CoI

No conflict of interest to disclose

Plausible dose-response relationships for cancer risk in the very low, low and moderate dose ranges
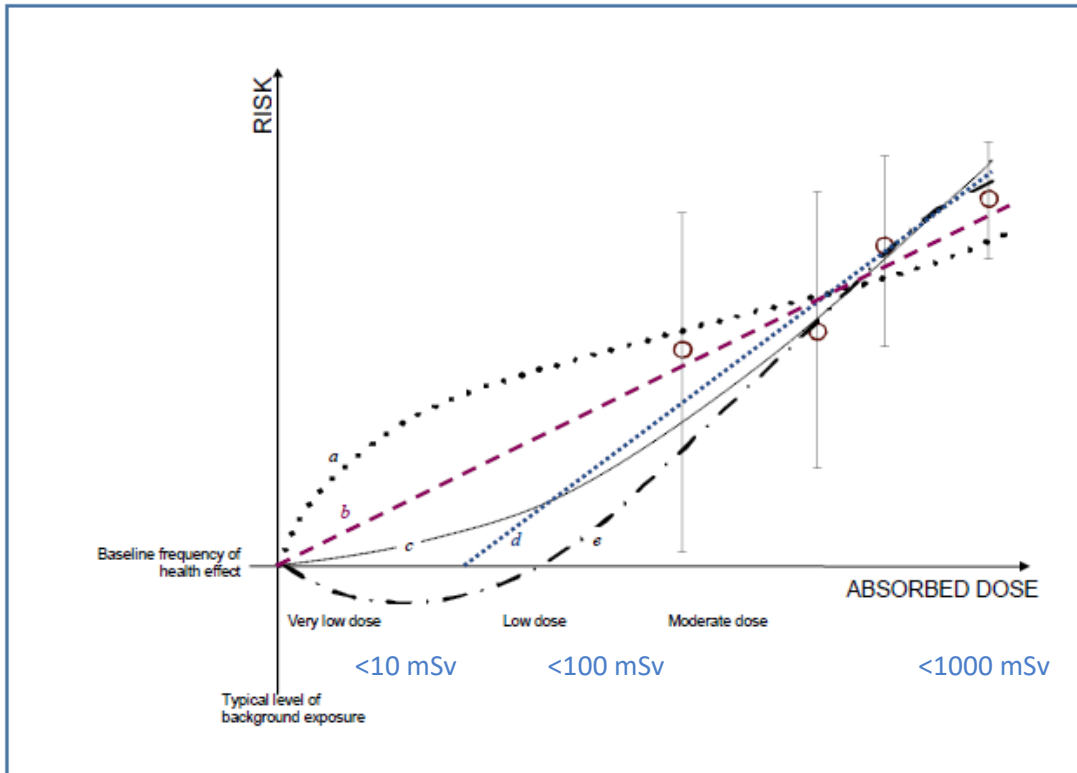
[UNSCEAR report 2012 Annex A (fig 1), 2015]

Doses are considered in addition to baseline exposure (natural sources)

Points (and confidence intervals) represent observations of increased cancer incidence at moderate doses

The different curves represent plausible dose-response relationships for low and very low dose exposures: (a) supralinear; (b) linear without threshold (LNT); (c) linear-quadratic; (d) threshold and (e) hormetic (natural sources)Points (and confidence intervals) represent observations of increased cancer incidence at moderate doses The different curves represent plausible dose-response relationships for low and very low dose exposures: (a) supralinear; (b) linear no-threshold (LNT); (c) linear-quadratic; (d) threshold and (e) hormetic

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

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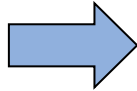
radiation induced cancers
estimates of the dose-risk relationship
latency between exposure and increased risk
effect of age
non cancer diseases

Life Span Study - dose-risk relationship

Excess relative risk of solid cancer in A-bomb survivors

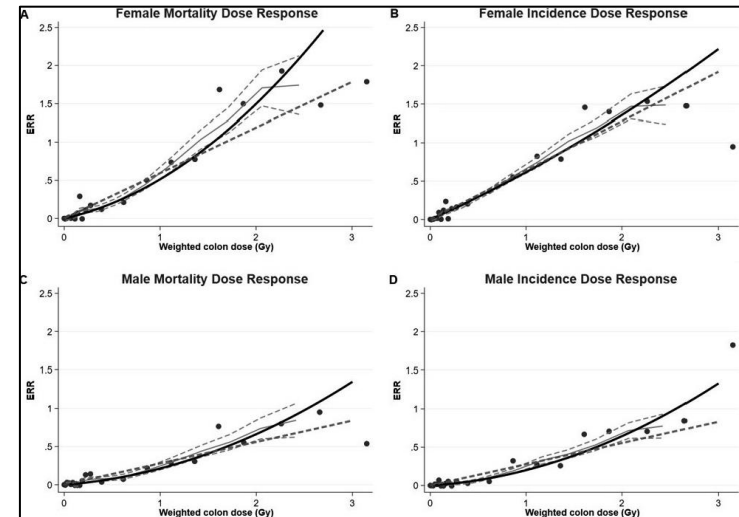**Incidence** [Grant *et al., Radiat Res* 2017]
- Sex-averaged model significant on the range 0-100 mGy
- No evidence against a threshold of zero

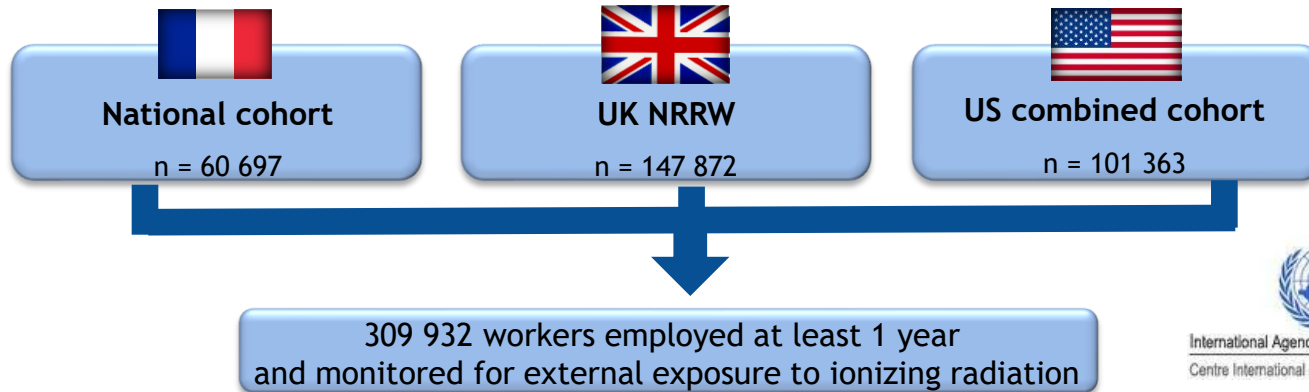**Incidence and mortality** [Brenner et al., Radiat Res 2022]
- Differences in the shape of the dose risk relationship between men and women and between incidence and mortality

➡ **The shape of the dose-response depends on the composition of sites comprising all solid cancer group and age at exposure or time**

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**

International Agency for Research on Cancer
Centre International de Recherche sur le Cancer

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

IRSN

INWORKS - Dose-risk relationship

Relative rate of mortality due to solid cancer
by categories of cumulative colon dose
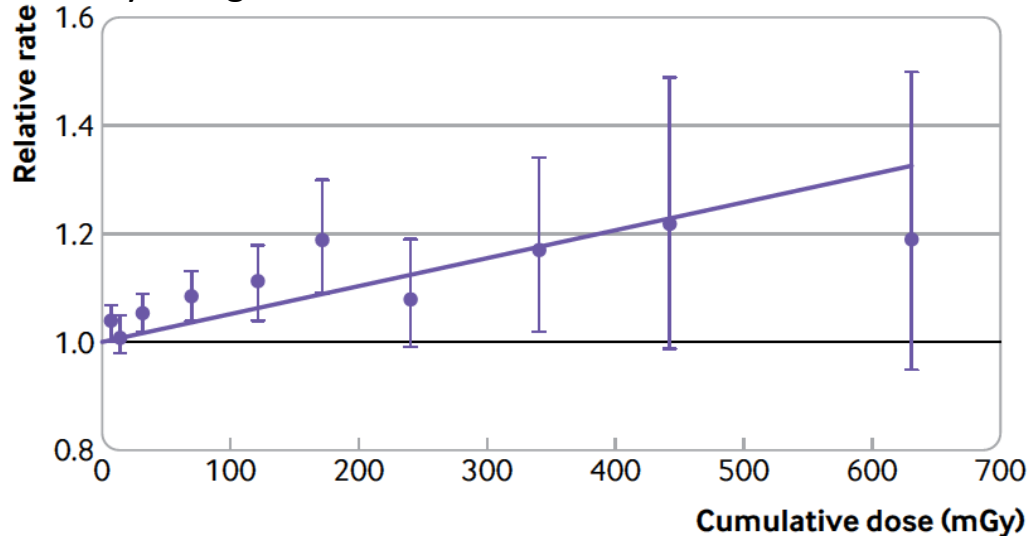
ERR/Gy = 0.52 (90%CI: 0.27; 0.77)

Relationship still significant when dose range is restricted to < 100 mGy

Indication of downward curvature of the dose-risk relationship

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

[Richardson et al. BMJ 2023]
https://www.bmj.com/content/382/bmj-2022-074520

INWORKS - Calculation of attributable risk

Among 1000 « INWORKS workers »
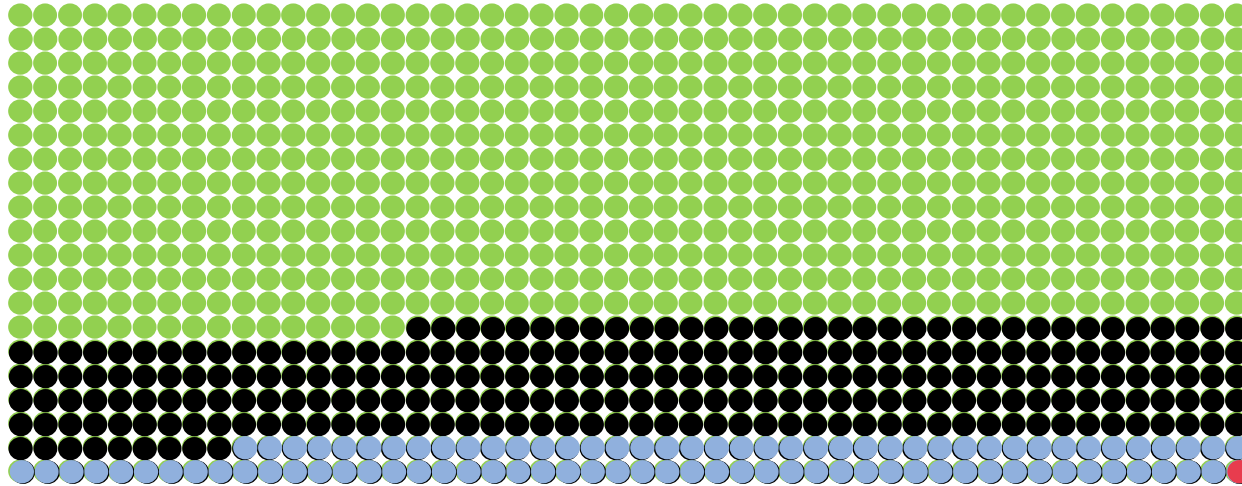
334 deaths

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)

INWORKS – Summary of results

- **Significant dose-risk relationship** for mortality from solid cancer associated with repeated external exposure to ionising radiation

- Risk coefficient **compatible with** that of **A-bomb survivors**

- **Consistent results** (no heterogeneity between countries, little variation in sensitivity analyses)

- **Low attributable risk** (about 1% of all observed cancers)

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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

Norway 20 000
Sweden 95 000
Denmark 30 000
UK 400 000
Netherlands 40 000
Germany 140 000
Belgium 30 000
France 100 000
Spain 200 000

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Pooled analysis of brain cancer risk after childhood CT-scan

- 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
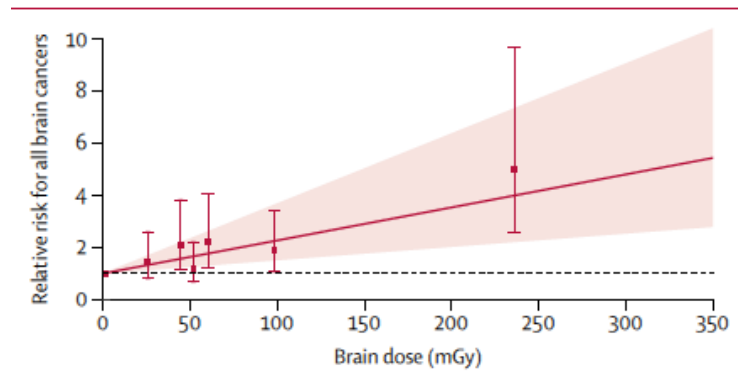

Figure: Relative risks for all brain cancers by cumulative brain dose (lagged by 5 years and with a 5-year exclusion period)

[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 (dose of 8 mGy), about **1.4 radiation-induced case** of hematological malignancy is expected 2–12 years after the CT examination

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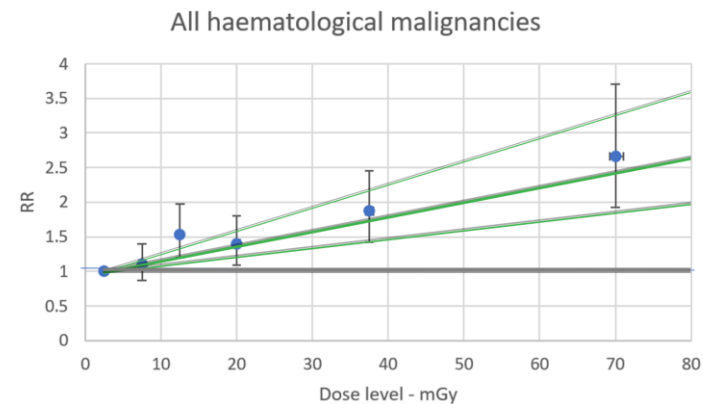
[Bosch de Basea Gomez et al. Nature Medicine 2023]
https://www.nature.com/articles/s41591-023-02620-0

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

Leukemia

Radiation exposure from head CTs in children and adolescents with minor head trauma is associated with an increased incidence of hematologic malignant neoplasms
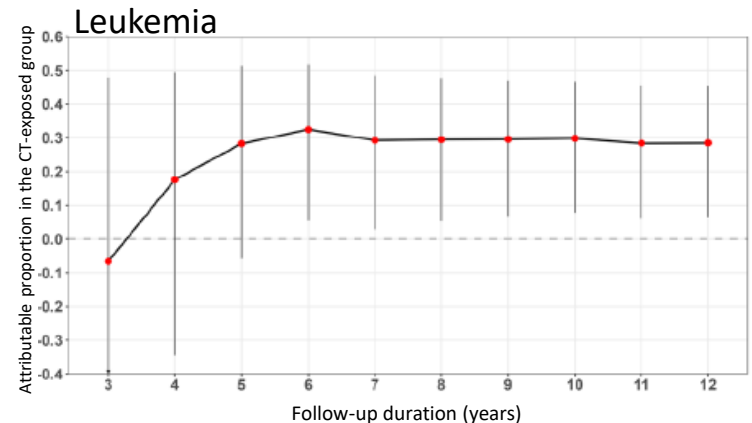
[Lee et al. European Radiology 2024]
https://doi.org/10.1007/s00330-024-10646-2

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Pooled analysis of cancer risk after childhood CT-scan - Discussion

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

IRSN

Radiation epidemiology: results at low dose and low 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)

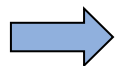[Little et al. Lancet Haematol 2018]

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

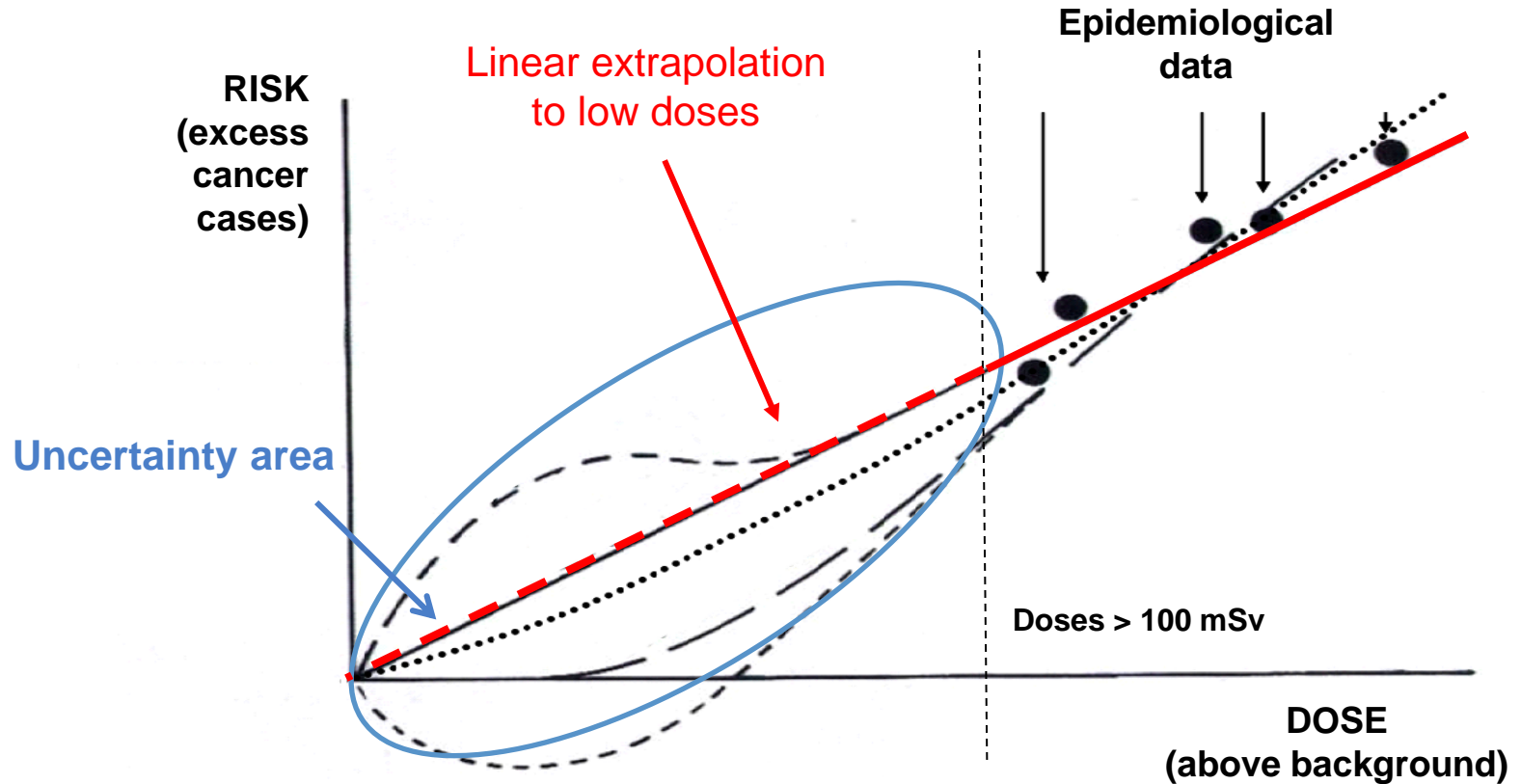[Hauptmann et al. Lancet Oncol 2023; Bosch de Basea et al. Nature Med 2023]

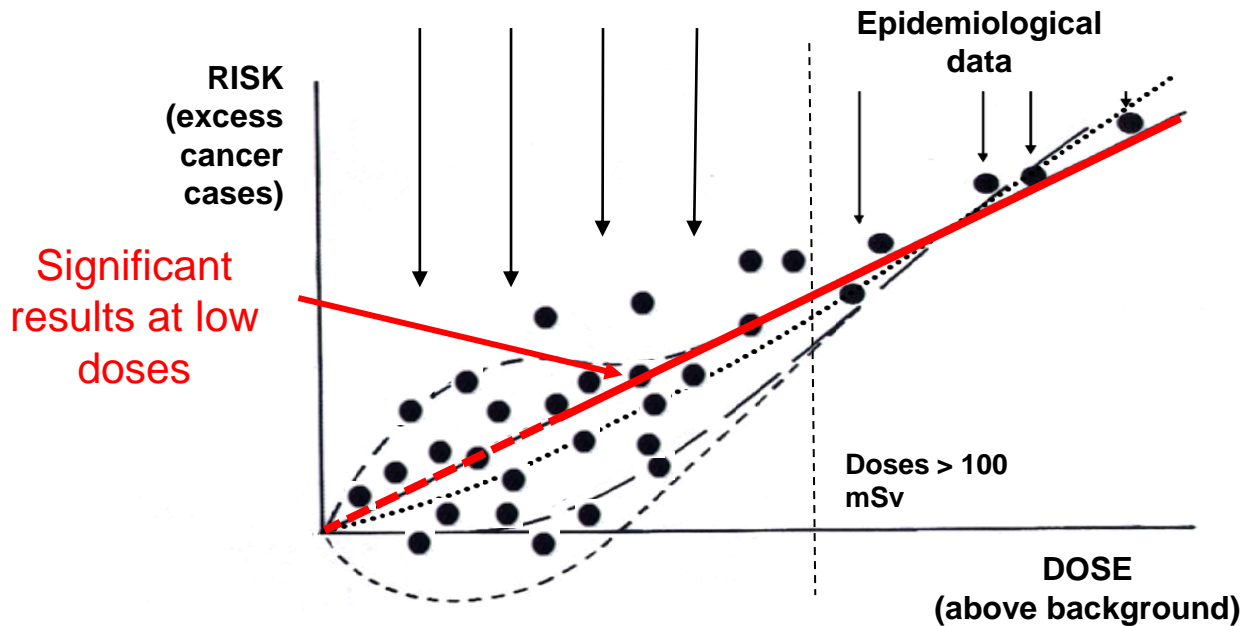⟹ **Significant association when excluding doses above 100 mGy**

Radiation epidemiology - obtained results on cancer risks

- Low dose studies are **difficult** to design, conduct, and reliably interpret

- Still **lack of knowledge** and **uncertainties**

- 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**

Dose response relationship: extrapolation of epidemiological observations toward low doses

Linear extrapolation to low doses

Epidemiological data

RISK (excess cancer cases)

Uncertainty area

Doses > 100 mSv

DOSE (above background)

Dose response relationship: epidemiological observations at low doses

Radiation epidemiology - support for radiological protection in the medical field

- Information on the risk of cancer after exposure at **low doses** and after protracted exposure at **low dose-rate**

- Improved basis for the assessment of the **balance** between risks and benefits

- Support to **justification** and **optimisation** in the medical field

Thank you
for your attention

Enhancing nuclear safety