Do the Epidemiologic Data Support the Use of the Linear Nonthreshold (LNT) Model for Radiation Protection? – NCRP Commentary 27

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Outline of Presentation

- What is Radiation Epidemiology?
- Models for predicting cancer risks
- NCRP Commentary No. 27 – LNT
- Dose rate effectiveness factor (DREF)
- Leukemia studies
- Is LNT model appropriate?
Radiation Epidemiology

- Radiation epidemiology is the study of ionizing radiation as a cause of disease in human populations.
- Radiation epidemiology is the basis for radiation protection standards and for compensation schemes.
Radiation Epidemiology Dates Back 100 Years

- X-Rays Discovered 1895
- Skin/Bone Cancer
- Radium Dial Painters
- Thorotrast Imaging
- Radiologists
- A-Bomb Data
- Duffy Thyroid Cancer
- Medically Treated Populations
- Underground Miners (Radon)
- Nuclear Workers
- Chernobyl
- Cancer Survivors (therapy)

Radiation epidemiology (United Nations 2008) tells us that:

- a single exposure to radiation increases cancer risk for life.
- the young are more susceptible than the old, with exceptions.
- in utero susceptibility is no greater than early childhood.
- females are more susceptible than males.
- risks differ by organ or tissue.
- some cancers don’t appear related to radiation, e.g., chronic lymphocytic leukemia, Hodgkin & non-Hodgkin lymphoma, melanoma; cancers of the cervix, prostate, pancreas; & some only at very high doses, e.g., sarcomas.
Models of Risk and High- to Low-Dose Estimation:
Life Span Study (LSS) of Japanese Atomic Bomb Survivors

Comparison of Linear and LQ ERR Models

- Sex-averaged upward curvature (p=0.03)
- Further allowing curvature to differ by sex led to further improvement (p=0.02)
- Dose response is consistent with linear for women
- Dose response is not consistent with linear for men


Comparison of Linear and LQ ERR Models (detail)

- Note:
  - Close agreement for female response for L and LQ models
  - Male smoothed response and LQ match well (but below linear response)

Examples of Dose-Response Analyses
of Low-Dose or Low Dose-Rate (LD/LDR):
Data for ‘Solid Cancer’ or
Closest Surrogates
INWORKS and LSS, Mortality from All Cancer except Leukemia by Radiation Dose

Error bars show 90% confidence intervals.

ERR/Gy = 0.48 (90% CI 0.20, 0.79)

(Slide, courtesy of Richard Wakeford) (Richardson et al., BMJ 2015; 351:h5359)
Mayak Workers – External Radiation and Mortality from Solid Cancer (Excluding Lung, Liver & Bone – main Plutonium deposition sites)

ERR/Gy = 0.12 (95% CI 0.03, 0.21)*

* Risk estimate adjusted for estimated plutonium deposition.

(Sokolnikov, *PLoS One*, 2015;e0117784)
Dose Response for Solid Cancer Incidence, Techa River Cohort

Data adjusted for smoking. (Davis et al, Radiat Res, 2015; 184:56-65)

\[
\text{ERR/Gy} = 0.77 \ (95\% \ CI \ 0.13, \ 1.5)
\]
Relative Risk for Incidence of All Cancer except Leukemia by Cumulative Dose – High Natural Background Radiation Area in Kerala, India

N=1349 cases


(Slide courtesy of John Boice, Jr.)
UK Study of Leukemia Incidence after CT Examinations at Ages 0-21

ERR/Gy = 36 (95% CI 5, 120)

CT Examination Studies are Inconclusive

- The NCRP Committee judged this study to be inconclusive.
- Dosimetry was especially weak and there was no individual data evaluated.
- UNSCEAR, NCRP, and others concluded that the children who receive frequent examinations may have an underlying condition related to the outcome of interest. And it was this disorder that prompted the physician to order the CT examinations -- that eventually resulted in a cancer diagnosis.
- The CT examinations were likely caused by the condition and not the reverse.
- Small studies in Germany, France and the U.S. addressing the possibility of “confounding by indication”, found no evidence for a dose response.
NCRP Commentary No. 27 –
LNT for Low Dose or Low Dose-Rate Data?
Selection of the 29 Studies

- The papers selected for review focused on low dose-rate studies.
- The selection was by consensus of the Committee and checked against recent comprehensive meta-analyses.
- Preferences was for relatively large cohorts with individual dosimetry and radiation dose-response risk coefficients for total solid cancers.
- Also included were groups of special interest (fallout, in utero, and early childhood exposures), and studies of specific tumors: breast, thyroid and non-CLL leukemia.
NCRP Commentary No. 27: Review of LSS and LD/LDR Epidemiologic Studies

- Life Span Study (LSS) of Japanese Atomic Bomb Survivors
- INWORKS (International Nuclear Workers Study)
- Mayak workers
- Million Person Study – Rocketdyne, Mound, U.S. atomic veterans, industrial radiographers, U.S. nuclear power plant workers, etc.
- Japanese nuclear workers
- Canadian nuclear workers
- Chernobyl clean-up workers
- Other Worker Studies – Chinese x-ray workers, U.S. radiologic technologists, French uranium processing workers
- Techa River cohort
- High Natural Background Areas – Kerala, India; Yangjiang, China
- Taiwan residents of radiocontaminated buildings
- Chernobyl and other radiation fallout studies
- Pooled studies of external irradiation and thyroid cancer
- Medical studies: Pediatric CT scans, TB multiple fluoroscopic exams
Commentary No. 27: Reviews of Epidemiologic Studies of Total Solid Cancer Risks - 1.

- **Critique of Epidemiology**
  - Study design and study population appropriate?
  - Quality of available data – adequacy and length of follow-up?
  - Adequate ascertainment of cancer incidence/mortality?
  - Accurate/complete cause-of-death ascertainment?
  - Get information on potential sources of confounding or bias?

- **Critique of Dosimetry**
  - Adequacy of dose information (missing gamma, neutron or internal exposures?)
  - Dose reconstruction: adequate methods & available information?
  - Adequate estimation of dose uncertainties?
  - Incorporation of dose uncertainties into risk estimates & shape of the dose-response curve?
Critique of Statistical Modeling

- Appropriateness of analytic methods?
- Also modeled alternatives to a linear dose-response?
- Analyses to evaluate whether confounding by lifestyle or sociodemographic variables?
- Conducted sensitivity analyses or other clarifying analyses?

Overall Evaluation of Each Study’s Degree of Support for the LNT Model

- Composite of specific strengths and weaknesses identified in the epidemiologic, dosimetric and statistical critiques
- Plus, how supportive of the LNT model are the risk coefficient and the dose-response shape?
Commentary No. 27: Evaluations of Consistency with the LNT Model of Epidemiologic Studies

- **Strong support** – 5 studies (17%)
  - INWORKS: US, UK and French combined cohorts (Richardson 2015; Leuraud 2015)

- **Moderate support** – 6 studies (21%)
  - Mayak nuclear workers (Sokolnikov 2015, 2017)

- **Limited-to-Moderate support** – 9 studies (31%)
  - Chernobyl clean-up workers, Russia (Kashcheev 2015)

- **No support** – 5 studies (17%)
  - Kerala, India – high natural background radiation area (Nair 2009)

- **Inconclusive** – 4 studies (14%)
  - CT examinations of young people, Australia (Mathews 2013)
  - Nuclear weapons test fallout studies (e.g., Marshall Islands)
<table>
<thead>
<tr>
<th>Epidemiologic Study (or groups of studies)</th>
<th>Classification (support for LNT model)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life Span Study, Japan atomic bombs (Grant et al., 2017)</td>
<td>Strong</td>
</tr>
<tr>
<td>INWORKS (French, United Kingdom, United States combined worker cohorts) (Richardson et al., 2015)</td>
<td>Strong</td>
</tr>
<tr>
<td>Tuberculosis fluoroscopic examinations, breast cancer (Little and Boice, 2003)</td>
<td>Strong</td>
</tr>
<tr>
<td>Childhood Japan atomic-bomb exposure (Preston et al., 2008)</td>
<td>Strong</td>
</tr>
<tr>
<td>Childhood thyroid cancer studies (Lubin et al., 2017)</td>
<td>Strong</td>
</tr>
<tr>
<td>Mayak nuclear workers (Sololnikov et al., 2015)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Chernobyl fallout, Ukraine and Belarus thyroid cancer (Brenner et al., 2011)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Breast cancer studies, after childhood exposure (Eidemuller et al., 2015)</td>
<td>Moderate</td>
</tr>
<tr>
<td>In utero exposure, Japan atomic bombs (Preston et al., 2008)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Techa River, nearby residents (Schonfeld et al., 2013)</td>
<td>Moderate</td>
</tr>
<tr>
<td>In utero exposure, medical x ray (Wakeford, 2008)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Japan nuclear workers (Akiba and Mizuno, 2012)</td>
<td>Weak-to-moderate</td>
</tr>
<tr>
<td>Chernobyl cleanup workers, Russia (Kashcheev et al., 2015)</td>
<td>Weak-to-moderate</td>
</tr>
<tr>
<td>U.S. radiologic technologists (Liu et al., 2014; Preston et al., 2016)</td>
<td>Weak-to-moderate</td>
</tr>
<tr>
<td>Mound nuclear workers (Boice et al., 2014)</td>
<td>Weak-to-moderate</td>
</tr>
<tr>
<td>Rocketdyne nuclear workers (Boice et al., 2011)</td>
<td>Weak-to-moderate</td>
</tr>
<tr>
<td>French uranium processing workers (Zhitvin et al., 2016)</td>
<td>Weak-to-moderate</td>
</tr>
<tr>
<td>Medical x-ray workers, China (Sun et al., 2016)</td>
<td>Weak-to-moderate</td>
</tr>
<tr>
<td>Taiwan radiocontaminated buildings, residents (Hsieh et al., 2017)</td>
<td>Weak-to-moderate</td>
</tr>
<tr>
<td>Background radiation levels and childhood leukemia (Kendall et al., 2013)</td>
<td>Weak-to-moderate</td>
</tr>
<tr>
<td>In utero exposures, Mayak and Techa River (Akleyev et al., 2016)</td>
<td>No support</td>
</tr>
<tr>
<td>Hanford ¹³¹I fallout, thyroid cancer (Davis et al., 2004)</td>
<td>No support</td>
</tr>
<tr>
<td>Kerala, India, high background radiation area (Nair et al., 2009)</td>
<td>No support</td>
</tr>
<tr>
<td>Canadian worker study (Zablotska et al., 2014)</td>
<td>No support</td>
</tr>
<tr>
<td>U.S. nuclear weapons test participants (Caldwell et al., 2016)</td>
<td>No support</td>
</tr>
<tr>
<td>Yangjiang, China, high background radiation area (Tao et al., 2012)</td>
<td>Inconclusive</td>
</tr>
<tr>
<td>Computed-tomography examinations of young persons (Pearce et al., 2012)</td>
<td>Inconclusive</td>
</tr>
<tr>
<td>Childhood medical x rays and leukemia (aggregate of &gt;10 studies) (Little, 1999; Wakeford, 2008)</td>
<td>Inconclusive</td>
</tr>
<tr>
<td>Nuclear weapons test fallout (aggregate of eight studies) (Lyon et al., 2006)</td>
<td>Inconclusive</td>
</tr>
</tbody>
</table>
### All Solid Cancer Mortality or Incidence: Excess Relative Risk (ERR) Gy⁻¹ in the Largest LD/ LDR Studies (>250 cases)

<table>
<thead>
<tr>
<th>Study</th>
<th>ERR Gy⁻¹ (95% CI)</th>
<th>No. Solid Cancers</th>
<th>Mean Dose (mGy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayak nuc (Sokolnikov-15) ^A</td>
<td></td>
<td>1,825</td>
<td>354</td>
</tr>
<tr>
<td>China, med x-ray (Sun-16) [I]</td>
<td></td>
<td>1,643</td>
<td>40.6</td>
</tr>
<tr>
<td>INWORKS (UK,US,Fr.) nuc (Richardson-15)</td>
<td></td>
<td>17,957</td>
<td>20.9</td>
</tr>
<tr>
<td>Techa River (Schonfeld-13)</td>
<td></td>
<td>2,303</td>
<td>35</td>
</tr>
<tr>
<td>Kerala HBRA (Nair-09) [I] ^B</td>
<td></td>
<td>1,349</td>
<td>161</td>
</tr>
<tr>
<td>Chernobyl clean-up (Kashcheev-15)</td>
<td></td>
<td>2,442</td>
<td>132</td>
</tr>
<tr>
<td>Japan nuc (Akiba-12)</td>
<td></td>
<td>2,636</td>
<td>12.2</td>
</tr>
<tr>
<td>Yangjiang HBRA (Tao-12)</td>
<td></td>
<td>941</td>
<td>63.2</td>
</tr>
<tr>
<td>US NPPs (Howe-04)</td>
<td></td>
<td>368</td>
<td>25.7</td>
</tr>
<tr>
<td>Rocketdyne (Boice-11)</td>
<td></td>
<td>651</td>
<td>13.5</td>
</tr>
<tr>
<td>German U millers (Kreuzer-15)</td>
<td></td>
<td>434</td>
<td>26</td>
</tr>
<tr>
<td>Canada nuc (Zablotska-13)</td>
<td></td>
<td>324</td>
<td>21.64</td>
</tr>
</tbody>
</table>

^A Nuc = nuclear workers
^B HBRA = high background radiation area
[I] = incidence data

Linear Nonthreshold Model: Dose Rate Effectiveness Factor (DREF)?
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### Meta-Analysis Estimates of DREF from Comparisons of LD/LDR Studies to the Life Span Study

<table>
<thead>
<tr>
<th>LD/LDR Studies in the Comparison</th>
<th>DREF (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All 23 LD/LDR studies B</td>
<td>3.0 (1.9, 7.7)</td>
</tr>
<tr>
<td>All studies, except Mayak workers B</td>
<td>1.9 (1.0, 11)</td>
</tr>
<tr>
<td>All studies, but including only the Mayak workers without potential plutonium exposure B</td>
<td>2.0 (1.2, 6.2)</td>
</tr>
<tr>
<td>Hoel analysis of 12 LD/LDR studies C</td>
<td>2.6 (1.6, 7.1)</td>
</tr>
</tbody>
</table>

A Comparisons used statistical modeling to match the LSS to individual LD/LDR studies on sex, mean age at initial exposure, mean final attained age, and dose conversion factors.


[slide removed at request of author]
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Is the LNT Model Appropriate for Assessing Cancer Risk in the Context of Radiation Protection?

• Various studies of radiation and total solid cancer showed risk at low doses or low dose rates and little evidence of a dose-response threshold or of strong upward curvature. However, uncertainties in doses & epidemiologic weaknesses in various studies exist, and risk estimates below 100 mGy have substantial uncertainties.

• Preponderance of the quantitative epidemiologic LD/LDR data broadly support the LNT model for total solid cancer and leukemia, though with a few notable exceptions, and data are not precise enough to definitively exclude other models.

(Adapted from NCRP Commentary No. 27)
Based on current epidemiologic data, no notably different alternative to the LNT model appears more practical and prudent for radiation protection purposes.

“All who are prudent act with knowledge”

(Proverbs 13:16)
Gratitude for Outstanding Group Efforts and Expertise to Address LD/LDR Questions

NCRP SC 1-25 - LNT
L Dauer, co-chair
H Beck
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H Grogan
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