

**BEIR VII:
Epidemiology and Models for
Estimating Cancer Risk**

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Dose Reconstruction**

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Outline of talk today

- Highlights of epidemiologic studies
 - Important new data since BEIR V (1990)
 - IARC 15-country nuclear worker study
- Approach for estimating cancer risks
- Example risk estimates




Review of Epidemiologic Studies

- Japanese A-Bomb Survivor Studies
- Medical Radiation Studies
- Occupational Radiation Studies
- Environmental Studies

A-bomb survivors

- Life Span Study (LSS) cohort
 - 87,000 atomic bomb survivors in Hiroshima and Nagasaki with individual dose estimates
- Primary source of data for risk assessments



Strengths of A-bomb Survivor Study for Use in Risk Assessment

- Large population size
- All ages and both sexes
- Long term follow-up for both mortality and cancer incidence
- Whole body exposure
- Well-characterized dose estimates for individual study subjects
- Useful range of doses

A-bomb survivors: Useful range of doses

- 30,000 (62%) exposed survivors with doses 0.005 to 0.1 Sv
- 18,000 survivors with higher doses (0.1-4 Sv)
 - allow reasonably precise risk estimates
- Doses lower than in many studies of persons exposed for therapeutic medical reasons



A-bomb survivors: New since BEIR V

- Improved DS02 dosimetry system
- 15 additional years of mortality follow-up
- Cancer incidence data for both Hiroshima and Nagasaki
- Non-cancer mortality linked with radiation



A-bomb survivors: DS02 dosimetry

- Result of major international effort to reassess and improve dose estimates
- Dosimetry system includes improved methods for
 - Calculating gamma and neutron doses
 - Adjusting for shielding by factory buildings and local terrain feature.

A-bomb survivors: DS02 dosimetry

- Impact on risk estimates minor
- Solid cancer and leukemia risk estimates decreased by about 8%
- Shape of dose-response not modified by dosimetry revision

Preston et al. Radiat. Res. 2004

A-bomb survivors: Updated mortality data

	BEIR V	BEIR VII
Follow-up period	1950-1985	1950-2000
Solid cancer deaths	5,600	10,100
Leukemia deaths	200	300
Solid cancer deaths (Age at exposure < 20)	600	2,000



A-bomb survivors: Cancer incidence data

- Obtained from high quality cancer registries in Hiroshima and Nagasaki
- Diagnostic information of higher quality than that based on death certificates
 - Especially important for estimating site-specific risks
- Includes non-fatal cancers

A-bomb survivors: Cancer incidence data

	Incidence	Mortality
Follow-up period	1958-1998	1950-1997
All solid cancer	12,778	10,127 (-2000)
Stomach cancer	3,602	2,867
Colon cancer	1,165	478
Lung cancer	1,344	1,264
Female breast cancer	847	275
Bladder cancer	352	150



A-bomb survivors: Non-cancer mortality

- Dose-response for non-cancer mortality has been clearly demonstrated
- Associations seen for diseases of the circulatory, digestive, respiratory, and hematopoietic systems
- Data inconclusive regarding
 - Shape of dose-response
 - Modifying effects of age at exposure and other factors



Medical studies

- Huge number of studies
- Radiotherapy for malignant disease
- Radiotherapy for benign disease in children
- Radiotherapy for benign disease in adults
- Diagnostic radiation

Medical studies

- Huge number of studies
- Radiotherapy for malignant disease
(cancers of the cervix, breast, ovary, testis, thyroid, Hodgkin disease, childhood cancer)
- Radiotherapy for benign disease in children
(skin hemangioma, tinea capitis, enlarged tonsils, enlarged thymus)
- Radiotherapy for benign disease in adults
(ankylosing spondylitis, peptic ulcer, breast and gynecological disease, hyperthyroidism)
- Diagnostic radiation
(chest fluoroscopy, I-131, scoliosis)



Medical Studies

- Many studies lack individual dose estimates
 - Doses usually vary markedly by organ
- Therapeutic doses often very high (10+ Gy)
 - Limited usefulness for quantifying risks at low doses
- Risk estimates often very imprecise
- Diseased persons may not be typical of general population



Pooled Analyses

- Medical data strongest for thyroid and breast cancer
- Thyroid cancer after exposure to external radiation: A pooled analyses of seven studies (Ron et al. Radiat. Res. 1995)
- Radiation effects on breast cancer risk: A pooled analysis of eight cohorts (Preston et a. 2002)



Occupational Radiation Studies

- Nuclear industry workers
- Workers at the Mayak facility
- Chernobyl clean-up workers
- Airline and aerospace employees
- Medical and dental occupational exposures



Nuclear industry workers

- Exposures deliberately limited as a protection to the worker
- Provide a direct assessment of risks at low doses and dose rates
- Dose estimates obtained from personal dosimeters worn by workers

Two Large Worker Studies

- International Agency for Research on Cancer (IARC) 3-country study
 - 96,000 workers in the US, UK, and Canada
 - Cardis et al. Radiation Research 1995
- National Registry of Radiation Workers (NRRW)
 - 125,000 workers at several selected facilities in UK
 - Muirhead et al. J Radiol Prot 1999



IARC* 15-Country Nuclear Worker Study

- Cardis et al., British Medical Journal, 2006
- More detailed paper expected soon
- Largest worker study ever conducted
 - ~ 400,000 workers
 - ~ 6500 cancer deaths
 - Most workers in previous studies in US, UK, and Canada
 - Several new studies in US and other countries

*International Agency for Research on Cancer

15-Country Study (Cancer deaths)

United States (2,841)

United Kingdom (2,273)

Japan* (432)

Canada (417)

France (348)

Sweden (194)

Belgium (90)

Hungary (40)

Finland (34)

Lithuania (25)

Spain (25)

Korea (21)

Switzerland (24)

Australia (20)

Slovakia (10)

*Included only in leukemia analyses

15-Country Study (Cancer deaths)

- United States Studies (2,841)
 - Hanford (1,279)
 - Idaho National Engineering Laboratory* (886)
 - Nuclear Power Plant Workers (314)
 - Oak Ridge National Laboratory (225)

*Included only in leukemia analyses

Dosimetry for 15-Country Study

- **Extensive attention given to dosimetry**
 - Dosimetry subcommittee
 - Questionnaires on dosimetry practices and radiation environments
 - Special studies of representative facilities
 - Testing of several representative dosimeters
- **Objective:** Develop factors for converting recorded doses to organ doses and evaluate uncertainties in these factors

Excess Relative Risk (ERR) per Gy for Leukemia excluding CLL

3-country study:	2.2 (0.13, 5.7)
NRRW*:	2.6 (-0.03, 7.2)
15-country study:	1.9 (< 0, 8.5)

A-bomb survivors**:

Linear	3.2 (1.6, 5.7)
Linear-quadratic	1.5 (<0, 5.3)

*National Registry of Radiation Workers

**Estimates for males exposed at ages 20-60

Excess Relative Risk (ERR) per Gy for All Cancers Excluding Leukemia

3-country study: -0.07 ($-0.29, 0.30$)

NRRW*: 0.09 ($-0.28, 0.52$)

15-country study: 0.97 ($0.14, 1.97$)

A-bomb survivors**: 0.23 ($0.15, 0.36$)

*National Registry of Radiation Workers

**Linear estimate for males exposed at ages 30+

Excess Relative Risk (ERR) per Gy for 15-Country Study

All solid cancers (4770)	0.87 (0.02, 1.9)
Solid cancers unrelated to smoking (2033)	0.62 (−0.5, 2.2)
Smoking related cancers (2737)	0.91 (−0.1, 2.2)
Lung cancer	1.85 (0.26, 4.0)
Other smoking-related cancers	0.21 (< 0, 2.0)

15-Country study

“Taken together, these findings indicate that a confounding effect by smoking may be partly, but not entirely, responsible for the estimated increased risk for mortality from all cancers other than leukaemia.”

Cardis *et al.* (2006)

Heterogeneity Among Countries

All Cancer Excluding Leukemia

Cohorts

Canada

Sweden

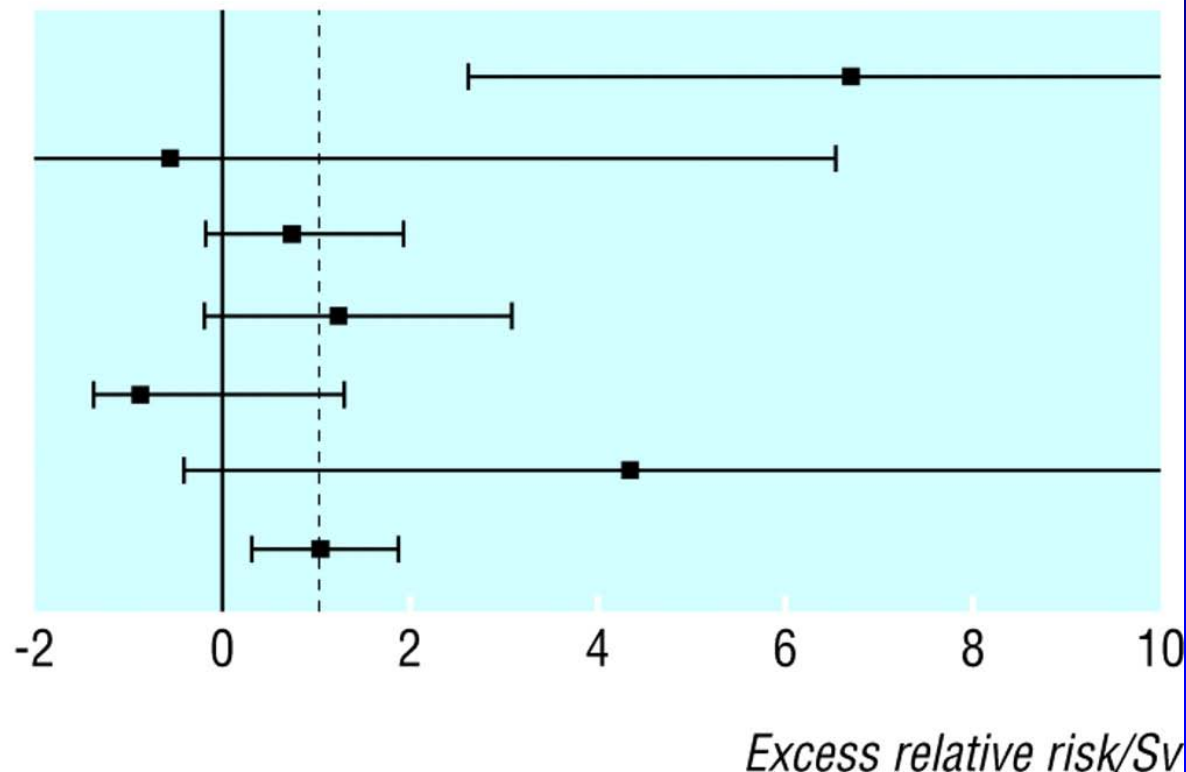
UK - all

USA - Hanford

USA - NPP

USA - ORNL

All combined



Heterogeneity Among Countries

All Cancer Excluding Leukemia

- p-value for heterogeneity = 0.18
- Estimate with all countries: 0.97 (0.14, 2.0)
Estimate with Canada excluded: 0.58 (-0.2, 1.6)
- Estimate remained statistically significant when other studies were excluded individually



Limitations of Low Dose Worker Studies

- Increase in risk likely to be at most a few percent
- Low statistical power and imprecisely estimated risks
- Strong potential for confounding



Environmental Studies

- Populations living around nuclear facilities
- Populations exposed from environmental releases
- Populations exposed from the Chernobyl accident
- Children of adults exposed to radiation
- Exposure to radioactive iodine-131



Environmental Studies

- Most studies are of limited usefulness for quantitative risk assessment
- Some studies show promise for the future including persons exposed as result of
 - Chernobyl accident
 - Releases from Mayak nuclear facility

Outline of talk today

- Highlights of epidemiologic studies
 - Important new data since BEIR V (1990)
- Approach for estimating cancer risks
- Example risk estimates

Estimating Cancer Risks

- **From the Statement of Task:**

“The primary objective will be to develop the best possible risk estimate for exposure to low-dose, low-LET radiation in human subjects.”

- BEIR VII committee defined “low dose” as
 - < 100 mGy (0.1 Gy) or
 - < 0.1 mGy/min over months or a lifetime



Estimating Cancer Risks

- Estimate lifetime risk allowing for dependencies on
 - Dose
 - Sex
 - Age at exposure

Lifetime risk: Risk of developing (fatal) cancer over exposed person's lifespan



BEIR VII Cancer Endpoints

- Cancer mortality
- Cancer incidence
- Separate estimates for
 - leukemia
 - all solid cancers
 - cancers of several specific sites



Cancer sites evaluated by BEIR VII

- Stomach
- Colon
- Liver
- Lung
- Female breast
- Prostate
- Uterus
- Ovary
- Bladder
- Thyroid
- All other solid cancers
- Leukemia



Estimating Lifetime Risk

- Use data from epidemiologic studies to develop risk models
- Apply models to estimate lifetime risk from low-dose exposure to the US population

Estimating Lifetime Risk

- Use data from epidemiologic studies to develop risk models; that is
 - Express age-specific risk as a function of dose and other factors such as sex, age at exposure, attained age, and time since exposure
- Apply model to estimate lifetime risk from low-dose exposure to the US population

BEIR VII models: What data were used?

- **Breast cancer:** Pooled analysis of data on A-bomb survivors and medically exposed persons
 - Preston et al. 2002
- **Thyroid cancer:** Pooled analysis of data on A-bomb survivors and medically exposed persons
 - Ron et al. 1995
- **All other cancer sites:**
 - A-bomb survivor cancer incidence and mortality data
 - All analyses based on DS02 dosimetry
 - Analyses conducted by BEIR VII Committee

BEIR VII Models

Models developed for:

- **Excess Relative Risk (ERR):**

$$\text{Risk} = \text{Baseline risk} [1 + \text{ERR}]$$

- **Excess Absolute Risk (EAR):**

$$\text{Risk} = \text{Baseline risk} + \text{EAR}$$

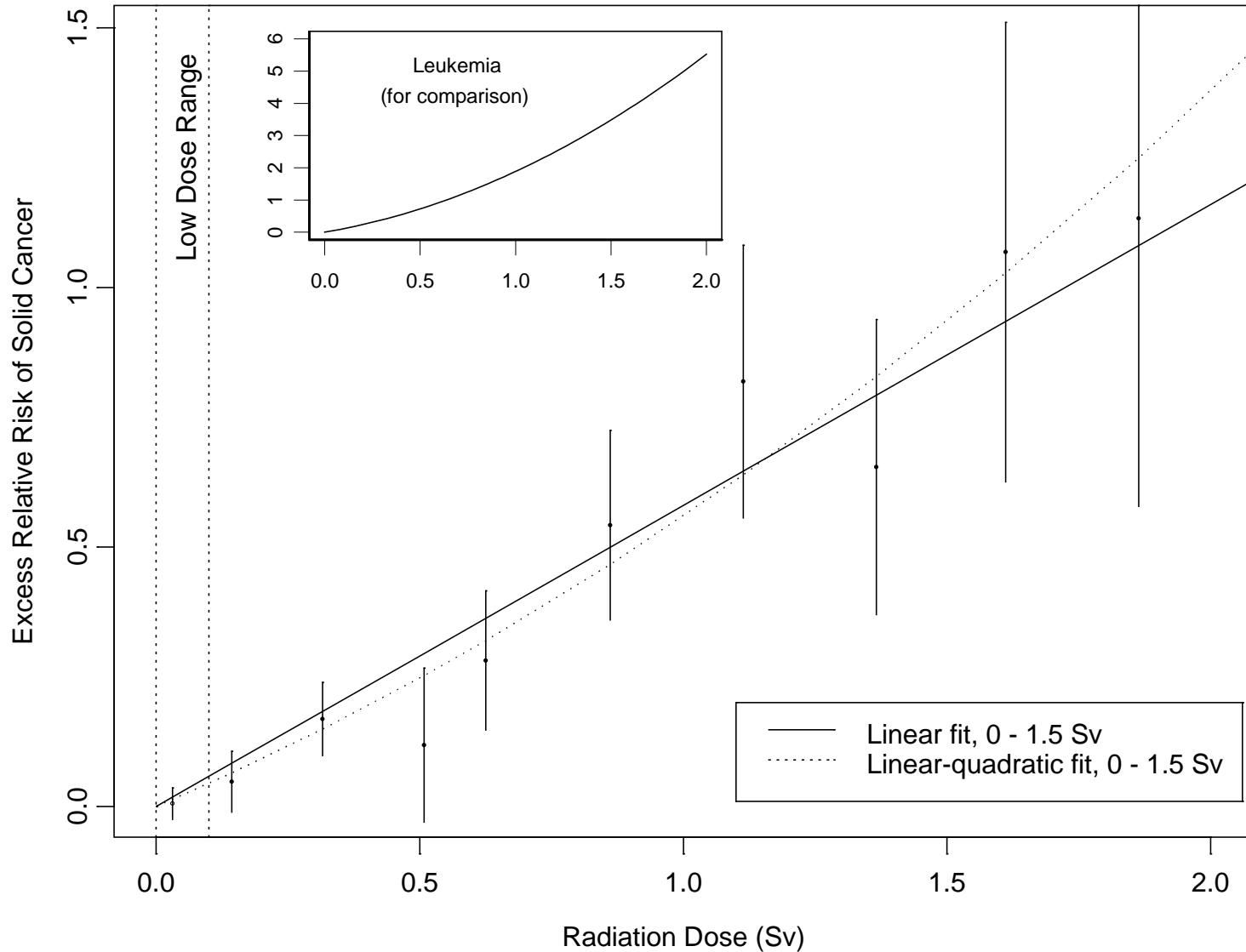
- **Both ERR and EAR**

- Depend on dose
- May depend on sex, age at exposure, attained age, time since exposure

BEIR VII models: Dose-response

- **Solid cancers:** Risk expressed as a linear function of dose
- **Leukemia:** Risk expressed as a linear-quadratic function of dose
- These choices supported by
 - A-bomb survivor data
 - Pooled analyses of breast and thyroid cancer data
 - Radiobiological considerations

LSS solid cancer incidence: Excess relative risk



BEIR VII,
Fig. ES-1



BEIR VII Models for Solid Cancers

Selected Models:

- Both ERR and EAR decreased with increasing age at exposure over the range 0 to 30 years
 - No further decrease after age 30
- Both ERR and EAR depended on attained age
 - ERR decreased with attained age
 - EAR increased with attained age

Estimating Lifetime Risk

- Use data from epidemiologic studies to develop risk models
- Apply models to estimate lifetime risk from low-dose exposure to the US population



Applying Risk Model : Two Issues of Importance

- Use of model to estimate risk at low doses and dose rates
- “Transporting” risk from Japanese A-bomb survivors to US population
- Both issues discussed in Chapter 10: Integration of Biology and Epidemiology

Use of model to estimate risk at low doses and dose rates

- Linear estimates from A-bomb survivors reduced by a Dose and Dose Rate Effectiveness Factor (DDREF)
- Many past risk assessment have used a DDREF of 2

Dose and Dose Rate Effectiveness Factor (DDREF)

- BEIR VII DDREF derived from Bayesian analyses of
 - A-bomb survivor solid cancer incidence data
 - Data from relevant studies in mice
- Estimate with 95% interval: 1.5 (1.1 – 2.3)
- Referred to as “LSS DDREF”

LSS = Life Span Study of A-bomb survivors

Applying Risk Model : Assumptions

- Use of model to estimate risk at low doses and dose rates
- “Transporting “ risk from Japanese A-bomb survivors to the US population

Baseline Cancer Incidence Rates in US and Japan (Females)

	US	Japan
All	280	185
Stomach	3.5	34
Colon	22	17
Liver	1.3	9.8
Lung	34	12
Breast	89	30
Bladder	5.9	2.6

Source: Cancer Incidence in Five Continents, 1997

Approaches for Transporting Risks from Japan to US

- **Absolute risk transport (AR):** Absolute risks the same for Japan and US (BEIR III)
- **Relative risk transport (RR):** Excess relative risks the same for Japan and US (BEIR V)
- Intermediate approaches
(EPA, NIH Radio-epidemiological Tables)



Model for transporting risks: How do we decide?

- Compare epidemiologic data on non-Japanese populations and A-bomb survivors
- Evaluate interaction of radiation and factors that contribute to differences in baseline risks
- Biological considerations (initiation/promotion)

BEIR VII approach to transport

Breast and thyroid cancer

- Estimates based on pooled analyses that included non-Japanese populations
- Breast cancer: EAR model from Preston et al. 2002
- Thyroid cancer: ERR model from Ron et al. 1995

BEIR VII approach to transport

Sites other than breast and thyroid:

- Provide estimates based on both relative and absolute risk transport
 - Use ERR and EAR models
 - Range reflects uncertainty
- Use weighted mean for point estimates
 - All sites except lung: 0.7 for RR; 0.3 for AR
 - Lung: 0.3 for RR; 0.7 for AR
 - Weighting conducted on logarithmic scale

Example: Lifetime Risk* of Stomach Cancer Incidence in Males

Estimate based on RR transport:	25
Estimate based on AR transport:	280
Weighted mean:	52
Weighted estimate reduced by DDREF of 1.5:	34

*Number of cases per 100,000 persons exposed to 0.1 Gy
RR = Relative Risk transport; AR = Absolute Risk transport

Lifetime Risk Estimates for Cancer Incidence. Males.

	RR	AR	Estimate**
Stomach	25	280	34
Colon	260	180	160
Liver	23	150	27
Lung	250	190	140
Prostate	190	6	44
Bladder	160	120	98

*Number of cases per 100,000 persons exposed to 0.1 Gy
RR = Relative Risk transport; AR = Absolute Risk transport

**Weighted mean reduced by DDREF of 1.5

Lifetime Risk Estimates* for Leukemia Incidence.

	RR	AR	Estimate**
Incidence			
Males	120	64	100
Females	94	38	72

*Number of cases per 100,000 persons exposed to 0.1 Gy

RR = Relative Risk transport; AR = Absolute Risk transport

**Weighted mean based on linear-quadratic model

Lifetime risk estimates



- Estimates for “all solid cancers” obtained by summing site-specific estimates.

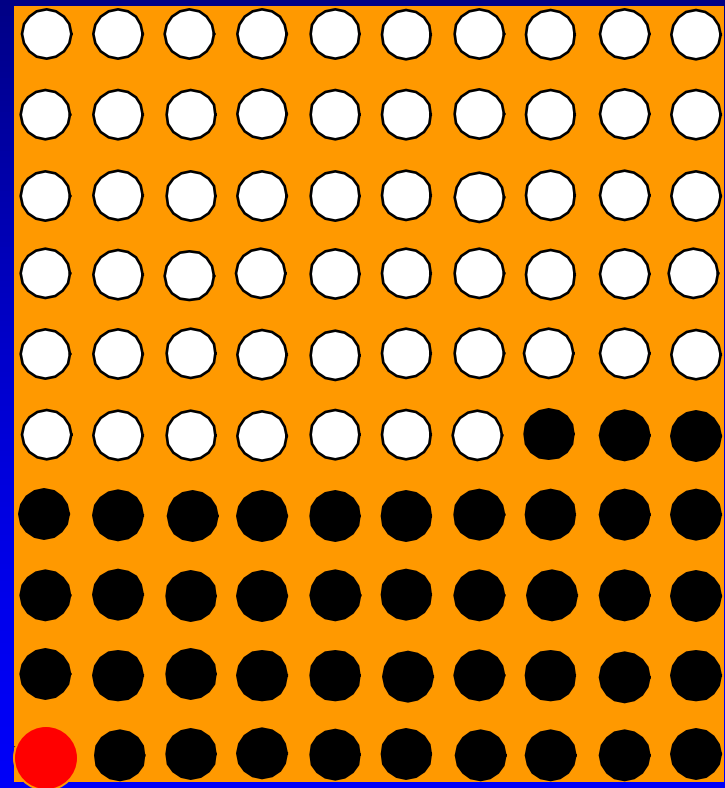
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Lifetime risk for incidence of solid cancer and leukemia

If 100 people exposed to 0.1 Gy (100 mGy), expect

- 1 cancer from this exposure 
- 42 cancers from other causes 





Sources of Uncertainty Included in Quantitative Assessment

- Statistical uncertainties in estimating model parameters
- Use of model to estimate risk at low doses and dose rates (DDREF)
- Transporting risk from Japanese A-bomb survivors to US population

Lifetime Risk Estimates. Number of cases or deaths per 100,000 persons exposed to 0.1 Gy

	Incidence	Mortality
All solid cancers		
Males	800 (400-1600)	410 (200-830)
Females	1300 (690-2500)	610 (300-1200)
Leukemia		
Males	100 (30-300)	70 (20-250)
Females	70 (20-250)	50 (10-190)

Estimates with 95% subjective confidence intervals

Lifetime Risk Estimates* for Cancer Incidence and Mortality in Females

	Incidence	Mortality
Stomach	43 (5-390)	25 (3-220)
Colon	96 (34-270)	46 (16-130)
Liver	12 (1-130)	11 (1-130)
Lung	300 (120-780)	270 (110-660)
Breast	310 (160-610)	73 (37-150)
Ovary	40 (9-170)	24 (6-98)
Bladder	94 (30-290)	28 (10-81)

Number of cases or deaths per 100,000 persons exposed to 0.1 Gy

BEIR VII Example exposure scenarios

- Single exposure of 0.1 Gy to population of mixed ages
- Single exposure of 0.1 Gy to persons aged 0, 5, 10, 15, 20, 30, 40, 50, 60, 70 and 80
- Exposure of 1 mGy per year throughout life
- Exposure of 10 mGy per year from ages 18 to 65

- Estimates for each scenario shown for
 - Cancer incidence and mortality
 - Each of 12 specific cancer categories



Lifetime risk estimates for solid cancer incidence by age at exposure

	Males	Females
Age at exposure		
10	1330 (660-2660)	2530 (1290-2660)
30	600 (290-1260)	1000 (500-2020)
50	510 (240-1100)	680 (350-1320)
All ages	800 (400-1600)	1300 (690-2500)

Number of cases per 100,000 persons exposed to 0.1 Gy

Lifetime risk estimates for solid cancer incidence and mortality: Both sexes

Exposure scenario	Incidence	Mortality
Single exposure of 100 mGy	1060	510
1 mGy per year throughout life	760	380
10 mGy per year from ages 18 to 65	3300	1790

Number of cases per 100,000 persons

Comparison of Lifetime Risk Estimates for Solid Cancer* Mortality. Both sexes.

	Estimate	DDREF
BEIR VII (2005)	510	1.5
BEIR V (1990)	695	No DDREF
ICRP (1991)	450	2
EPA (1999)	520	2

*Or all cancers except leukemia

Number of cases per 100,000 persons exposed to 0.1 Gy

Comparison of Lifetime Risk Estimates for Solid Cancer* Mortality. Both sexes.

	Estimate	DDREF	Estimate using DDREF of 1.5
BEIR VII (2005)	510	1.5	510
BEIR V (1990)	695	No DDREF	460
ICRP (1991)	450	2	600
EPA (1999)	520	2	690

*Or all cancers except leukemia

Number of cases per 100,000 persons exposed to 0.1 Gy



Lifetime Risk Estimates for Leukemia* Mortality.
Number of deaths per 100,000 persons exposed to 0.1 Gy.
Both sexes.

	Estimate
BEIR VII: Mortality	60
BEIR VII: Incidence	85
BEIR V (1990)	95
ICRP (1991)	50
EPA (1999)	56

*Leukemia excluding chronic lymphatic leukemia



Sources of Uncertainty Included in Quantitative Assessment

- Statistical uncertainties in estimating model parameters
- Use of model to estimate risk at low doses and dose rates (DDREF)
- Transporting risk from Japanese A-bomb survivors to US population

Uncertainties in Lifetime Cancer Incidence

Estimates for Females

Percent of variance due to

	Estimation	Transport	DDREF	95% factor*
All solid	11	6	83	1.9
Stomach	4	89	7	9.2
Colon	54	14	32	2.8
Liver	21	73	6	10.9
Lung	16	44	39	2.6
Breast	25	0	75	2.0
Ovary	79	5	17	4.2

*Ratio of upper 95% bound to estimate



Features of BEIR VII Risk Estimates (1)

- Equal attention to cancer incidence and mortality
- Based on greatly strengthened epidemiologic data
 - A-bomb survivor incidence and mortality data
 - 13,000 incident cases
 - 10,000 solid cancer deaths (5600 for BEIR V)
 - DS02 dosimetry
 - Pooled analyses including several medical studies for estimating breast and thyroid cancer risks



Features of BEIR VII Risk Estimates (2)

- Expanded list of cancer sites
- DDREF estimated using Bayesian analyses
 - A-bomb survivor data
 - Experimental data in mice
- Explicit attention to transport of risks
- Quantitative evaluation of major sources of uncertainty