Development of Probability Distribution of DDREF for Solid Cancers

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Purpose of Study

[1] Develop probability distribution of dose and dose-rate effectiveness factor (DDREF) for solid cancers for use in future revision of Interactive RadioEpidemiological Program (IREP)

Probability distribution of possibly true values to represent uncertainty in DDREF

[2] DDREF distribution intended to be suitable for use in any risk assessments for solid cancers that account for uncertainty

What Is a DDREF?

[1] Adjustment factor used in estimating cancer risks from exposure to low-LET radiation (photons and electrons) at low acute doses or low dose rates

[2] Represents assumption that risk per unit dose (Gy) at low acute doses or low dose rates (R_L) may differ from risk per Gy at higher acute doses (R_H)

DDREF defined as R_H/R_L –

$R_L = R_H/\text{DDREF}$

R_H estimated from studies of Japanese atomic-bomb survivors [Life Span Study (LSS) cohort)]

When Is a DDREF Used?

DDREF is used in estimating cancer risks at low acute doses or low dose rates of low-LET radiation whenever linear dose-responses are assumed –

$$\text{Risk} = \alpha D$$

Use of DDREF means that risk per Gy (α) may depend on dose or dose rate

Risks of most specific solid cancers and all solid cancers combined in LSS cohort can be described by linear models at doses up to about 2–3 Gy

Original Bases for Use of DDREF

[1] "True" dose-response from acute exposure to low-LET radiation is linear-quadratic (LQ)

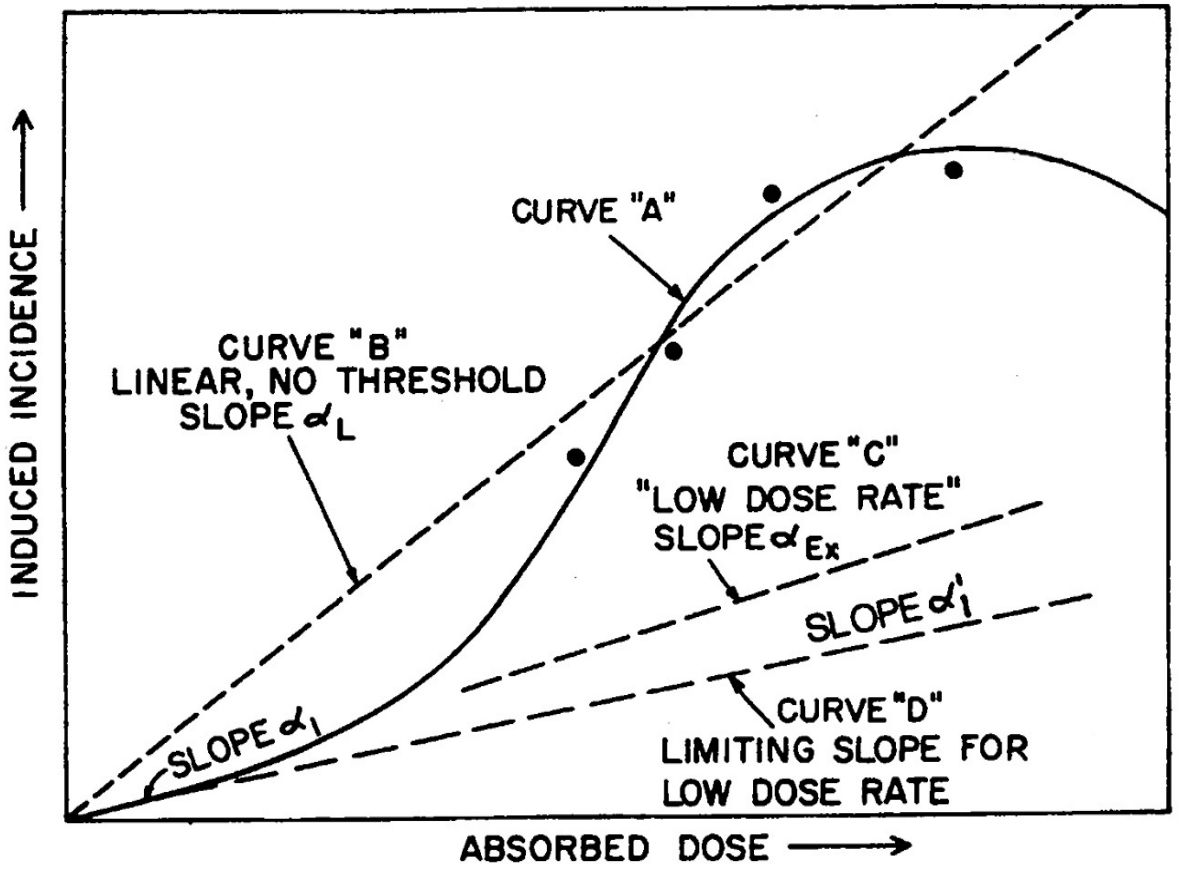
$$\text{Risk} = \alpha D + \beta D^2,\ \beta > 0$$

Dose-response may level off at high doses due to effect of cell sterilization [$\exp(-\gamma D)$ term]

[2] Risk from chronic exposure at low dose rates is determined by linear term in LQ dose-response from acute exposure

Firm basis for assumption of LQ model is lacking

Illustration of Concept of DDREF for Low-LET Radiation



Implications of LQ Dose-Responses

[1] When LQ dose-response is assumed, risk per Gy [$(\alpha + \beta D)$, $\beta > 0$] increases with increasing dose (DDREF > 1)

[2] LQ models incorporate dose-dependent DDREF –

$$\text{DDREF} = R_H/R_L = (\alpha + \beta D)/\alpha$$
$$= [1 + (\beta/\alpha)D]$$

β/α referred to as “curvature parameter”

Since LQ model lacks firm basis, other dose-responses (e.g., supra-linear, DDREF < 1) not ruled out

Solid Cancers vs Leukemias

DDREFs for solid cancers and leukemias should be considered separately –

[1] Linear dose-responses for most solid cancers in LSS cohort adjusted by possible DDREF at low acute doses or low dose rates

[2] LQ dose-responses for all leukemias in LSS cohort (incorporate dose-dependent DDREF)

Dose-responses for all leukemias do not inform DDREF for solid cancers

Why Use a DDREF for Solid Cancers?

[1] Linear fits to dose-responses for solid cancers in LSS cohort may not describe responses at doses below limits of detection (< 0.1–0.2 Gy)

Linear fits may conceal small nonlinearities in dose-responses at low acute doses

[2] Linear fits to dose-responses for solid cancers in LSS cohort may not describe dose-responses (risks per Gy) at low dose rates

Components of DDREF (1)

DDREF represents two distinct concepts –

[1] Low-dose effectiveness factor (LDEF)

Effect of dose from acute exposure on risk per Gy

Estimated by analyzing possible nonlinearities in dose-responses from acute exposure

Usually estimated from fits to dose-responses for all solid cancers in LSS cohort using LQ models

Components of DDREF (2)

[2] Dose-rate effectiveness factor (DREF)

Effect of dose rate on risk per Gy

Usually estimated by comparing risks of all solid cancers or all cancers except leukemias from chronic exposure of workers or public with risks in LSS cohort assuming linear dose-responses-

$$\mathrm{DREF} = \frac{(\text{Risk per Gy})_{\text{LSS,acute}}}{(\text{Risk per Gy})_{\text{chronic}}}$$

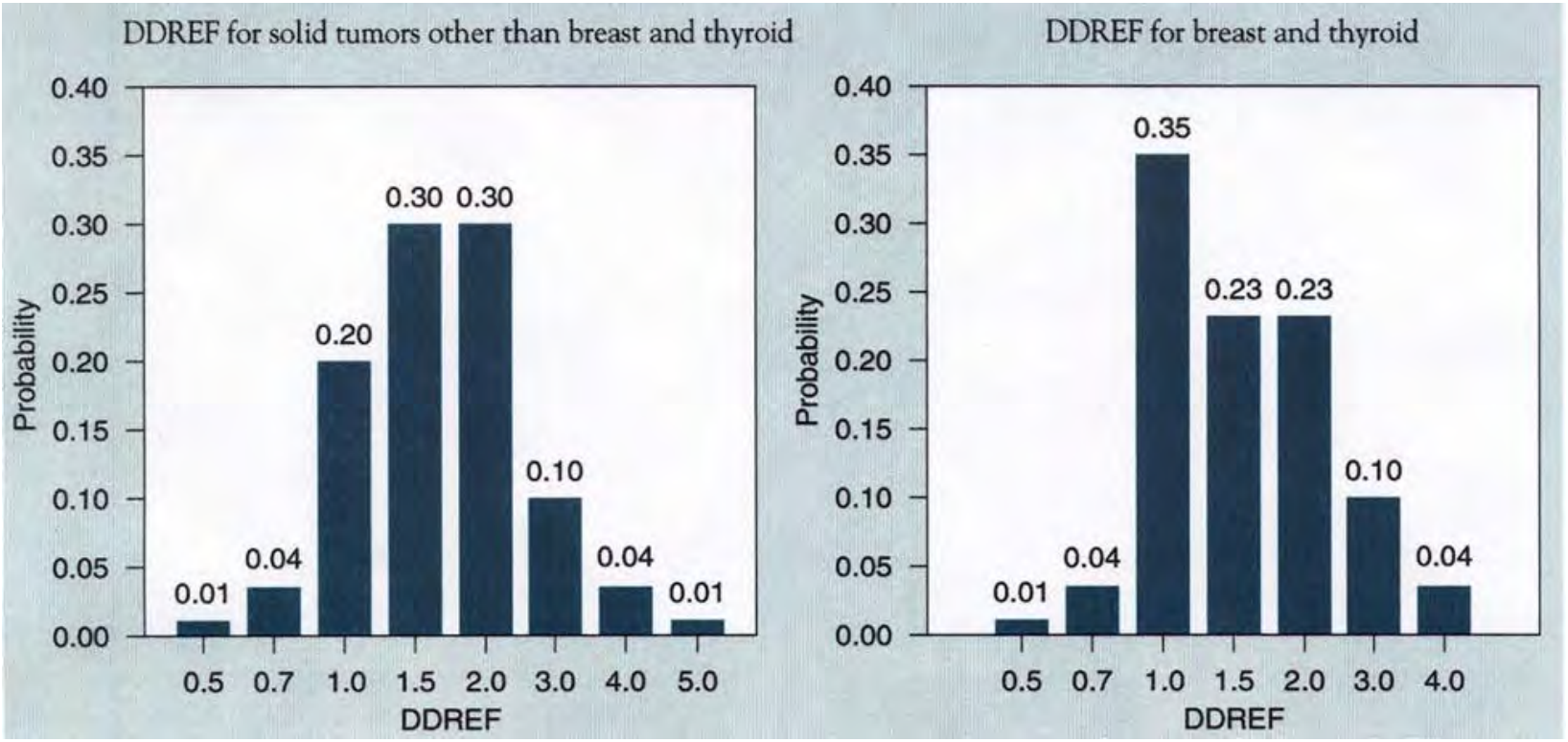
Importance of Uncertainty in DDREF

[1] IREP and other state-of-the-art cancer risk assessments account for all sources of uncertainty

Objective is to obtain subjective confidence intervals (CIs) to represent uncertainty in estimated risks ("state of knowledge")

[2] Uncertainty in DDREF can be important source of uncertainty in estimating risks of solid cancers at low acute doses or low dose rates

Probability Distributions of DDREF in IREP



Basic Issues in Developing DDREF Distribution for Solid Cancers

[1] Which studies are relevant in developing DDREF distribution for solid cancers?

Human epidemiologic studies only, or inclusion of radiobiologic (cell and animal) studies?

Can radiobiologic data be used to quantify (inform) uncertainty in DDREF for solid cancers in humans?

Selection of relevant epidemiologic studies

[2] How should selected DDREFs be combined?

What weights should be given to relevant studies?

Present Study to Develop DDREF for Solid Cancers

Developed state-of-knowledge probability distribution of DDREF for solid cancers using data from human epidemiologic studies only

- Analysis of LDEFs and DREFs for incidence and mortality from all solid cancers combined (four data sets in all; unique)
  - DDREFs for specific solid cancers estimated but not used in analysis

Distribution intended to apply to specific solid cancers when linear dose-responses are assumed

Estimation of LDEF from Analyses of Dose-Responses in LSS Cohort

Two ways of estimating LDEF from fits to acute dose-responses in LSS cohort using LQ models –

[1] LDEF = R_H/R_L = [1 + (β/α)D] at D = 1 Gy

Based on ratio of coefficients of quadratic and linear terms; β/α is curvature parameter

[2] LDEF = α_L/α_{LQ} (independent of dose)

α_L = coefficient of linear fit to dose-response

α_{LQ} = coefficient of linear term in LQ fit

Studies of LSS Cohort Used to Estimate LDEFs

[1] Solid cancer incidence (DS02 dosimetry)

BEIR VII Report (2006), two estimates

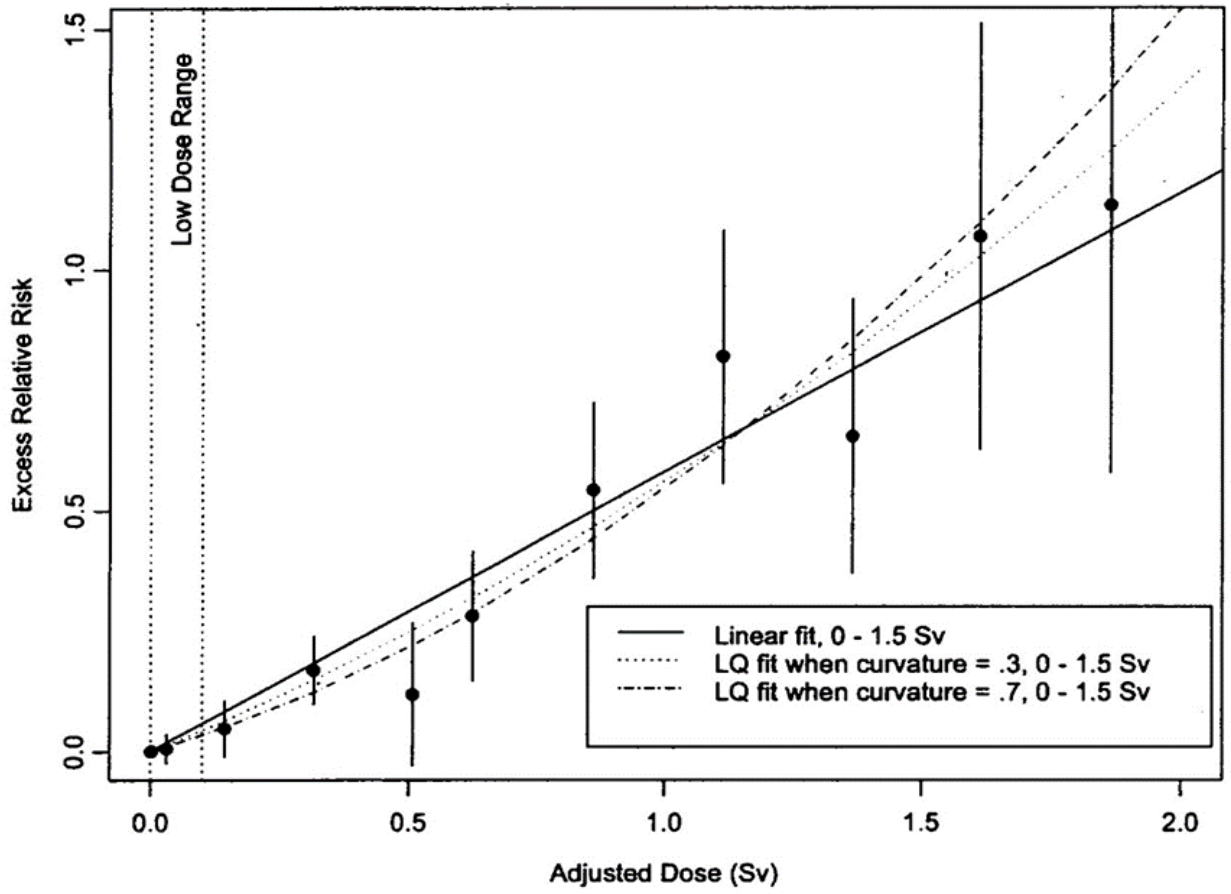
Preston et al. (2007) – RERF

[2] Solid cancer mortality (DS02 dosimetry)

Little et al. (2008) – Analysis for UNSCEAR, two estimates (ERR and EAR models)

Ozasa et al. (2012) – RERF, four estimates

Solid Cancer Incidence in LSS Cohort (BEIR VII, 2006)



Recent Studies of LSS Cohort Not Included in Analysis

Studies at RERF using recently revised dosimetry system (DS02R1), including sex-specific LDEFs

[1] Solid cancer incidence – Grant et al. (2017)

Includes longer follow-up of cohort

[2] Solid cancer mortality – Cullings et al. (2017)

Analysis of data used by Ozasa et al. (2012); longer follow-up of cohort not included

Studies Used to Estimate DREFs from Comparisons with Risks in LSS Cohort (1)

[1] Solid cancer incidence

U.K. workers, Muirhead et al. (2009)

Risk in LSS cohort from Jacob et al. (2009)

Techa River cohort, Davis et al. (2015)

Risk in LSS cohort assuming BEIR VII model

Risks in LSS cohort matched by age at exposure, attained age, and male fraction

Studies Used to Estimate DREFs from Comparisons with Risks in LSS Cohort (2)

[2] Solid cancer mortality

U.K. workers, Muirhead et al. (2009)

Risk in LSS cohort from Jacob et al. (2009)

Workers in France, U.K., and U.S. (INWORKS), Richardson et al. (2015)

Risk in LSS cohort assuming BEIR VII model

Techa River cohort, Schonfeld et al. (2013)

Risk in LSS cohort assuming BEIR VII model

Challenges in Estimating DREFs

[1] Selection of age at exposure and attained age in LSS cohort to match age distributions in workers or public

[2] Accounting for exposures of workers or public to neutrons and alpha particles and nonuniform exposures from internal beta emitters

Exposures to lower-energy x rays and ^{3}H beta particles (increased biological effectiveness)

[3] Risk transfer between populations (should be unimportant for all solid cancers combined)

Studies Not Used to Estimate DREFs

[1] Workers in 15 countries (IARC, Cardis et al. 2007)

Positive dose-response due entirely to estimated risk in Canadian cohort now believed to be invalid

Non-significant dose-responses in workers in other 14 countries, some with undefined lower bounds

[2] Mayak workers, Chernobyl emergency workers (concerns about reliability of dosimetry)

[3] Any studies with non-significant dose-responses (uninformative about uncertainty in DDREF)

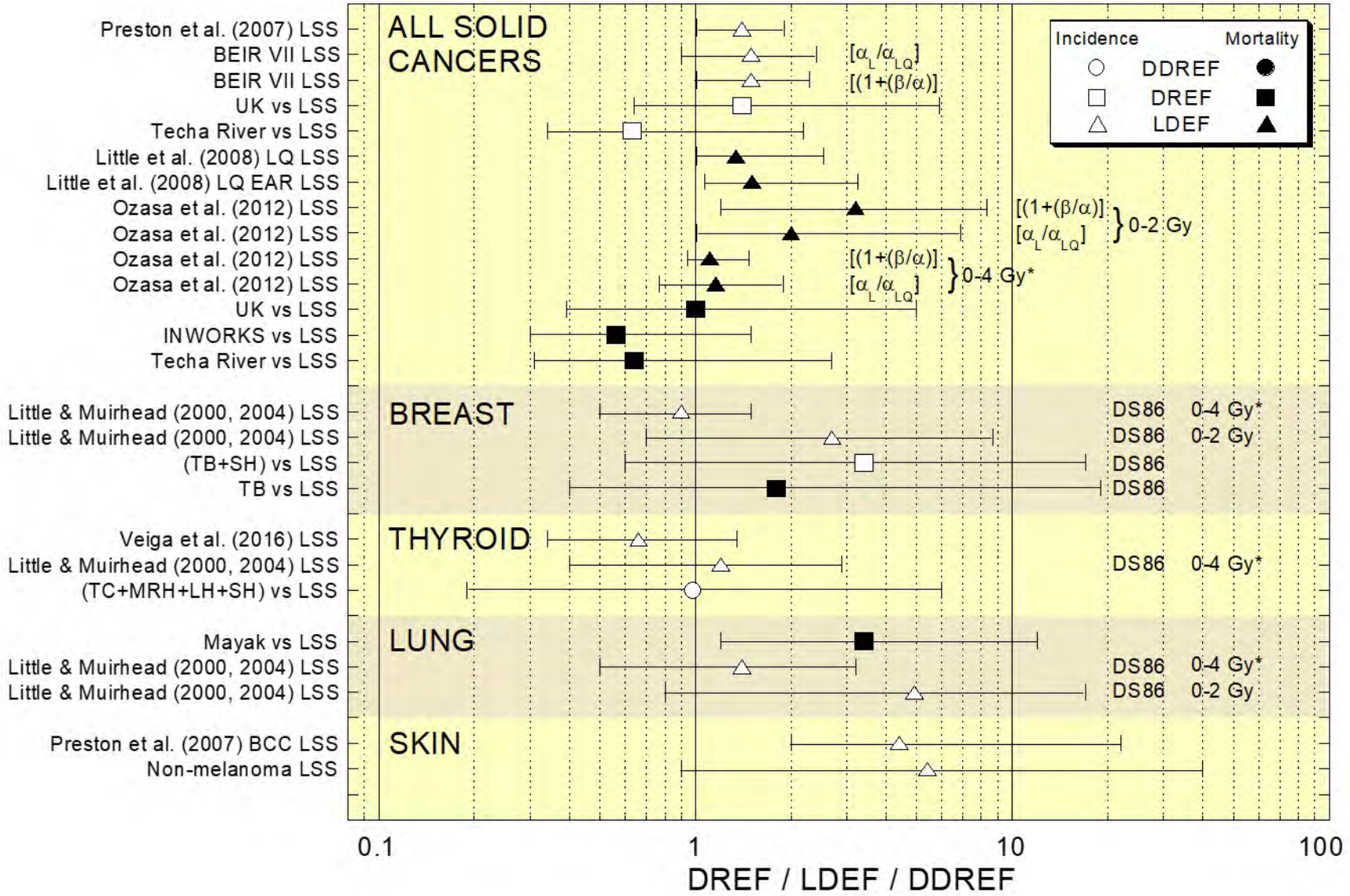
Interpretations of Data from Individual Studies

[1] Reported central values of risks, risk coefficients (α, β) and curvature parameters (β/α) assumed to be maximum likelihood estimates (MLEs)

[2] Reported MLEs and CIs of risk quantities were represented by Weibull distributions with modes at MLEs (flexible; allow values < 0)

Normal distributions assumed in some analyses

[3] Our estimates of LDEFs, DREFs, and DDREFs are 50^{th} percentiles (medians) and 90% CIs


Preston et al. (2007) LSS
BEIR VII LSS
BEIR VII LSS
UK vs LSS
Techa River vs LSS
Little et al. (2008) LQ LSS
Little et al. (2008) LQ EAR LSS
Ozasa et al. (2012) LSS
Ozasa et al. (2012) LSS
Ozasa et al. (2012) LSS
Ozasa et al. (2012) LSS
UK vs LSS
INWORKS vs LSS
Techa River vs LSS
Little & Muirhead (2000, 2004) LSS
Little & Muirhead (2000, 2004) LSS
(TB+SH) vs LSS
TB vs LSS
Veiga et al. (2016) LSS
Little & Muirhead (2000, 2004) LSS
(TC+MRH+LH+SH) vs LSS
Mayak vs LSS
Little & Muirhead (2000, 2004) LSS
Little & Muirhead (2000, 2004) LSS
Preston et al. (2007) BCC LSS
Non-melanoma LSS
ALL SOLID CANCERS
BREAST
THYROID
LUNG
SKIN
[αL/αLQ]
[(1+(β/α)]
[(1+(β/α)]
[αL/αLQ]
0-2 Gy
[(1+(β/α)]
[αL/αLQ]
0-4 Gy*
DS86 0-4 Gy*
DS86 0-2 Gy
DS86
DS86
DS86 0-4 Gy*
DS86 0-4 Gy*
DS86 0-2 Gy
Incidence
Mortality
DDREF
DREF
LDEF
0.1
1
10
100
DREF / LDEF / DDREF

Approach to Combining Estimates of LDEF and DREF (1)

[1] Approach based on concept of multi-model inference (model averaging) (UNSCEAR 2012)

Each estimate of LDEF or DREF considered to be distinct model to represent DDREF (not repeated measurement of same quantity)

[2] Uncertain estimates of LDEF and DREF are combined by assigning subjective weights to represent their relevance to estimating DDREF

Weights account for quality of underlying studies

Approach to Combining Estimates of LDEF and DREF (2)

Important property of model averaging –

- CI obtained by combining multiple probability distributions of LDEFs or DREFs is always wider than narrowest CI of individual distributions
- Differs from CI using inverse-variance weighting of LDEFs or DREFs [statistical (random) uncertainties in model fits to dose-responses only]; deflation of uncertainty compared with individual CIs
  - Approach used in meta-analyses of epidemiologic studies

Assumptions in Combining Estimates of LDEF (1)

[1] Combined LDEF for solid cancer incidence

50% weight to LDEF from Preston et al. (2007)

25% weight to each LDEF from BEIR VII report (2006)

Equal weight to results from two expert groups

Assumptions in Combining Estimates of LDEF (2)

[2] Combined LDEF for solid cancer mortality

25% weight to each LDEF from Little et al. (2008)

15% weight to each LDEF from Ozasa et al. (2012) at 0–2 Gy colon dose

10% weight to each LDEF from Ozasa et al. (2012) at 0–4 Gy shielded kerma

Equal weight to results from two expert groups

Assumptions in Combining Estimates of DREF (1)

[1] Combined DREF for solid cancer incidence

80% weight to DREF based on risk in U.K. workers (Muirhead et al. 2009)

20% weight to DREF based on risk in Techa River cohort (Davis et al. 2015)

Only public cohort in which risks of all solid cancers are estimated; lower weight reflects concerns about uncertainties in estimated doses

Assumptions in Combining Estimates of DREF (2)

[2] Combined DREF for solid cancer mortality

40% weight to DREF based on risk in U.K. workers (Muirhead et al. 2009)

40% weight to DREF based on risk from INWORKS (Richardson et al. 2015) [data in U.K. workers from Muirhead et al. (2009)]

20% weight to DREF based on risk in Techa River cohort (Schonfeld et al. 2013)

Assumptions in Combining Estimates of LDEF and DREF

DDREF distribution obtained from distributions of combined LDEFs and DREFs for solid cancer incidence and mortality assuming –

[1] Relative weights of 2:1 to incidence- vs mortality-based LDEFs and DREFs

[2] Equal weights to resulting LDEF and DREF for incidence and mortality combined

[3] Distribution truncated to range of 0.2–20 (about 1.3% of values removed, mostly < 0.2)

Final DDREF Distribution

[1] Properties of probability distribution of DDREF

Median and CIs –

1.3 (0.47, 3.6), 90% CI
(0.39, 5.6), 95% CI

Probability about 27% to DDREF < 1 and 17% to DDREF > 2

[2] Distribution intended to represent state of knowledge of DDREF

Comparisons with Other Estimates

[1] BEIR VII (2006) – 1.5 (0.91, 2.46), 90% CI

Accounts for data in LSS cohort and animals

Essentially LDEF for solid cancer incidence

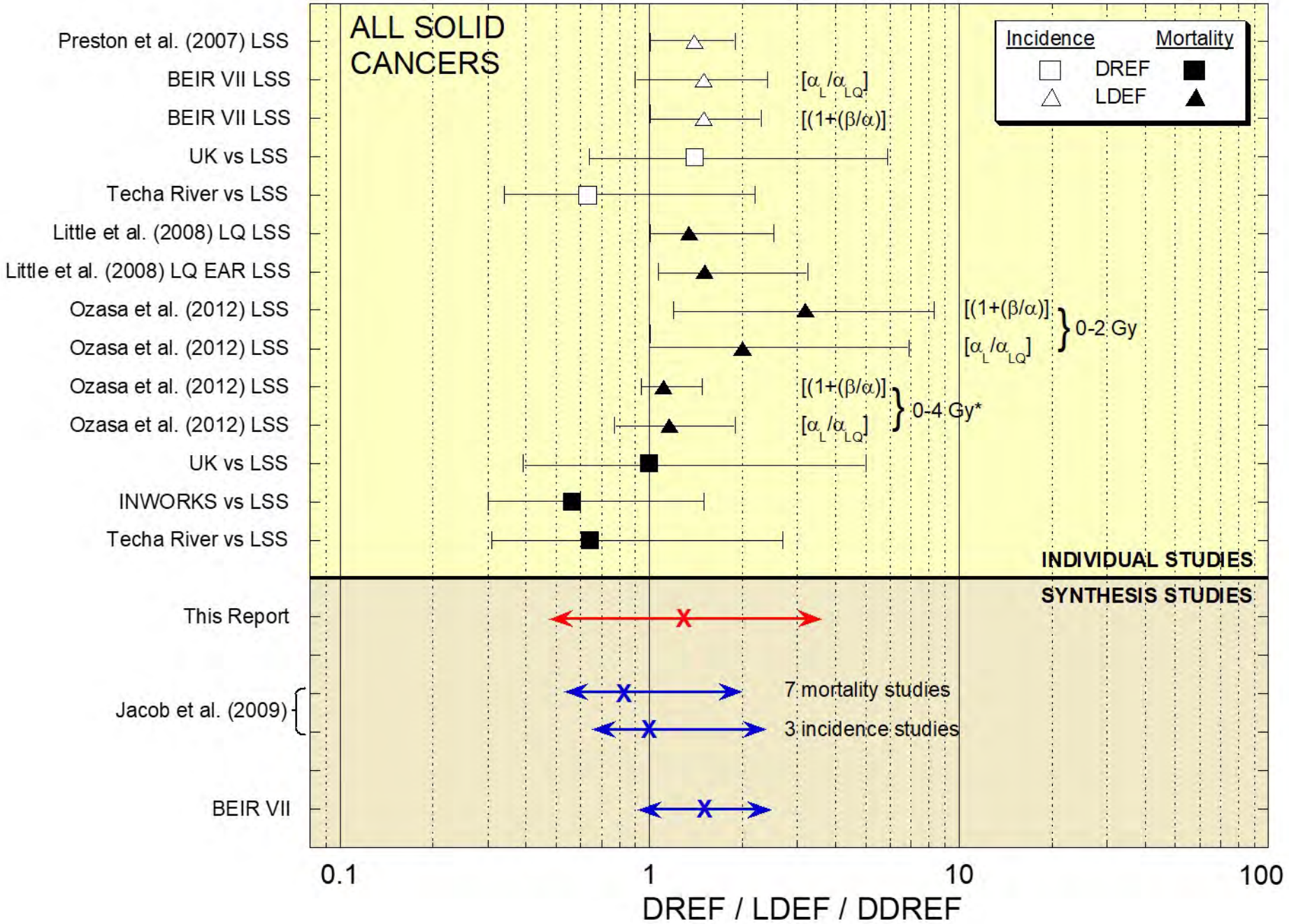
[2] Jacob et al. (2009) – Comparisons of risks in workers/public and LSS cohort (meta-analyses)

Solid cancer mortality (7 studies; main result) –

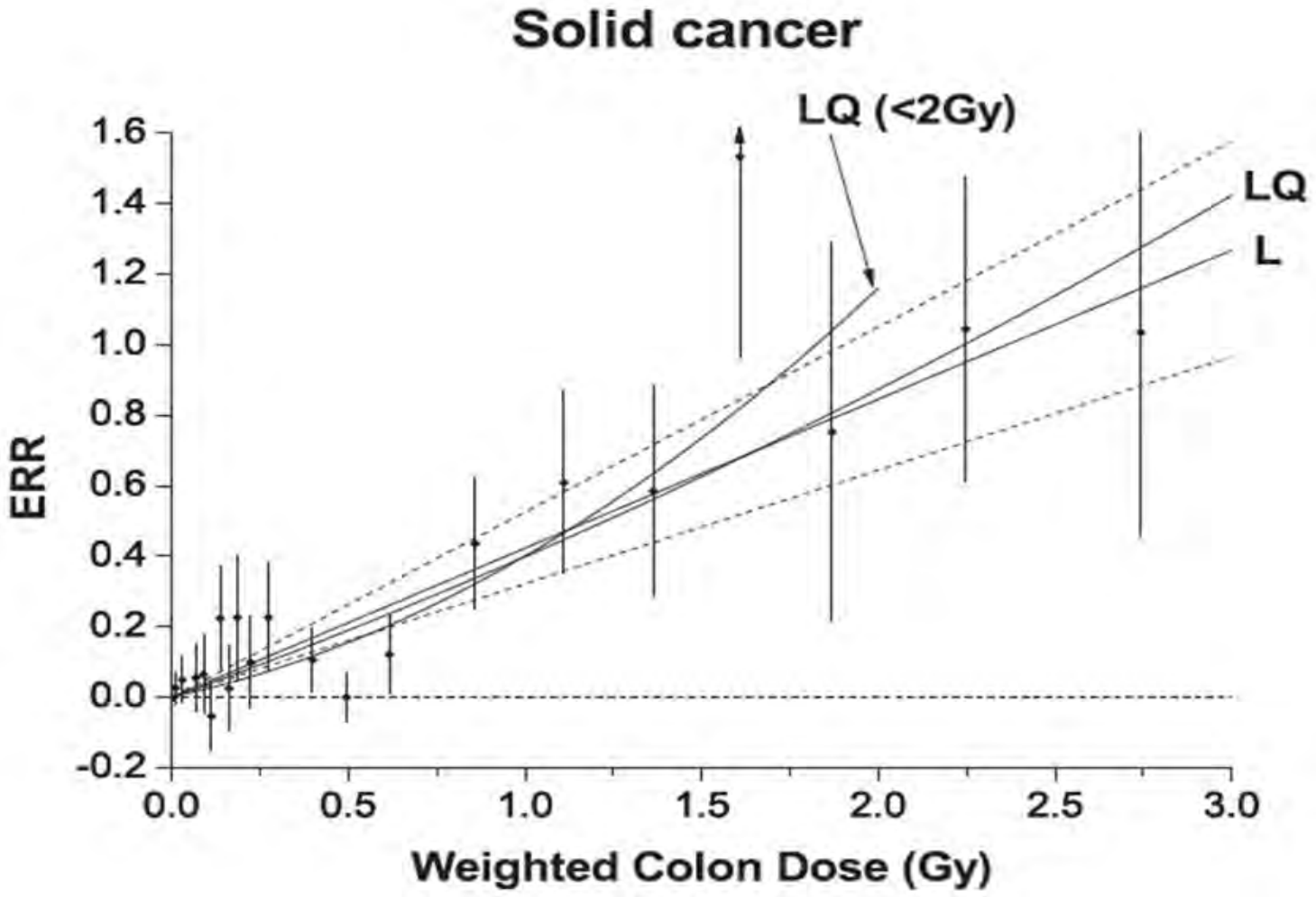
DREF = 0.83 (0.53, 2.0), 90% CI

Solid cancer incidence (3 studies) –

DREF = 1.0 (0.65, 2.4), 90% CI


ALL SOLID CANCERS
Incidence
Mortality
DREF
LDEF
Preston et al. (2007) LSS
BEIR VII LSS
BEIR VII LSS
UK vs LSS
Techa River vs LSS
Little et al. (2008) LQ LSS
Little et al. (2008) LQ EAR LSS
Ozasa et al. (2012) LSS
Ozasa et al. (2012) LSS
Ozasa et al. (2012) LSS
Ozasa et al. (2012) LSS
UK vs LSS
INWORKS vs LSS
Techa River vs LSS
[α_L /α_LQ]
[(1+(β/α)]
[(1+(β/α)]
[α_L /α_LQ]
0-2 Gy
[(1+(β/α)]
[α_L /α_LQ]
0-4 Gy*
INDIVIDUAL STUDIES
SYNTHESIS STUDIES
This Report
Jacob et al. (2009)
7 mortality studies
3 incidence studies
BEIR VII
0.1
1
10
100
DREF / LDEF / DDREF

Dependence of LQ Fit on Dose Range (Ozasa et al. 2012; LSS mortality)



Harmonic Mean of DDREF Distribution

[1] DDREF appears in denominator of equation to estimate risks at low acute doses or low dose rates

Arithmetic mean (average) of uncertain risk at low acute doses or low dose rates is proportional to reciprocal of harmonic mean (HM) of DDREF

$HM = n/\Sigma(1/a_i)$, HM < arithmetic mean

[2] HM of DDREF distribution = 1.1 (mean = 1.6)

Reduction in average risks at low acute doses or low dose rates only about 10% (not ≈ 40%)

Estimates of LDEFs from Recent Analyses of Data in LSS Cohort (1)

LDEFs for solid cancer incidence (MLEs and CIs) –

[1] Preston et al. (2007), 0–2 Gy to colon –

1.3 (1.01, 1.90), 90% CI

[2] Grant et al. (2017), 0–4 Gy kerma, DS02R1 dosimetry, longer follow-up –

1.22 (1.01, 1.60), 90% CI

Estimates of LDEFs from Recent Analyses of Data in LSS Cohort (2)

LDEFs for solid cancer mortality (MLEs and CIs) –

[1] Ozasa et al. (2012), preferred estimate –

1.8 (1.1, 9.6), 95% CI, 0–2 Gy to colon, [1+(β/α)]

[2] Cullings et al. (2017), DS02R1 dosimetry –

2.0 (1.2, 18), 95% CI, 0–2 Gy to colon, [1+(β/α)]

No significant curvature at 0–4 Gy kerma (similar to previous analysis using DS02 dosimetry)

Sex-Dependence of LDEFs (MLEs)

[1] Grant et al. (2017), solid cancer incidence –

2.3 (M) 1.1 (F) (0–4 Gy kerma)

[2] Cullings et al. (2017), solid cancer mortality –

1.1 (M) 1.1 (F) (0–4 Gy kerma)

2.1 (M) 2.0 (F) (0–2 Gy to colon)

[3] Ozasa et al. (2012), solid cancer mortality –

1.1 (M) 1.1 (F) (0–4 Gy kerma)

4.2 (M) 1.5 (F) (0–2 Gy to colon)

Issues with Recent Estimates of LDEF Based on Data in LSS Cohort

[1] Dependence of LDEF for solid cancer mortality on dose range in analyzing dose-response

Effect of dose range on LDEF for solid cancer incidence not reported (but probably small)

Should same dose range be used to estimate LDEF and risk per Gy (R_H)?

[2] Are LDEFs in males and females significantly different; is sex-dependence different for solid cancer incidence vs mortality?

Recent Estimates of DREFs by ICRP Task Group (Shore et al. 2017) (1)

Estimates of DREFs from meta-analyses of studies of solid cancer mortality (19) and incidence (3) in workers or public; inverse-variance weighting

DREFs (medians and 95% CIs) –

2.8 (1.8, 7.1), mortality only

3.0 (1.9, 7.7), mortality and incidence

Estimates dominated by DREF for solid cancer mortality in Mayak workers (weights of 91 and 80%)

Recent Estimates of DREFs by ICRP Task Group (Shore et al. 2017) (2)

DREFs most comparable to our DDREF distribution exclude Mayak workers (medians and 95% CIs) –

0.89 (0.54, 2.5), mortality only

1.9 (1.0, 11), mortality and incidence

1.3 (0.39, 5.6), our DDREF (includes LDEFs)

DREFs based on studies with mean dose < 100 mGy –

0.94 (0.55, 3.3), mortality only (excl. Mayak)

1.7 (0.94, 10), mortality and incidence

Critique of Inverse-Variance Weighting (Meta-Analyses)

Assumptions in using inverse-variance weighting to combine estimated DREFs or LDEFs (meta-analyses)

[1] Each estimate represents direct (repeated) measurement of same quantity

[2] Each estimate is free from bias (systematic error), or biases in different estimates cancel out

Assumptions generally not met in combining estimates from different epidemiologic studies

CIs are too narrow to represent state of knowledge

Concluding Remarks (1)

Estimation of DDREF and its uncertainty always involves important subjective judgments –

- Epidemiologic data to be included; approach to combining estimates of LDEF and DREF
- There is no purely objective approach ("right way") to selecting data and combining estimates

Our approach of subjective weighting based on relevance and use of model averaging differs from inverse-variance weighting used in meta-analyses

Our analysis and all others are works in progress!

Concluding Remarks (2)

[1] Increasing tendency over time toward central estimate of DDREF ≈ 1

[2] Unresolved issues with LSS data

Significant dependence of LDEF on sex (?)

Differences in LDEFs for solid cancer incidence and mortality (?)

Dependence of LDEF on dose range analyzed

[3] Important challenges in estimating DREFs

[4] Uncertainties in LDEFs and DREFs matter!

Concluding Remarks (3)

[1] Our analysis is unique in including LDEFs and DREFs for solid cancer incidence and mortality

[2] Weighting of LDEFs and DREFs based on relevance and quality of studies and use of model averaging also unique

[3] We believe that both approaches are necessary to obtain probability distribution of DDREF that represents state of knowledge

Basing DDREF distribution only on statistical uncertainties in underlying estimates of risk does not fully represent state of knowledge

Documentation of Study

Report providing documentation of entire study available at –

https://www.cdc.gov/niosh/ocas/pdfs/dps/orcra-lowletrad-r0.pdf