AN OVERVIEW OF THE CURRENT KNOWLEDGE ON THE LOW-DOSE EFFECTS ON HUMAN HEALTH

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No conflict of interest to disclose
Plausible dose-response relationships for cancer risk in the very low, low and moderate dose ranges

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

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

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

<table>
<thead>
<tr>
<th>National cohort</th>
<th>UK NRRW</th>
<th>US combined cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 60,697</td>
<td>n = 147,872</td>
<td>n = 101,363</td>
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<table>
<thead>
<tr>
<th>Statistic</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Mean duration of employment (y)</td>
<td>15</td>
</tr>
<tr>
<td>Mean age at last observation (y)</td>
<td>66</td>
</tr>
<tr>
<td>Mean duration of follow-up (y)</td>
<td>34</td>
</tr>
<tr>
<td>Total person years (million)</td>
<td>10.7</td>
</tr>
<tr>
<td>Mean cumulative whole body dose (Hp10, mSv, exposed)</td>
<td>20</td>
</tr>
<tr>
<td>Number of deaths</td>
<td>103,553</td>
</tr>
<tr>
<td>solid cancers</td>
<td>28,089</td>
</tr>
<tr>
<td>leukaemia (excluding chronic lymphatic leukaemia)</td>
<td>771</td>
</tr>
</tbody>
</table>
INWORKS - 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

- 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

[Richardson et al. BMJ 2023]
https://www.bmj.com/content/382/bmj-2022-074520
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)
Pooled analysis of cancer risk after childhood CT-scan

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

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
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

[ 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

[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

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
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
Radiation epidemiology: results at low dose and low dose rate

**Solid cancers** - INWORKS
Pooled analysis - 3 cohorts of workers - n > 308000

**Solid cancers** - ICRP TG91
Meta-analysis - 22 Low Dose Rate studies - n > 900000

**Thyroid cancer** - PIRATES
Pooled analysis - 9 cohorts of children - n > 107000 - low-dose (< 200 mGy)

**Leukemia (excluding CLL)**
Pooled analysis - 9 cohorts of children - n = 262000 - low-dose (< 100 mSv)

**Solid cancers** - NCI Monograph
Meta-analysis - 22 studies - Mean dose < 100 mSv

**Brain tumors and hematological malignancies** - Epi-CT
Pooled analysis - 9 cohorts of children - n > 658000 - CT scans

Significant association when excluding doses above 100 mGy

[Richardson et al. BMJ 2015; Richardson et al. BMJ 2023]
[Shore et al IJRB 2017]
[Lubin et al. JCEM 2017]
[Little et al. Lancet Haematol 2018]
[Hauptmann et al. JNCI Monog 2020]
[Hauptmann et al. Lancet Oncol 2023; Bosch de Basea et al. Nature Med 2023]
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

- RISK (excess cancer cases)
- Uncertainty area
- Linear extrapolation to low doses
- Epidemiological data
- Doses > 100 mSv
- DOSE (above background)
Dose response relationship: epidemiological observations at low doses

Epidemiological data

Doses > 100 mSv

DOSE (above background)

RISK (excess cancer cases)

Significant results 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