Das LNT-Modell und die neuesten epidemiologischen Erkenntnisse

(Implications of recent epidemiological studies for the LNT model and radiation protection)

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Zuerst: ein paar Grundlagen (Risiko usw) und Begriffe (~ 14 Folien)

so dass

die Hauptthesen und

die Schlussfolgerungen

auch für Laien verständlich sind.

Strahlenwirkungen

Deterministische Strahlenwirkung

- beruht auf Zelltötung
- Sterilität, Blutarmut, Katarakt, Erythem, Fibrose
- für jeden Effekt jeweilige Schwellendosis
- Schwere der Wirkung nimmt mit Dosis zu

Stochastische Strahlenwirkung

- beruht auf Zellveränderung (Mutation)
- Induktion von Leukämien, Tumoren, genetischen Schäden
- keine Schwellendosis

Stochastische Strahlenwirkungen

Veränderungen von Körper- oder Keimzellen

- Krebs und Leukämien bei bestrahlten Personen
- Genetische Schäden bei Nachkommen

  Leukämie- und Krebsinduktion
- > zwei Mutationen (Tumorsuppressor oder Onkogene)
- Selektion, mehrstufiger Prozess

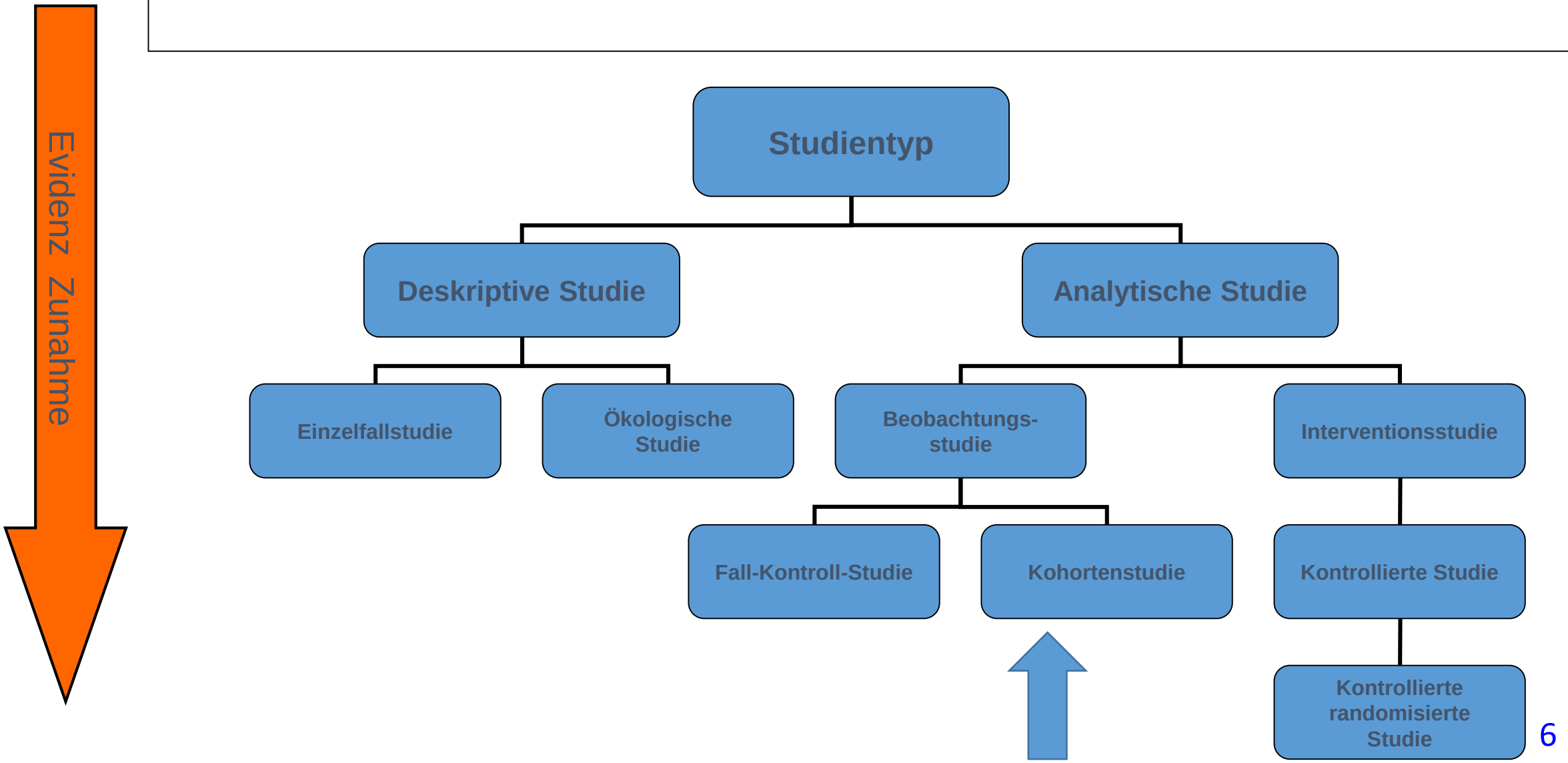
Stochastische Strahlenwirkungen

- Strahlenbedingte und spontane Krebserkrankungen **unterscheiden sich** im klinischen Erscheinungsbild **nicht**.

  Daher lässt sich eine Strahleninduktion nur mit **statistischen Methoden** dadurch feststellen, dass in bestrahlten Personengruppen mit zunehmender Dosis **häufiger Krebsfälle** auftreten.

- Epidemiologische Studien vergleichen Krebshäufigkeit in einer bestrahlten Studienpopulation mit einer unbestrahlten Kontrollpopulation (**Kohortenstudie**) oder bestimmen die Strahlenexposition bei erkrankten und gesunden Personen (**Fall-Kontroll-Studie**).

Stufen der epidemiologischen Argumentation



KOHORTEN: Cohort Studies (e.g., Japanese A-bomb survivors, various studies on nuclear workers, airline pilots)

A cohort was a 300-600-man unit in the Roman Army. 10 cohorts formed a legion (figure 1)

- A cohort is a group with something in common e.g., an exposure
- Start with disease-free "at-risk" population (susceptible to the disease of interest)
- Determine eligibility and exposure status
- Follow-up and count incident events (e.g., cancer incidence) or deaths from certain causes (the outcome)
- Analyse data to determine risks

Relatives Risiko - Bedeutung

- Spontanrisiko in der Bevölkerung bei Nicht-Strahlenexponierten, (*Baseline Risk*)
- RR = Relatives Risiko = Risikoverhältnis

  = Risiko Exponierte/ Risiko Nichtexponierte
- RR = 1,0 , keine Beziehung
- RR = 1,5 bedeutet: Exponierte haben ein 50 % größeres Erkrankungsrisiko als Nichtexponierte
- RR = 0,60 bedeutet ein 40 % niedrigeres Risiko

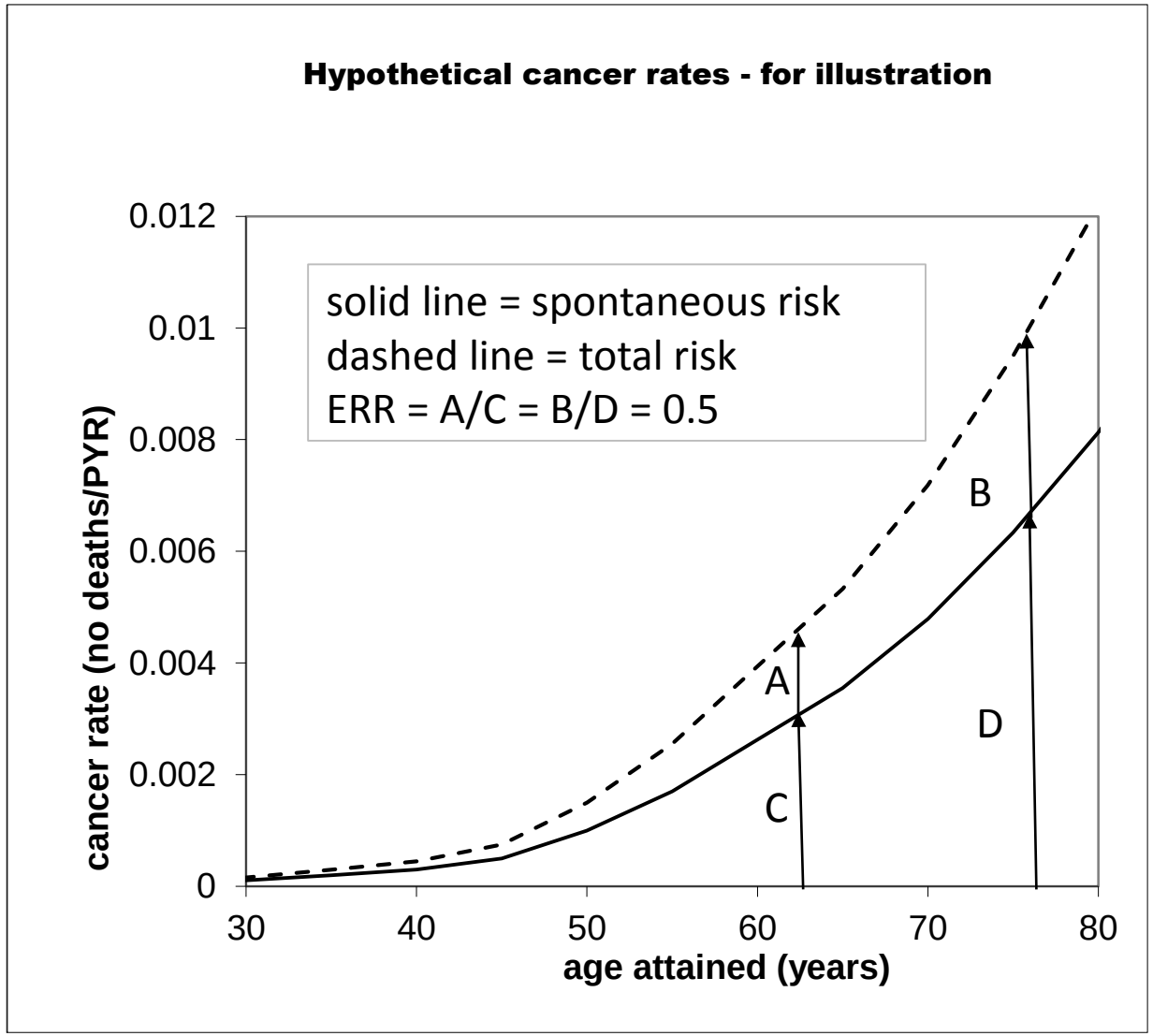
Das Exzess (oder zusätzliche) Relative Risiko = RR - 1

(Excess Relative Risk)

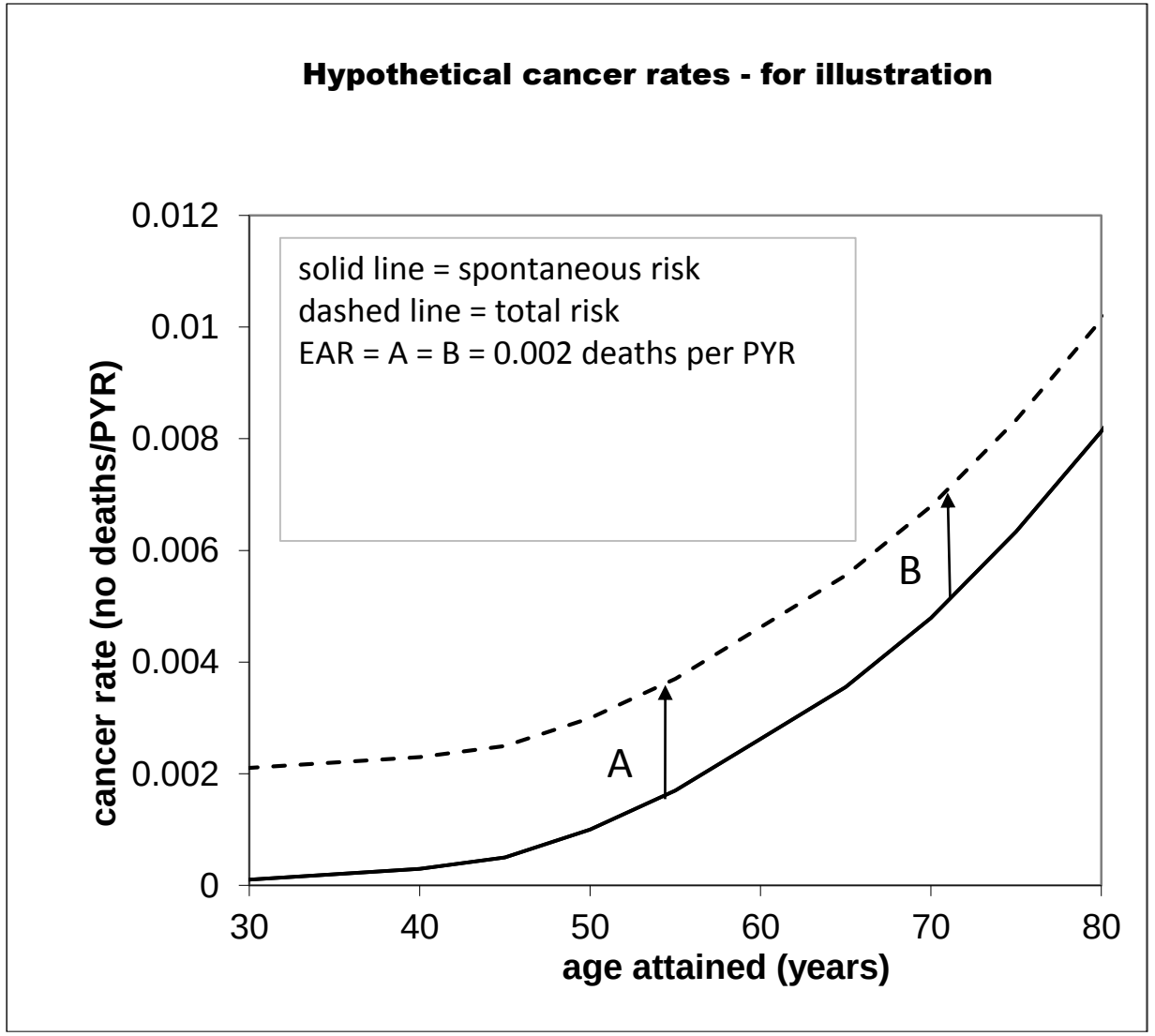
z.B. ERR = 0,5
d.h. das Spontanrisiko wird durch die Strahlenexposition um 50% erhöht

Strahlenexposition = 1 Sv

--------> ERR = 0,5 / Sv



EAR = Exzess Absolutes Risiko (Excess Absolute Risk)



Strahlenrisiko, ICRP 103, 2007

Detriment-adjusted nominal risk coefficients for stochastic effects after exposure to radiation at low dose

Exposed whole population cancer risk = 5.5% per 1Sv

Let‘s look at how these risk are calculated

ICRP 103 nominal risks for cancer are lifetime risks based on EAR and ERR from Japanese A-bomb survivors cancer INCIDENCE data (FU: 1958-1998, Preston et al 2007)

BUT
EAR and ERR depend on DOSE (D), SEX(s), AGE AT EXPOSURE(e), AGE ATTAINED(a), CANCER TYPE(O)
All of these variations need to be accounted for in lifetime risk calculations SO:-

A. For each CANCER TYPE and each SEX:-

1. Construct excess absolute INCIDENCE risk for ICRP reference populations using ref. pop. incidence rates m(a)

$$w_1 \text{ EAR } (D, e, a) + (1- w_1) (\text{ERR } (D, e, a) . m(a)).$$

2. Multiply this quantity by general survival probability to account for accidents etc.

$$LAR(D,e) = \int_{e+L}^{a_{max}} M(D,e,a) S_{aj}(a,g) / S_{aj}(e,g)\, da$$

D is dose
a is attained age
e is age at exposure
$S_{aj}(a, g)$ is the probability of surviving cancer free to age a
L is the minimum latency period (2 y for leukaemia, 3 y for thyroid cancers and 5 y for solid cancers and breast cancers).
M(D, e, a) is the excess absolute risk
M(D, e, a) = w_1 EAR (D, e, a) + (1- w_1) (ERR (D, e, a) . m(a)).
$w_1 = 0.5$ for all solid cancer, thyroid cancer and leukaemia, $w_1 = 1.0$ for breast cancer.

Detriment-adjusted nominal risk coefficients for stochastic effects after exposure to radiation at low dose

Exposed whole population cancer risk = 5.5% per 1Sv

Organs considered:-
oesophagus, stomach, colon, liver, lung, bone, skin, breast (EAR only), ovary, bladder, thyroid (ERR only)) (L-Q EAR for leukaemia-CLL-MM)

Examples of weighting factors:-
Lethality
Lung = 0.89
Female Breast =0.29
Skin =0.002

Exposed whole population cancer risk = 5.5% per 1Sv **HOW SHOULD THIS 5.5% per 1 Sv BE APPLIED?**

For 1 person exposed to 1 Sv? – NO! ICRP 103

p194 **"These estimates are intended to apply only to populations and are not recommended for use in estimating risks in individuals or subgroups."**

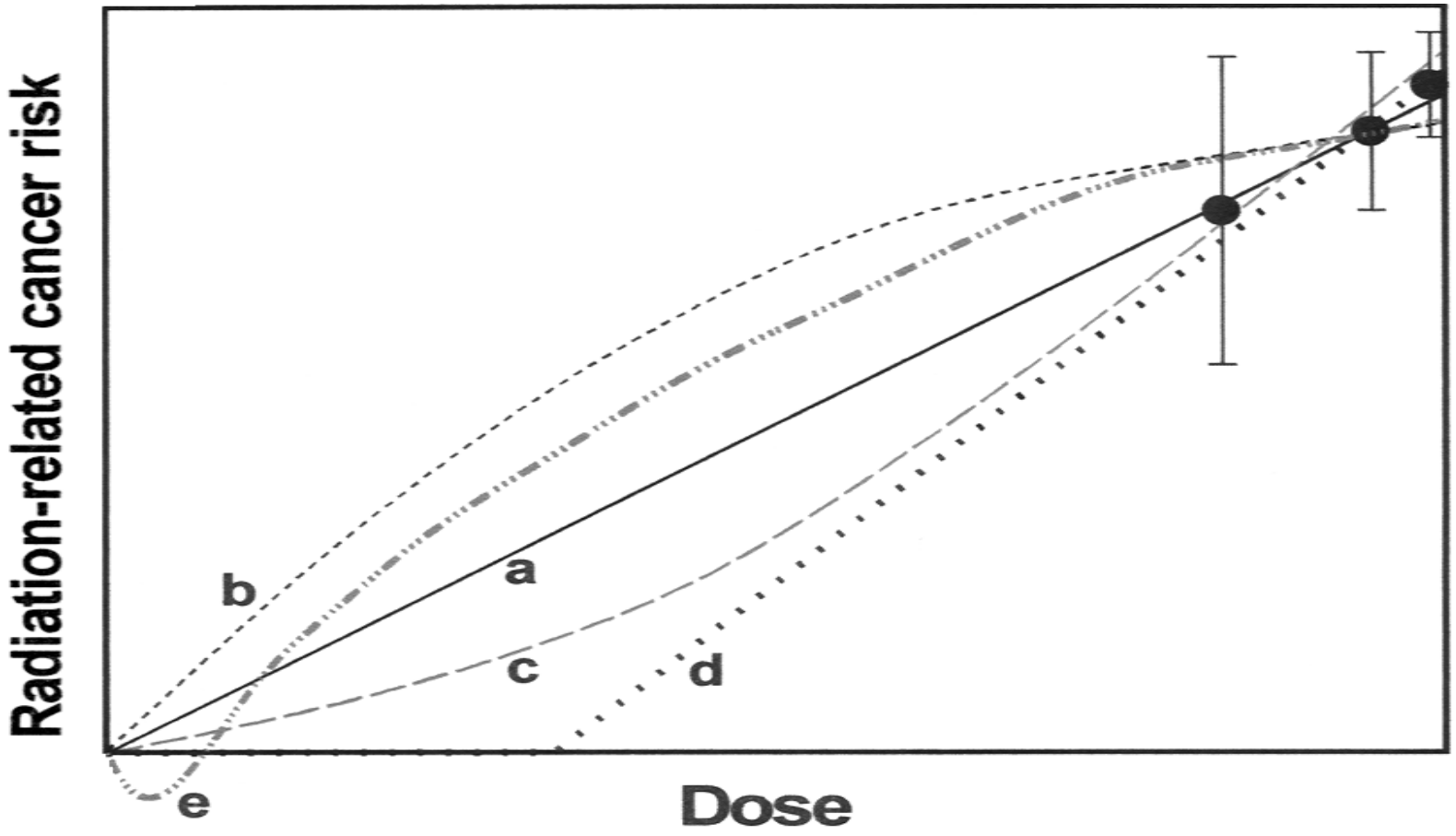
people	dose (Sv)	collective dose (persons-Sv)	Excess cancer deaths applying 5.5%/Sv	baseline deaths from cancer	
200,000	0.001	200	11	40,000-50,000	NO!
20,000	0.01	200	11	4,000-5,000	
2,000	**0.1**	**200**	**11**	**400-500**	**YES!**

ICRP 103

p. 76, **Specifically, the computation of cancer deaths based on collective effective doses involving trivial exposures to large populations is not reasonable and should be avoided.**

p. 51, ….**the Commission judges that it is not appropriate, for the purposes of public health planning, to calculate the hypothetical number of cases of cancer or heritable disease that might be associated with very small radiation doses received by large numbers of people over very long periods of time**

Types of Dose-response Curves



What is low dose ?

low absorbed doses (<100 mGy delivered acutely or accumulated over time)
and/or
low absorbed dose rates (LD/LDR) (<5 mGy h^{-1} for any accumulated dose)

Is there risk at low doses?

INWORKS, Dose response for all cancers except leukemia, at low doses

Range of Doses	Excess Relative Risk/Gy (90% CI)
Full dose range (0 - <max. 1331.7 mGy - 90th percentile 53.4 mGy,)	0.48 (0.20, 0.79)
0 – 150 mGy	0.69 (0.10, 1.30)
0 – 100 mGy	0.81 (0.01, 1.64)

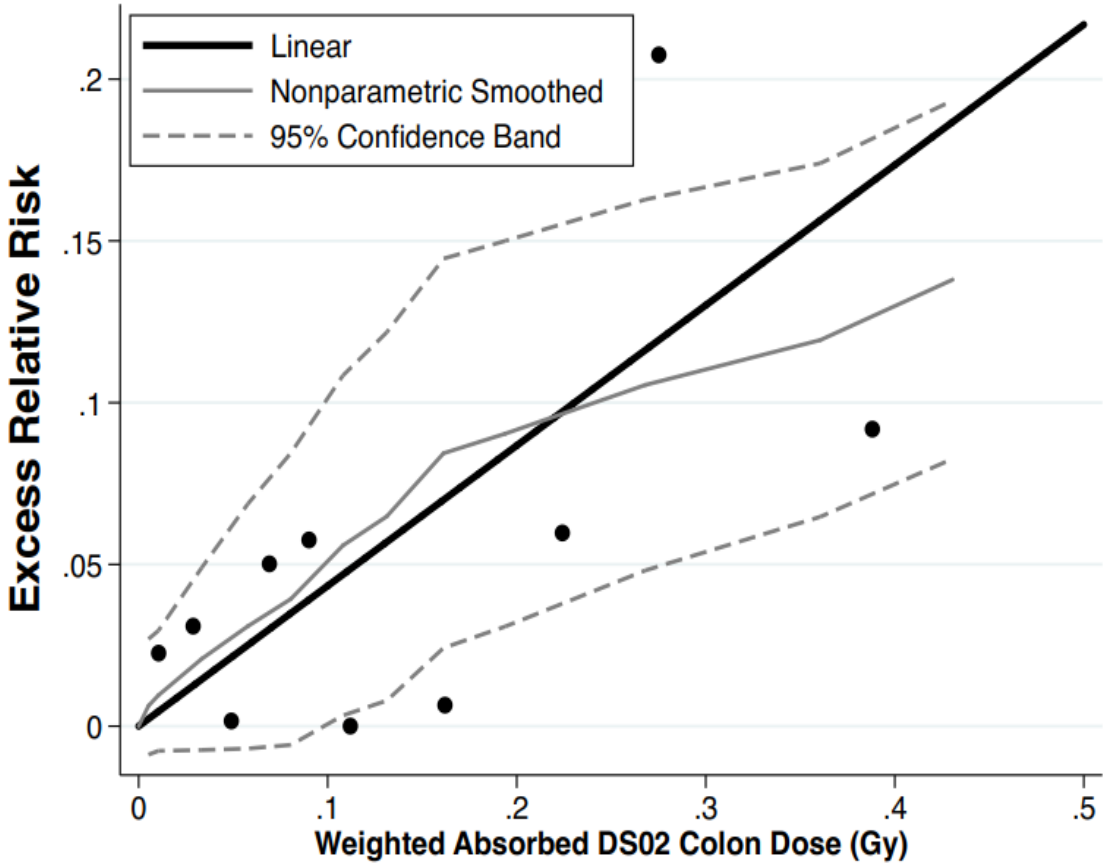
(Richardson *et al.*, *Br Med J,* 351: h5359, 2015)

LSS dose-response at 0-100 mGy for solid cancers, sexes combined

Solid Cancer Incidence

Dose Range	ERR Gy^{-1} (95% CI)
Full dose range <4Gy	0.50 (0.42, 0.59)
0-100 mGy	0.49 (0.026, 1.01)

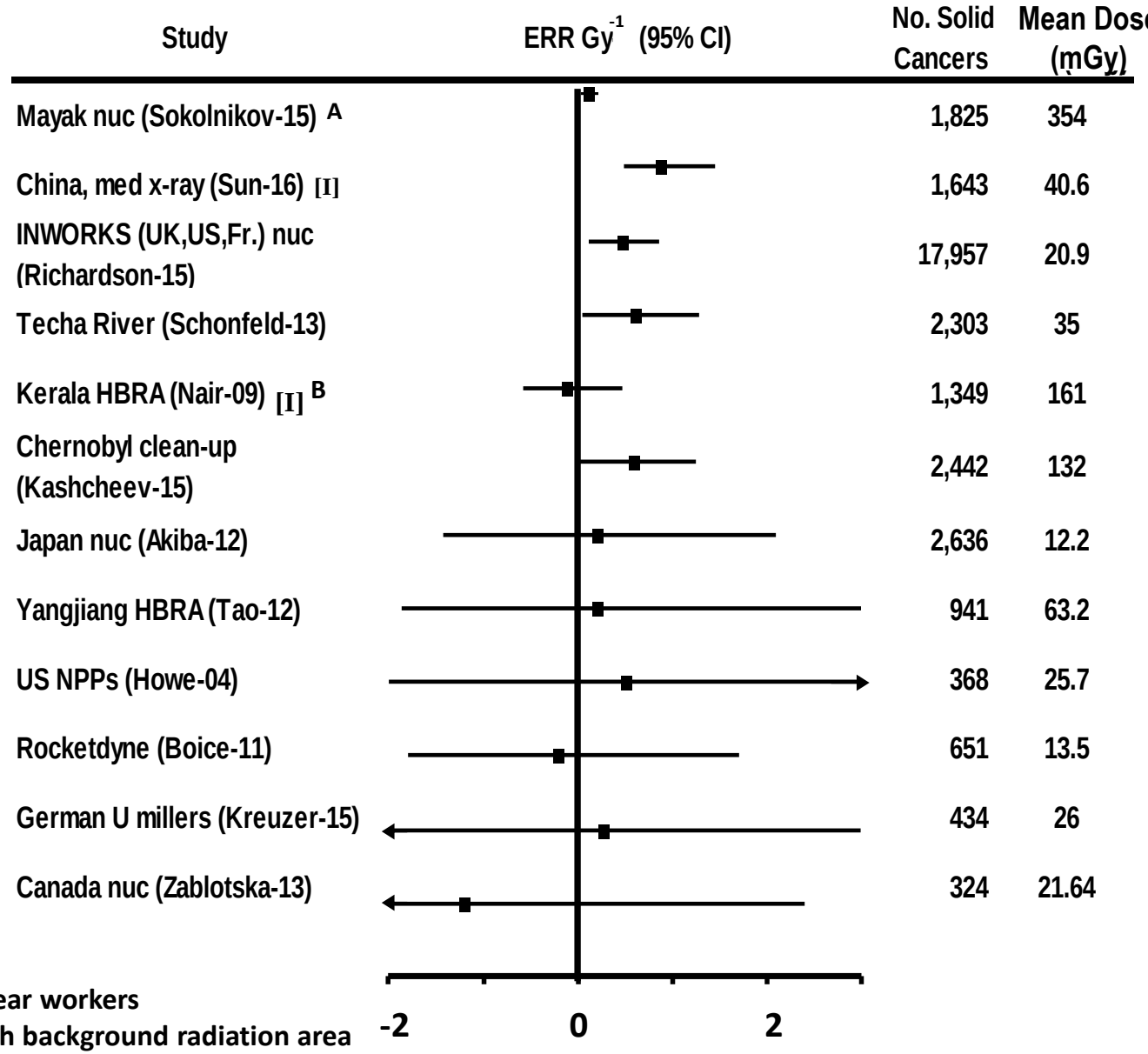
risk estimates from: Grant et al, *Radiat Res*, 187:513-37, 2017



Solid Cancer Mortality

LSS Report 14 (Ozasa, *Radiat Res*, 177:229-, 2012)

All Solid Cancer *(mortality or incidence)*:
Excess Relative Risk (ERR) Gy^{-1} in the 12 Largest LD/LDR Studies (>250 cases)



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

(Shore, Walsh et al, *Int J Radiat Biol*, 93:1064-78, 2017)

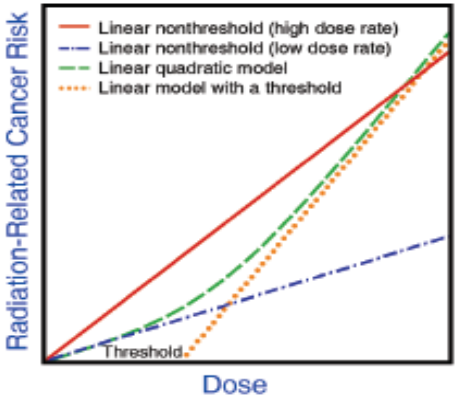
Published in April, 2018

Prepared by Scientific Committee 1-25

included experts with a broad purview of the recent radiation epidemiology literature

NCRP COMMENTARY No. 27

IMPLICATIONS OF RECENT EPIDEMIOLOGIC STUDIES FOR THE LINEAR-NONTHRESHOLD MODEL AND RADIATION PROTECTION



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Two associated publications (1 Memorandum, 1 Summary) in international journals:-

IOP Publishing | Society for Radiological Protection — Journal of Radiological Protection
J. Radiol. Prot. 38 (2018) 1217–1233 (17pp) — https://doi.org/10.1088/1361-6498/aad348

Memorandum

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

R E Shore[1,2,15], H L Beck[3,15], J D Boice[4,5], E A Caffrey[6], S Davis[7], H A Grogan[8], F A Mettler[9], R J Preston[10], J E Till[11], R Wakeford[12], L Walsh[13] and L T Dauer[14,16]

Submitted to Health Physics:
Recent Epidemiologic Studies and the Linear Nonthreshold Model for Radiation Protection –
A Summary of NCRP Commentary No. 27 – with the same author list

AIM:

To see if recent epidemiological studies of low-LET radiation, particularly those at
low absorbed doses
and/or
low absorbed dose rates (LD/LDR)
EITHER
broadly support the LNT model of carcinogenic risk
OR
demonstrate sufficient evidence that the LNT model is not appropriate for RP

WHY:

Last reviews by BEIR VII phase 2 report 2008 and UNSCEAR 2006 report ~10 years ago & included a large fraction of studies based on acute exposures to moderate and high doses.

Since then a considerable number of results for updated or new cohorts, many of them with LD/LDR exposures, have been published

STUDY SELECTION:

In accordance with a recent comprehensive meta-analysis of such studies (ICRP TG 91)

(Shore, Walsh, Azizova, Rühm, Int J Radiat Biol, 93:1064-78, 2017)

By consensus of the Committee

TYPES OF STUDY:

1) large cohorts
2) with individual dosimetry
3) with radiation risk to dose-response analyses and risk coefficients for total solid cancer, individual cancers or non-CLL leukemia.

Earlier reports containing redundant data were eliminated.

Analyses of the Japanese Life Span Study of atomic bomb survivors and LD/LDR studies of exposed groups or tumor sites of special interest (fallout, in utero and early childhood exposures; breast cancer, thyroid cancer) also were included.

Twenty-nine major studies were critically reviewed.

Review of A-bomb papers and LD/LDR Epidemiological 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, processing workers*
- **Techa River cohort**
- **High natural background areas – Kerala, India; Yangjiang, China**
- **Japanese nuclear workers**
- **Canadian nuclear workers**
- **Chernobyl clean-up workers**
- **Other worker studies – Chinese x-ray workers, U.S. radiological technologists, French uranium processing workers**
- **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**

Kritische Überprüfung einzelner epidemiologischer Studien in NCRP-Kommentar Nr. 27

- Epidemiologische Daten und Methodik – Grösse der Studie; Stichhaltigkeit der Methoden; Potenzial für Verzerrungen; epidemiologische Unsicherheiten berücksichtigt?
- Dosimetrie – Datenqualität; Methoden; untersuchte Dosisunsicherheiten?
- Statistische Methoden und Ergebnisse – zweckmässig; statistische Genauigkeit; Bewertung der Form der Dosis-Wirkungsbeziehung?
- Stärken und Grenzen untersuchen?
- Bedeutung für LNT und Strahlenschutz?

Bewertung der Konsistenz mit dem LNT-Modell

- **Starke Bestätigung – 5 Studien (17%)**
  - INWORKS: Kombinierte Kohorten aus USA, GB und Frankreich (Richardson 2015; Leuraud 2015)
- **Moderate Bestätigung – 6 Studien (21%)**
  - Nukleares Personal in Mayak (Sokolnikov 2015, 2017)
- **Begrenzt-moderate Bestätigung – 9 Studien (31%)**
  - Aufräumpersonal in Tschernobyl, Russia (Kashcheev 2015)
- **Keine Bestätigung – 5 Studien (17%)**
  - Kerala, India – Gegend mit hoher nat. Untergrundstrahlung (Nair 2009)
- **Nicht eindeutig – 4 Studien (14%)**
  - CT-Untersuchungen von jungen Personen, Australien (Mathews 2013)
  - Kernwaffentest Fallout-Studien (z.B. Marshall Islands)

Fast 70% ergaben eine gewisse Bestätigung für LNT, die von relativ schwach bis stark reichte.

Ist LNT angemessen für den Strahlenschutz?

Verschiedene Studien über Strahlung und solide Krebs- mortalität oder -inzidenz zeigten ein Risiko bei niedrigen Dosen oder niedrigen Dosisleistungen und sehr schwach bis keine Evidenz, dass eine Dosis-Wirkungsschwelle oder eine starke Aufwärtskrümmung vorliegt.
Allerdings gibt es Unsicherheiten bei den Dosen und epidemiologische Mängel in verschiedenen Studien, und Risikoschätzungen unter 100 mGy haben erhebliche Unsicherheiten.

Die Mehrheit der quantitativen epidemiologischen LD/LDR-Ergebnisse unterstützt weitgehend das LNT-Modell für solide Krebs- und Leukämie-mortalität oder -inzidenz, wenn auch mit wenigen bemerkenswerten Ausnahmen. Die aktuellen Daten sind nicht präzise genug, um andere Modelle endgültig auszuschließen.

Based on current epidemiological data, no notably different alternative to the LNT model appears more practical and prudent for *radiation protection purposes*.

Modest doubt is called the beacon of the wise.
William Shakespeare

Gratitude for outstanding group efforts and expertise in addressing LNT (and DREF)

NCRP SC 1-25 – LNT

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