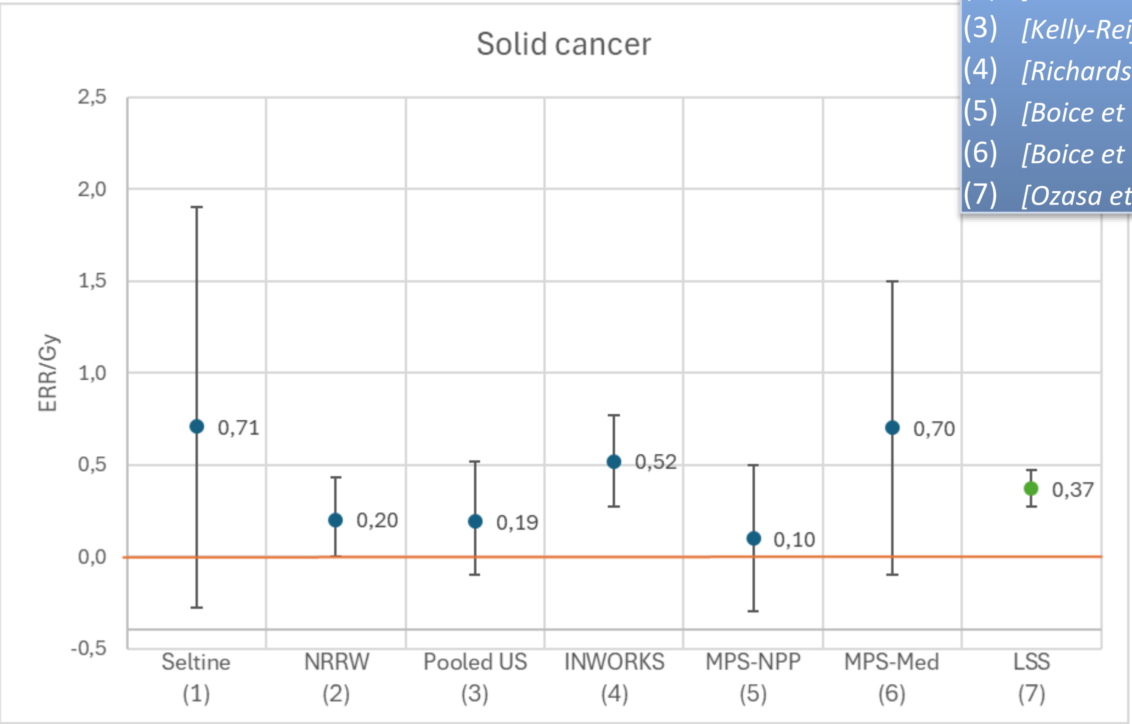
Out of which 1 attributable to radiation exposure

(based on the INWORKS cohort : 309 932 workers with 35 years of follow-up and age at end of follow-up of 66 years)

Comparaison of results of some recent studies: solid cancers

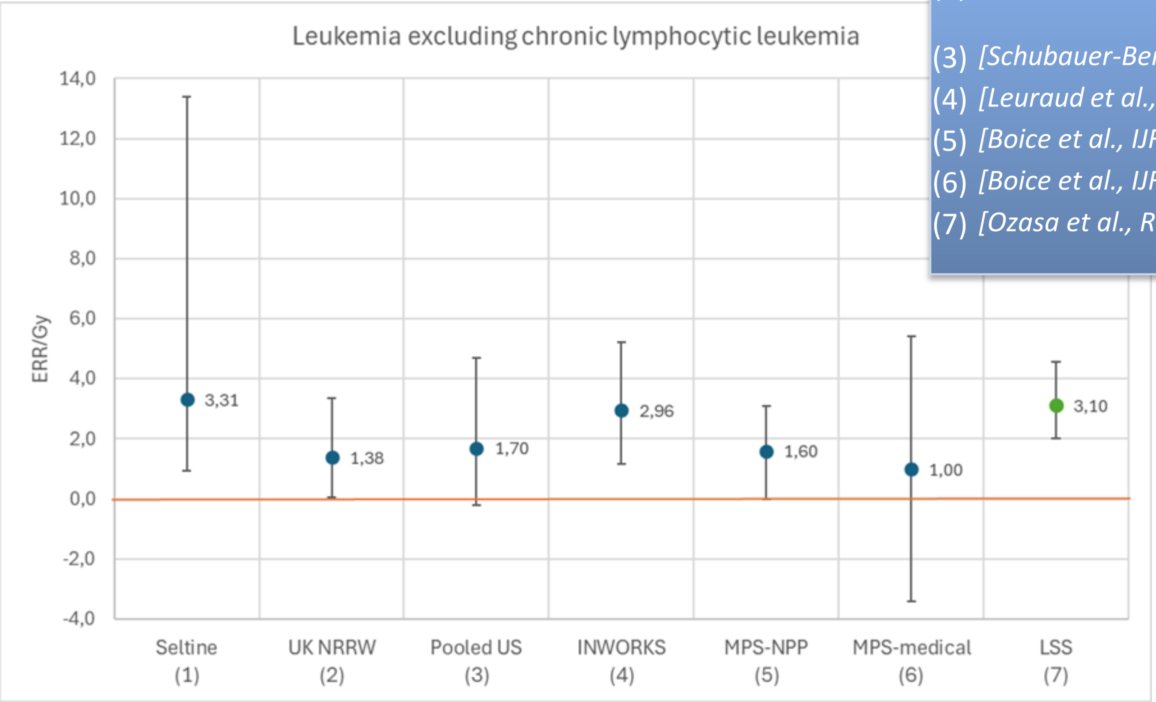
Excess relative rates of death per Gy of cumulative dose and 95% confidence intervals, estimated from a linear model

(1)	*[Laurent et al., Cancers 2023]*	males only
(2)	*[Hunter et al., Radiat Res 2023]*	incidence, dose in Sv
(3)	*[Kelly-Reif et al., Int J Epidemiol 2023]*	90%CI, dose in Sv
(4)	*[Richardson et al., BMJ 2023]*	90%CI
(5)	*[Boice et al., IJRB 2022]*	-
(6)	*[Boice et al., IJRB 2023]*	-
(7)	*[Ozasa et al., Radiat Res 2012]*	age at exposure ≥ 20 y



Comparaison of results of some recent studies: leukemia

Excess relative rates of death per Gy of cumulative dose and 95% confidence intervals, estimated from a linear model



(1)	*[Laurent et al., Cancers 2023]*	males only
(2)	*[Gillies et al., Radiat Res 2019]*	incidence, males only, 90%CI, dose in Sv
(3)	*[Schubauer-Berigan et al., Radiat Res 2015]*	dose in Sv
(4)	*[Leuraud et al., Lancet Haematol 2015]*	90%CI
(5)	*[Boice et al., IJRB 2022]*	-
(6)	*[Boice et al., IJRB 2023]*	-
(7)	*[Ozasa et al., Radiat Res 2012]*	age at exposure ≥ 20 y, all leukemia

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Studies of nuclear workers – Summary of results

- Large increase in information on radiation-disease associations in the last decades
- Pooled studies allow large number of workers and events, test for heterogeneity, and sensitivity analyses

- Overall show a healthy worker effect
- Consolidate the evidence of an excess risk of solid cancer and leukaemia after low-dose protracted exposure to low-LET external radiation
- Contribute to the discussion of some major underlying hypotheses of the system of radiological protection (LNT, DDREF, risk transport…)

- Additional analyses warranted to fully understand factors of variations of the dose-risk relationship in low dose studies (internal exposure, period of hire…)
- New studies (US Million Person Study, South-Korea, Japan…) will provide better sources of information in the future (incidence, occupational exposures, behavioural risk factors, clinical and biological data…)

Studies of pediatric CT-Scans

- CT-Scan is a very useful exam in medical practice: creates a three-dimensional image of the inside of the body
- Increased use for the last 30 years, even in pediatrics (10% of the CTs)
  11 millions of CTs in 2018
- Effective dose about 10 mSv
  58% of the collective dose for only 10% of examinations
- Paediatric exposure: children are more sensitive and have a longer lifespan, radiological protocols not always optimized for children

→ **About 20 studies conducted since 2000**

Pooled analysis of cancer risk after childhood CT-scan

EPI-CT

SEVENTH FRAMEWORK PROGRAMME

Thierry-Chef I et al. Radiat Res 2021
Bernier et al Int J Epidemiol 2019
Bosch de Basea M et al. J Radiol Prot 2015

Record based retrospective cohort study

- Children and young adults who underwent at least 1 CT scan before age 22
- 9 European countries
- Nearly 1 million individuals

Common core protocol

Particular attention to

- Identification and assessment of possible biases/uncertainty
- Individual dose (and uncertainty) reconstruction

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Pooled analysis of brain cancer risk after childhood CT-scan

EPI-CT

- 658,752 individuals followed up at least 5 years from 1st CT - Mean follow-up 7 years (max 30 yrs) - 4.5 M PY
- 165 malignant brain tumors
- 73% with at least 1 head / neck CT
- Mean cumulative dose to the brain 47 mGy (76 mGy in patients with brain cancer)

ERR per 100 mGy of 5-year lagged cumulative brain dose

- All brain cancers: 1·27 (95% CI 0·51–2·69)
- Gliomas: 1·11 (95% CI 0·36–2·59)

Risk estimates significantly elevated when the analysis included doses only up to 50 mGy or patients who only received a single CT examination

Attributable risk: **Per 10 000 people** receiving a single head CT examination (giving an average brain dose of 38 mGy), about **one radiation-induced brain cancer case** is expected 5–15 years after the CT examination

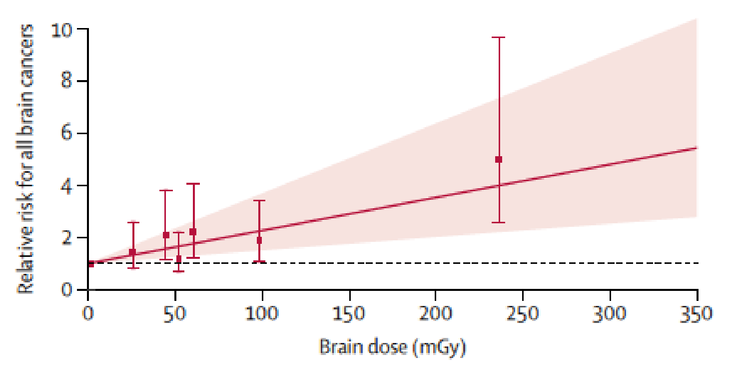


Figure: Relative risks for all brain cancers by cumulative brain dose (lagged by 5 years and with a 5-year exclusion period)

[Hauptmann M et al. Lancet Oncol. 2023]
https://doi.org/10.1016/S1470-2045(22)00655-6

Pooled analysis of the risk of hematological malignancy after childhood CT-scan

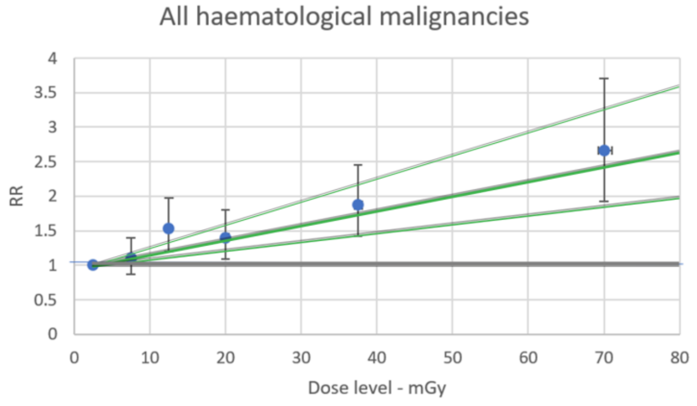
- 876,771 individuals followed up at least 2 years from 1st CT - median follow-up 7.8 years – 6,9 M PY
- 790 cases of haematological malignancies
- 1,331,896 CT-scans (mean 1.5 per individual)
- Mean cumulative active bone marrow dose: 15.5 mGy (20 among cases)

ERR per 100 mGy of 2-year lagged cumulative bone marrow dose

- All hematological malignancies (n=790) 1.96 (95% CI 1.10-3.12)
- Lymphoid malignancies (n=578) 2.01 (95% CI 1.02-3.42
- Myeloid malignancies and AL (n=203) 2.02 (95% CI 0.47-4.77)
- Leukemia excluding CLL (n=271) 1.66 (95% CI 0.43-3.74)

Risk estimates significantly elevated for dose categories > 10 mGy

Attributable risk: **Per 10 000 people** receiving a single CT examination today (ABM dose of 8 mGy), about **1.4 radiation-induced case** of hematological malignancy is expected 2–12 years after the CT examination

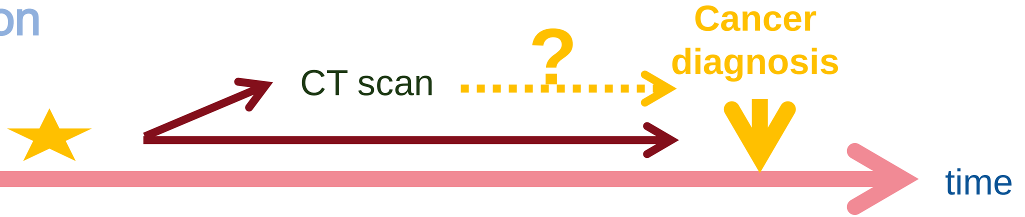


[Bosch de Basea Gomez et al. Nature Medicine 2023]
https://www.nature.com/articles/s41591-023-02620-0

Dose-response analysis in CT-Scan studies: methodological issues

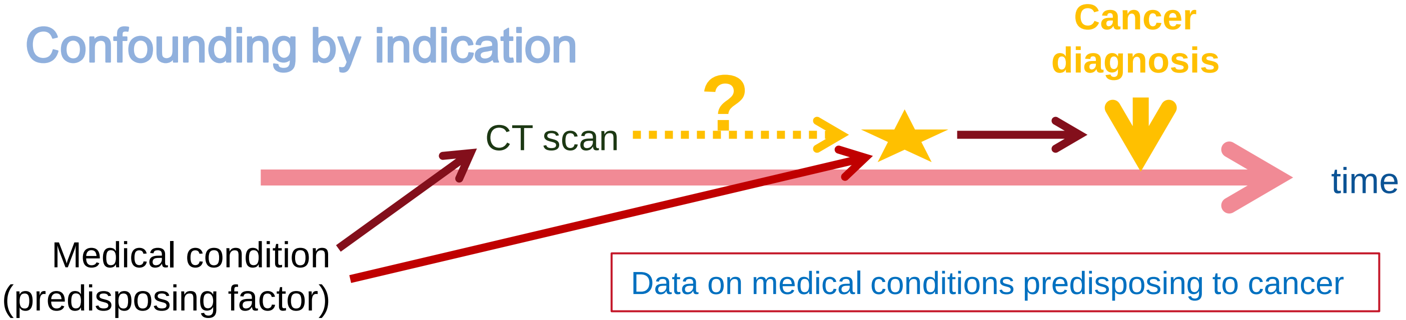
Cancer initiation

Reverse causation



Consider different delays between CT scan and cancer

Confounding by indication



Data on medical conditions predisposing to cancer

French cohort of childhood CT-scans

- Cohort of 103 015 patients born after 1995, exposed to at least 1 CT before age 10
- 159 621 CTs; 73% of patients with only 1 CT
- Mean duration of follow-up: 9.3 yrs
- Mean cumulative dose: brain 28 mGy; ABM 10 mGy
- Collection of individual data on predisposing factors (PF) to cancer (from medical databases and health Insurance sources): PF present in 3.1% of the children

Leukemia		RR per 10 mGy of 2-year lagged cumulative ABM dose	
Whole population	(N=39)	1.16	(95% CI 1.07-1,26)
Patients without PF	(N=35)	1.17	(95% CI 1.09-1.26)
Patients with PF	(N= 4)	0.27	(95% CI 0.02-3.49)

Brain tumor		RR per 10 mGy of 5-year lagged cumulative ABM dos	
Whole population	(N=75)	1.06	(95% CI 1.01-1.09)
Patients without PF	(N=50)	1.05	(95% CI 1.02-1.09)
Patients with PF	(N=25)	1,03	(95% CI 0.96-1.12)

⇨ **Statistically significant dose-risk relationships in patients without PFs for CNS tumors and leukemia**

[Foucault et al, Eur Radiol 2022]

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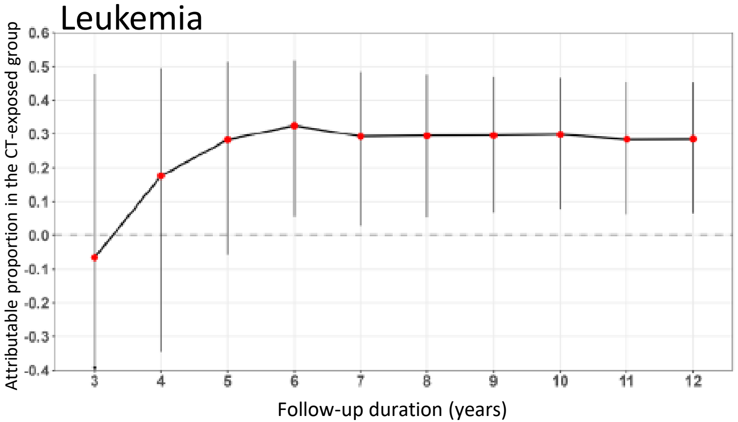
Korean study of hematologic malignant neoplasms risk after childhood head CT-scan

- Nationwide population-based cohort based on the South-Korea Health Insurance System
- 2,4 M patients of age 0-19 years with minor head trauma – mean follow up 6.5 years – 14.8 M PY
- Comparison of the frequency of hematologic malignant neoplasms between patient with / without scan
- Mean dose to red bone marrow: 4,7 mGy – lag period of 2 years

- CT-exposed group: 216 000 patients – 100 cases (66 leuk)
- Non-exposed group: 2195 000 patients – 808 cases (537 leuk)
- IRR hemato neoplasm = 1·29 (95% CI 1.03–1.60)
- IRR leukemia = 1.40 (98.3% CI 1.05–1.87)

- Limits: no individual dose
- Advantages: large numbers, control of the indication for the CT use



➡ **Radiation exposure from head CTs in children and adolescents with minor head trauma is associated with an increased incidence of hematologic malignant neoplasms**

[Lee et al. European Radiology 2024]
https://doi.org/10.1007/s00330-024-10646-2

Childhood CT-scan studies – summary of results

Advantages

- Very comprehensive statistical analysis of large datasets
- Multitude of sensitivity analyses addressing a number of concerns

Limits

- Potential bias: reverse causation & confounding by indication. Some studies with information about predisposing factors or controlling for indication still observe an increased risk
- Short duration of follow-up: Extension of follow up necessary to understand age trends
- Heterogeneity of risk estimates between countries or cancer type

Interpretation

- Results strengthen the evidence of a cancer risk following low doses
- Some results (variation of risk with age at exposure, association for NHL) need further investigation
- Extension of follow-up needed, especially to better understand the impact of age

Radiation epidemiology: results at low dose / dose rate

Solid cancers – INWORKS
Pooled analysis - 3 cohorts of workers - n > 308000
[Richardson et al. BMJ 2015; Richardson et al. BMJ 2023]

Solid cancers – ICRP TG91
Meta-analysis – 22 Low Dose Rate studies – n > 900000
[Shore et al IJRB 2017]

Thyroid cancer – PIRATES
Pooled analysis - 9 cohorts of children - n > 107000 - low-dose (< 200 mGy)
[Lubin et al. JCEM 2017]

Leukemia (excluding CLL)
Pooled analysis - 9 cohorts of children - n = 262000 - low-dose (< 100 mSv)
[Little et al. Lancet Haematol 2018]

Solid cancers – NCI Monograph
Meta-analysis – 22 studies – Mean dose < 100 mSv
[Hauptmann et al. JNCI Monog 2020]

Brain tumors and hematological malignancies – Epi-CT
Pooled analysis - 9 cohorts of children - n > 658000 – CT scans
[Hauptmann et al. Lancet Oncol 2023; Bosch de Basea et al. Nature Med 2023]

➡ **Significant association when excluding doses above 100 mGy**

Implications of recent epidemiologic studies for the linear-nonthreshold model and radiation protection

NCRP Commentary n°27, 2018

Critical review of recent studies (10y)

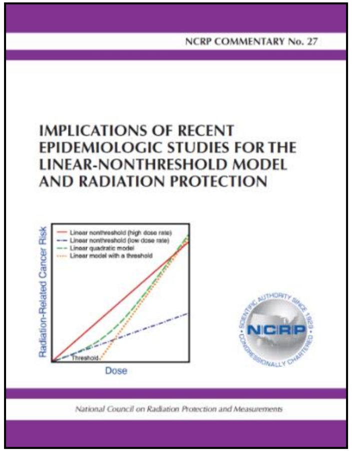
- 29 studies (occupational, medical, environmental)

Systematic application of quality criteria

- Epidemiology - Dosimetry – Modelling
- Composite score of specific strengths and weaknesses

Overall evaluation of the support to LNT

- Most of the quantitative low dose-rate epidemiological data broadly support a LNT model for total solid cancer and leukemia.



[NCRP 2018; Shore et al J Radiol Prot. 2018]

➡ **The LNT model, perhaps with a DREF >1, is prudent and practical for radiation protection purposes**

Content

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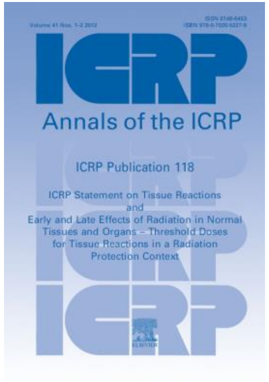
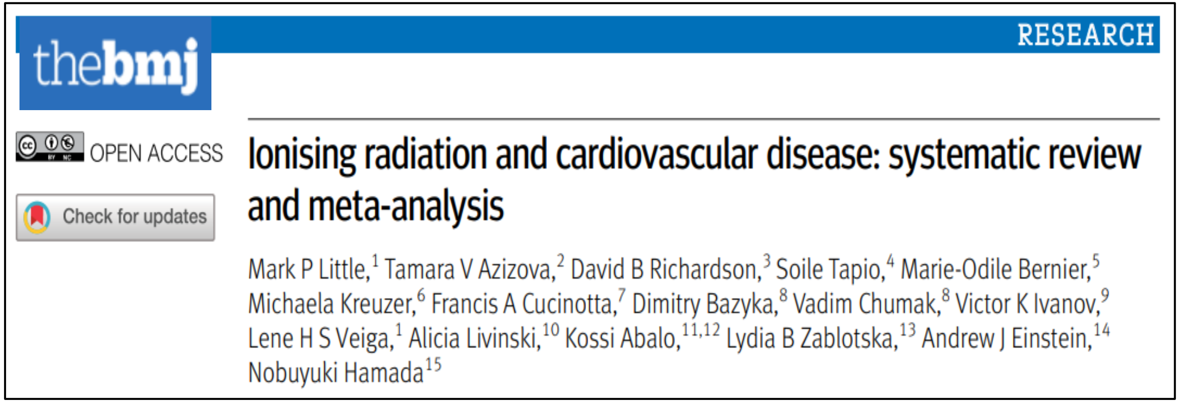
Risk of diseases of the circulatory system



Classification of cardiovascular diseases as a tissue reaction
with a dose threshold at 0.5 Gy by ICRP in 2012


thebmj RESEARCH

OPEN ACCESS

Check for updates

Ionising radiation and cardiovascular disease: systematic review and meta-analysis

Mark P Little,[1] Tamara V Azizova,[2] David B Richardson,[3] Soile Tapio,[4] Marie-Odile Bernier,[5] Michaela Kreuzer,[6] Francis A Cucinotta,[7] Dimitry Bazyka,[8] Vadim Chumak,[8] Victor K Ivanov,[9] Lene H S Veiga,[1] Alicia Livinski,[10] Kossi Abalo,[11,12] Lydia B Zablotska,[13] Andrew J Einstein,[14] Nobuyuki Hamada[15]

[Little BMJ 2023]

- Systematic review and meta-analysis
- 93 relevant studies
- Cardiovascular disease + 4 major subtypes (ischemic heart diseases, other heart diseases, cerebrovascular diseases, all other cardiovascular diseases)

Risk of diseases of the circulatory system

- Relative risk increased with dose for all cardiovascular dis and for the 4 subtypes
- Interstudy heterogeneity reduced when restricted to moderate doses (<0.5 Gy) or low rates (<5 mGy/h)

"Results provide evidence supporting a causal association between radiation exposure and cardiovascular disease at high dose, and to a lesser extent at low dose, with some indications of differences in risk between acute and chronic exposures, which require further investigation"

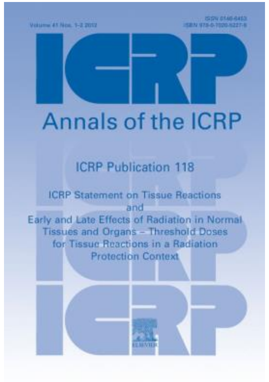
"Studies are needed to assess in more detail modifications of radiation effect by lifestyle and medical risk factors"

[Little BMJ 2023;380:e072924]

"Evidence for cardiovascular disease will soon need to be added to the existing list of radiation induced health risks. The consequences will be extensive: concepts and standards in radiological protection will need to be revisited by national and international professional and radiation protection organisations"

[Auvinen BMJ 2023;380:e074589]

Risk of cataract / lens opacity



Classification of cataracts as a tissue reaction

with a dose threshold at 0.5 Gy by ICRP in 2012

Several recent syntheses

[Hamada BJR 2020; Ainsbury Environ Int 2021; Little IJRB 2022]

Review of epidemiological results (12 studies since 1999)

- Accumulating evidence of excess risks at lower dose and low dose rate in various cohorts (Chernobyl liquidators, US Radiologic Technologists and Russian Mayak nuclear workers)
- Radiation-associated excess risk of both posterior subcapsular and cortical cataract
- Significant excess risk under 100 mGy in the USRT cohort

➡ **Results ”bordering on inconsistency” with the current classification**

[Little IJRB 2022]

Risk of neurocognitive diseases

Central nervous system diseases after adult exposure [Lopes Brain Sc 2022]

- Meta-analysis of 21 studies (Chernobyl cleanup workers, nuclear workers, miners, aircrew, medical staff, test veterans, medical patients)
- Significant positive excess relative risk at 100 mSv found for Parkinson's disease (4 studies)

➡ **"Findings suggest that adult low-to-moderate IR exposure may have effects on non-cancerous CNS diseases"**

Risk of dementia (Alzheimer's and Parkinson's disease) [Srivastava Rad Res 2023]

- Meta-analysis of 18 studies (nuclear workers, medical staff)
- Significant positive relative risk (>100 mSv) found for dementia and Parkinson's disease

➡ **"Results provide evidence that exposure to ionizing radiation increases the risk of dementia"**

Caution needed in interpreting the results
(small number of studies, variation in results…)

Hereditary effects

- Genetic effects observed at moderate to high doses among animals
- Risk of genetic damage from radiation introduced in the ICRP recommendations (*ICRP 1956*), considered as stochastic effects (*ICRP 1977*)

- Review of more than 130 epidemiological studies published over the last 30 years

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A systematic review of human evidence for the intergenerational effects of exposure to ionizing radiation

Jade Stephens[a], Alexander J. Moorhouse[a,b,c*], Kai Craenen[a], Ewald Schroeder[a], Fotios Drenos[a], and Rhona Anderson[a]

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Intergenerational effects of ionizing radiation: review of recent studies from human data (2018–2021)

A. Amrenova[a], C. Baudin[a], E. Ostroumova[b], J. Stephens[c], R. Anderson[c], and D. Laurier[a]

- Large heterogeneity of endpoints, and limitations of epidemiological studies
- No coherent evidence of effects in the offspring of exposed human populations
- "If adverse health effects do arise in children of exposed parents, then these effects are small and difficult to reproducibly measure"

Non-cancer effects – summary of results

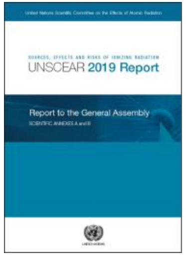
- Increasing number of epidemiological results on non-cancer long-term health effects in the last decades
- Suggestion of evidence of dose-risk relationships in the moderate to low dose-range, especially for lens opacities and diseases of the circulatory system
- Large heterogeneity of results, lack of knowledge on potential biological mechanisms
- Several expert groups currently reviewing the scientific literature, and assessing the potential impact on the System of radiological protection (UNSCEAR, ICRP)

Content

- Radiation Epidemiology
- Cancer risk
- Non-cancer diseases
- **Conclusions and perspectives**

Limitations of low dose epidemiology

- Low dose studies are **difficult** to design, conduct, and reliably interpret
- **Limitations** in all studies
  - LSS (Japanese population, acute exposure, neutron RBE…)
  - Workers (early years, neutron and internal exposures…)
  - CT-scan (reverse causation, indication, duration of exposure…)
- **Biases** at low doses are not major (NCI Monograph 2020)
- Impact of **uncertainties** can be quantified (UNSCEAR 2019)
- Interest of **pooled data and meta-analyses**
  (common design, statistical power, test of heterogeneity)



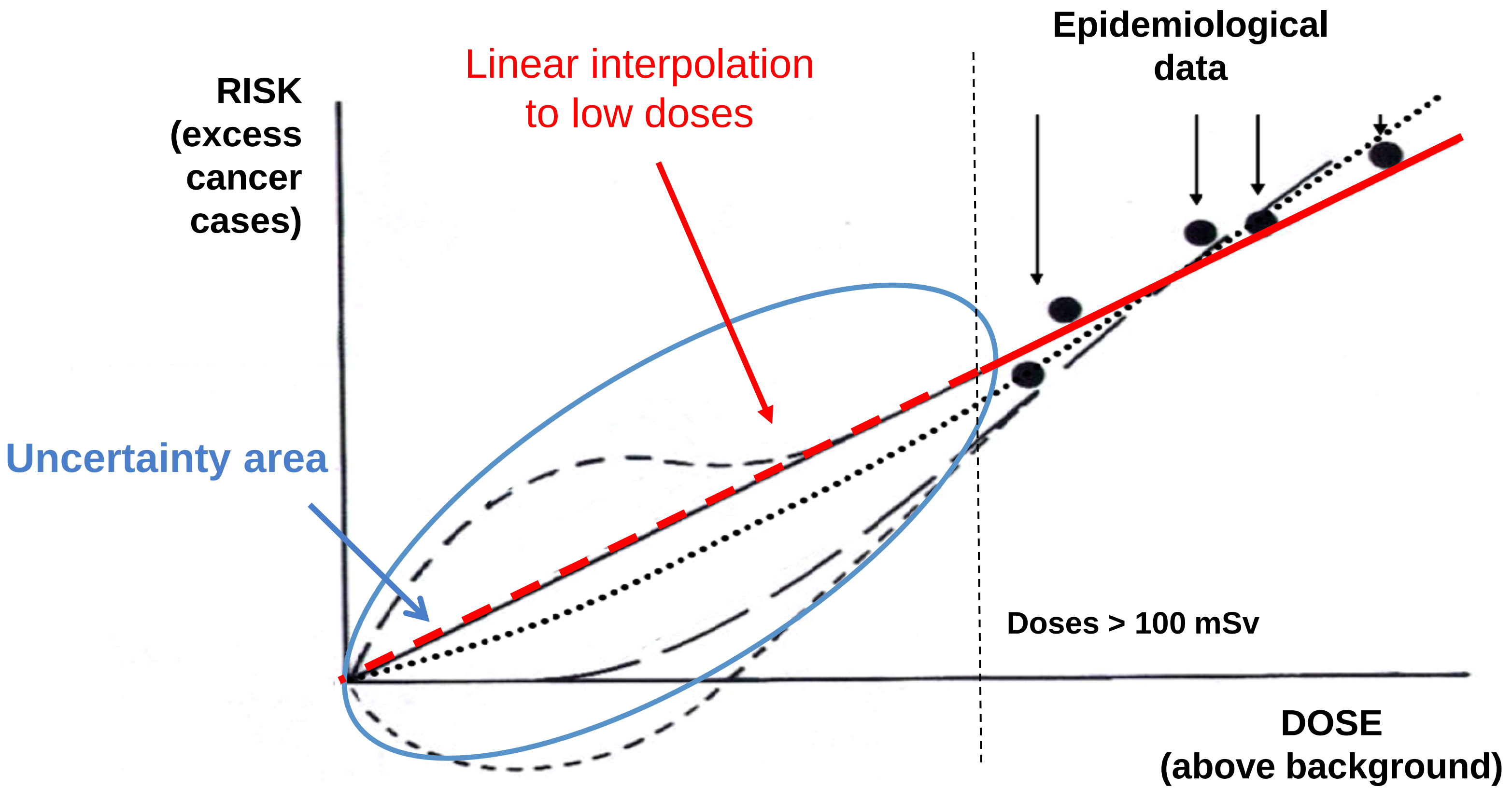
Radiation epidemiology: lacks of knowledge

- Uncertainties on the **shape of the dose-risk relationship** at low dose and dose-rate
- **Not all results are coherent** (background radiation studies…)
- **Variation** of radiation-induced cancer risk **between individuals/populations**
- Effects of **internal exposures**
- Risks of long term **non-cancer diseases** at low to moderate doses
- **Interactions** between radiation and other risk factors (exposome)
- Consistency of results between **epidemiology and radiobiology**

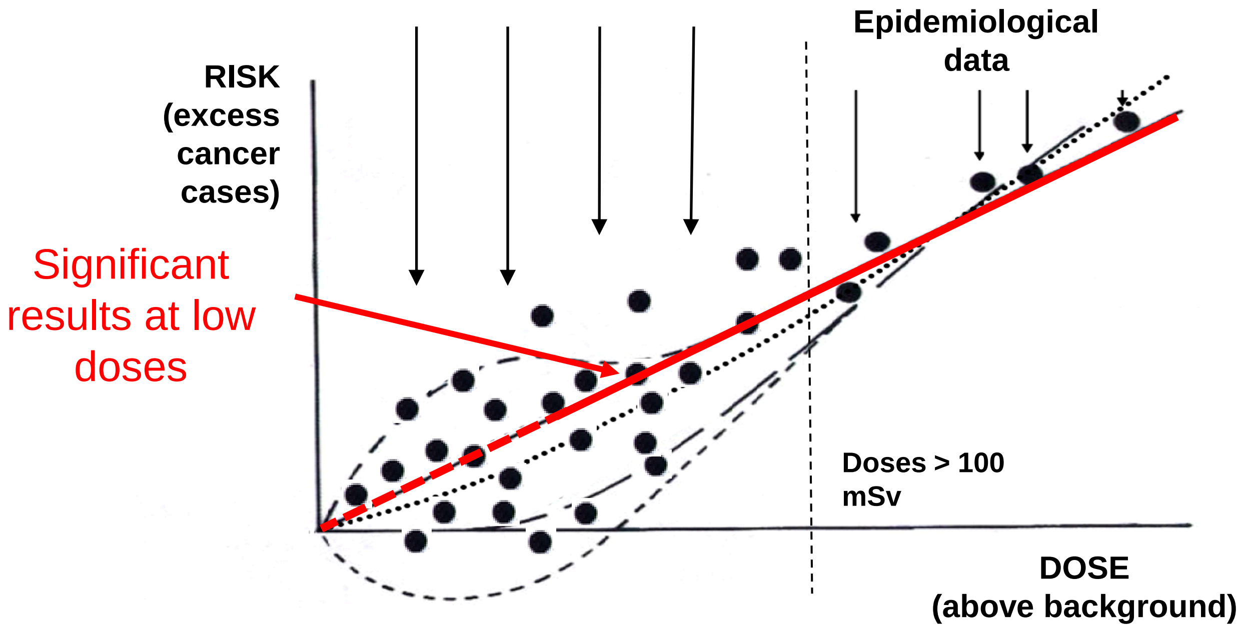
Low dose epidemiology: obtained results on cancer risks

- Clear **improvement in knowledge in the last 2 decades** about cancer risks associated with low doses
- There is **some evidence of some excess risk of some cancers** following low-level exposure to radiation
- There is some evidence of an **increased risk of cancer with repeated or protracted dose**
- **Low doses** are associated with **low excess risks**
- The epidemiological evidence for an overall material deviation from a **linear no-threshold dose-response at low doses or low dose-rates** is not persuasive

Dose response relationship: interpolation of epidemiological observations toward low doses



Dose response relationship: epidemiological observations at low doses



Radiation epidemiology: support for radiological protection

- **Shape of the dose-risk relationship at low doses and dose rates** (model for specific cancer sites, LNT, DDREF) - At present, the standard (LNT) risk model is the most parsimonious description of the available scientific evidence
- **Modifying effects of the dose-risk relationship** (sex, age at exposure, genetic specificity…)
- **Differences between populations** (baseline rates, multiplicative or additive transfer, specific exposure situations)
- **Non-cancer effects at low doses** (Diseases of the Circulatory System, cataracts, cognitive effects, effects among offspring)

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Thank you for your attention

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Enhancing nuclear safety