National Cancer Institute

Non-cancer Effects at Radiological Doses

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Typical diagnostic doses

TABLE 3.1 Typical heart, brain and effective doses for six common X-ray examinations in the UK
Effective dose based on ICRP Publication 103 (ICRP, 2007) methods for calculation (A-P – anterior-posterior, PA – posterior-anterior, Lat – lateral)

Examination	Brain dose (mGy)	Heart dose (mGy)	Effective dose (mSv)
Head (AP+PA+Lat radiographs)	0.68	0.0008	0.068
Chest (PA radiograph)	0.0002	0.016	0.014
Barium swallow (radiography/fluoroscopy)	0.028	3.4	1.5
Coronary angiography (radiography/fluoroscopy)	0.0072	13	3.9
Head CT scan	45	0.020	1.4
Chest CT scan	0.14	13	6.6

(HPA: Circulatory Disease Risk, 2010)

Estimating non-cancer risk at radiological doses

Key questions to address

- Types of diseases of concern
- Dose response in a low dose range
- Temporal pattern of the risk
- Modifying effects of age factors

Epidemiological data

- A-bomb survivor cohort
  - + Wide spectrum of diseases
  - + Long-term follow up
  - + Wide range of doses
  - + Wide range of age at exposure
  - – Acute exposure
- Populations with repeated exposures
  - – Medical exposure
  - – Occupational exposure

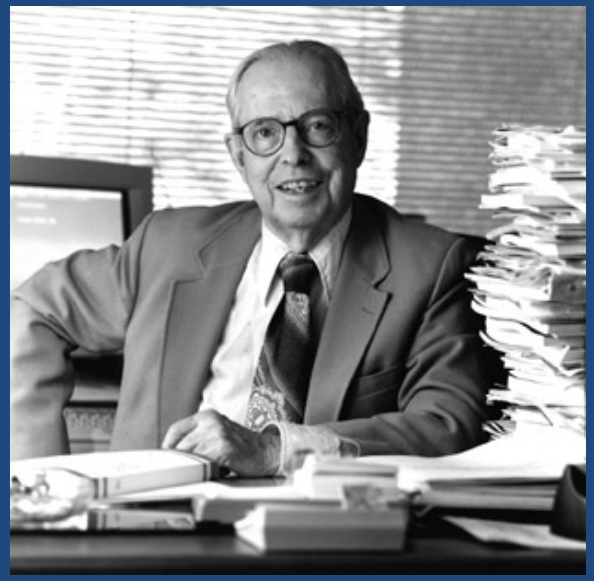
Atomic-bomb survivor cohort

Life Span Study (LSS)

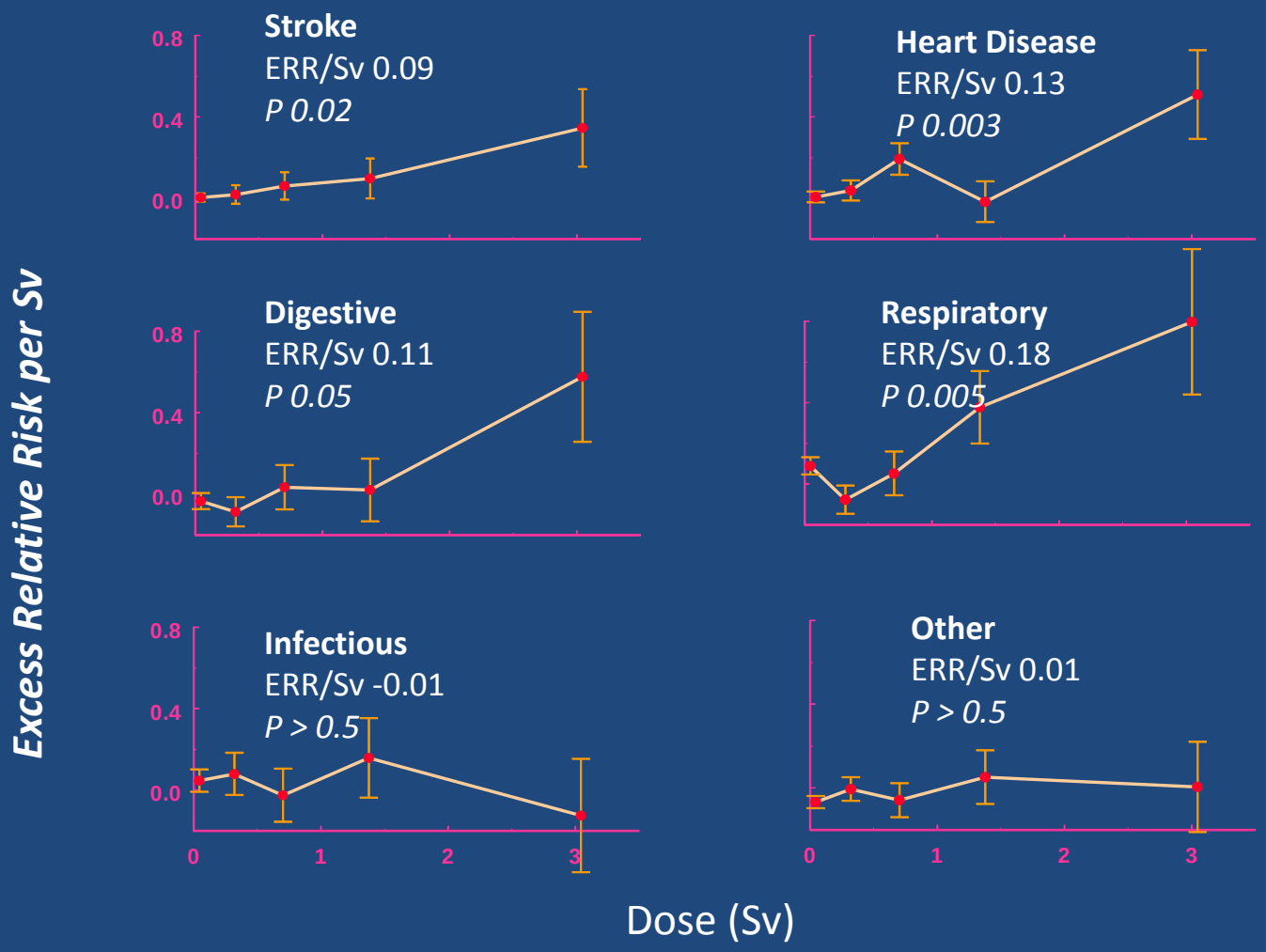
- 120,000 subjects including non-exposed persons in Hiroshima and Nagasaki
- Mortality follow up since 1950
- Mail survey data on lifestyle factors and other co-variables

Adult Health Study (AHS)

- Clinical subset of LSS of 20,000 persons
- Biennial health examination since 1958



LSS non-cancer mortality



(Shimizu, 1992)

LSS non-cancer mortality, 1968-97

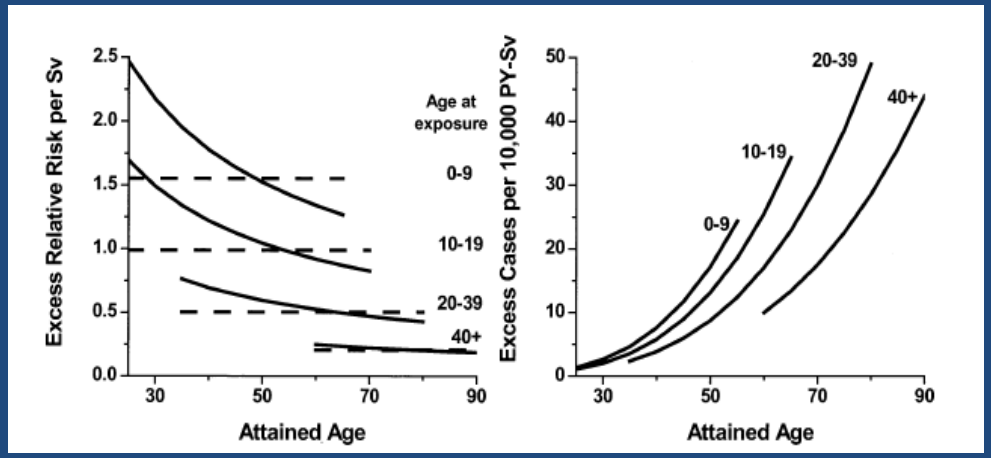
Cause of death	ERR/Sv	Total deaths	Excess deaths
All non-cancer	**0.14**	**14,459**	**273**
Heart	**0.17**	**4,477**	**101**
Stroke	**0.12**	**3,954**	**64**
Respiratory	**0.18**	**2,266**	**57**
Digestive	**0.15**	**1,292**	**27**
Infectious	-0.02	397	-1
Other	0.08	2,073	24
Solid cancer, 1950-97	**0.47**	**9,335**	**440**

ERR = Excess relative risk (Preston, 2003)

- ERR for non-cancer is smaller for non-cancer than for solid cancers
- However, non-cancer excess deaths are substantial
  - Reflecting high non-cancer baseline rates
  - Largely for cardiovascular disease

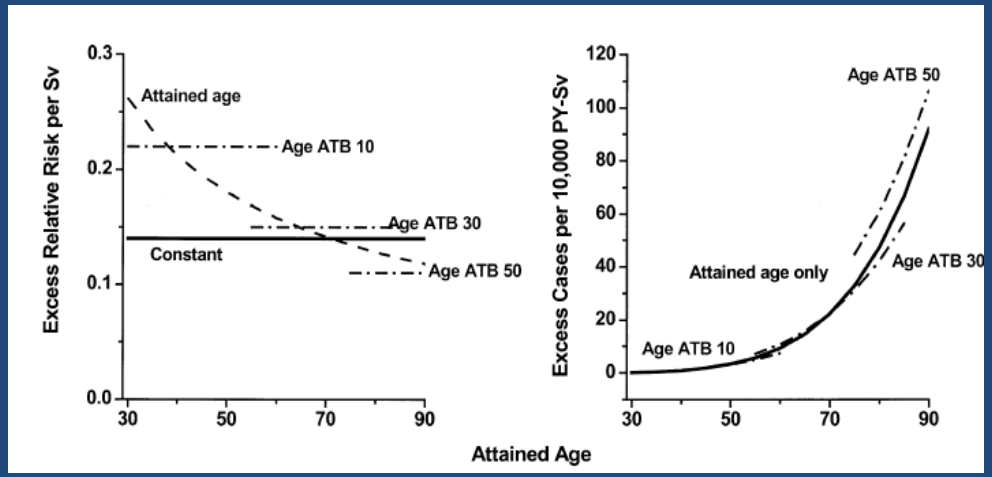
Age and time patterns

Non-cancer risk



- Precise characterization of modifying effects on non-cancer risk is difficult
  - Low ERR
  - High baseline rates

Solid cancer risk



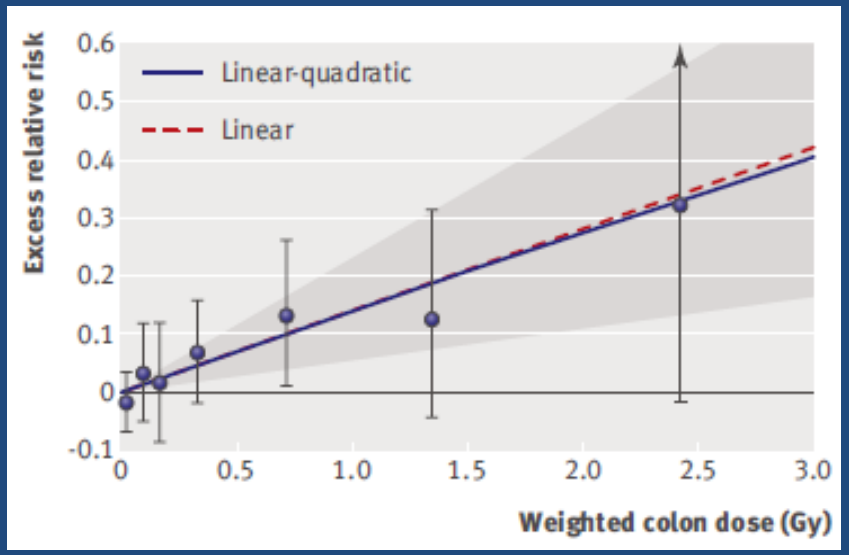
- Generally, age, time and gender patterns for non-cancer are similar to those for cancer
  - ERR/Gy for non-cancer: 0.11 (men); 0.17 (women)

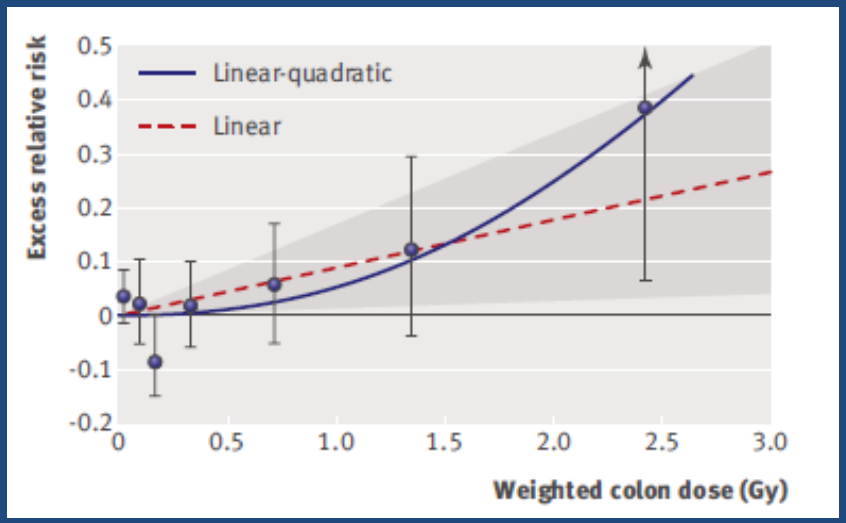
(Preston , 2003)

LSS heart and stroke mortality, 1950-2003

- Heart disease
  - ERR/Gy = 0.14 for full dose range, linear, and similar for low dose range
    - ERR = 0.14 (0-2 Gy)
      0.18 (0-1 Gy)
      0.20 (0-0.5 Gy)
    - Not significant in 0-0.5 Gy range
- Stroke
  - ERR/Gy = 0.9, linear
  - Possible upward curvature
    - ERR = 0.03 (0-1 Gy)
      0.07 (0-0.5 Gy)

(Shimizu, 2010)





Ischemic heart disease risk: Medium and low dose studies

TABLE 4.3 Ischaemic heart disease (ICD9 410–414) excess relative risks per Sv in various studies

Study	ERR Sv^{-1} (with 95% CI)
Atomic bomb morbidity (Yamada et al, 2004)	0.05 (–0.05, 0.16)
Mayak morbidity (Azizova and Muirhead, 2009, + Azizova et al, 2010)	0.11 (0.05, 0.17)
Chernobyl morbidity (Ivanov et al, 2006)	0.41 (0.05, 0.78)
Atomic bomb mortality (Shimizu et al, 2010)	0.02 (–0.10, 0.15) [a]
UK National Registry for Radiation Workers (Muirhead et al, 2009)	0.26 (–0.05, 0.61)
BNFL mortality (McGeoghegan et al, 2008)	0.70 (0.37, 1.07) [b,c]
US peptic ulcer mortality (Carr et al, 2005)	0.11 (0.01, 0.22)
UKAEA mortality (Atkinson et al, 2003)	–0.66 (–1.46, 0.23)
US Oak Ridge mortality (Richardson and Wing, 1999)	–2.86 (–6.90, 1.18)
All occupational studies	**0.12 (0.06, 0.18)**
All studies	**0.10 (0.05, 0.14)**

Notes
a Analysis using underlying cause of death.
b Analysis using underlying or contributing cause of death.
c 90% CI.

(Health Protection Agency, 2010)

HPA meta- analysis results

- There is statistical heterogeneity in risk among medium and low dose studies, possibly due to confounding with unmeasured lifestyle factors.
- The heterogeneity is diminished (but not eliminated) if allowance is made for endpoints (mortality vs. morbidity, heart disease vs. stroke) and fractionation effects.
- An estimated ERR is 0.09 per Gy (95% CI 0.07, 0.12).

AGIR Recommendations

6. In anticipation of the possible future emergence of evidence for radiation causality of circulatory disease below 0.5 Gy, the AGIR recommends that the HPA considers the implications of such evidence for radiation protection.

"Circulatory Disease Risk" – Report of the independent Advisory Group on Ionising Radiation (HPA, 2010)

Statement on Tissue Reactions
Approved by the Commission on April 21, 2011

(4) Although uncertainty remains, medical practitioners should be made aware that the absorbed dose threshold for circulatory disease may be **as low as 0.5 Gy** to the heart or brain. **Doses to patients of this magnitude could be reached during some complex interventional procedures, and therefore particular emphasis should be placed on optimisation in these circumstances.**

LSS digestive disease mortality

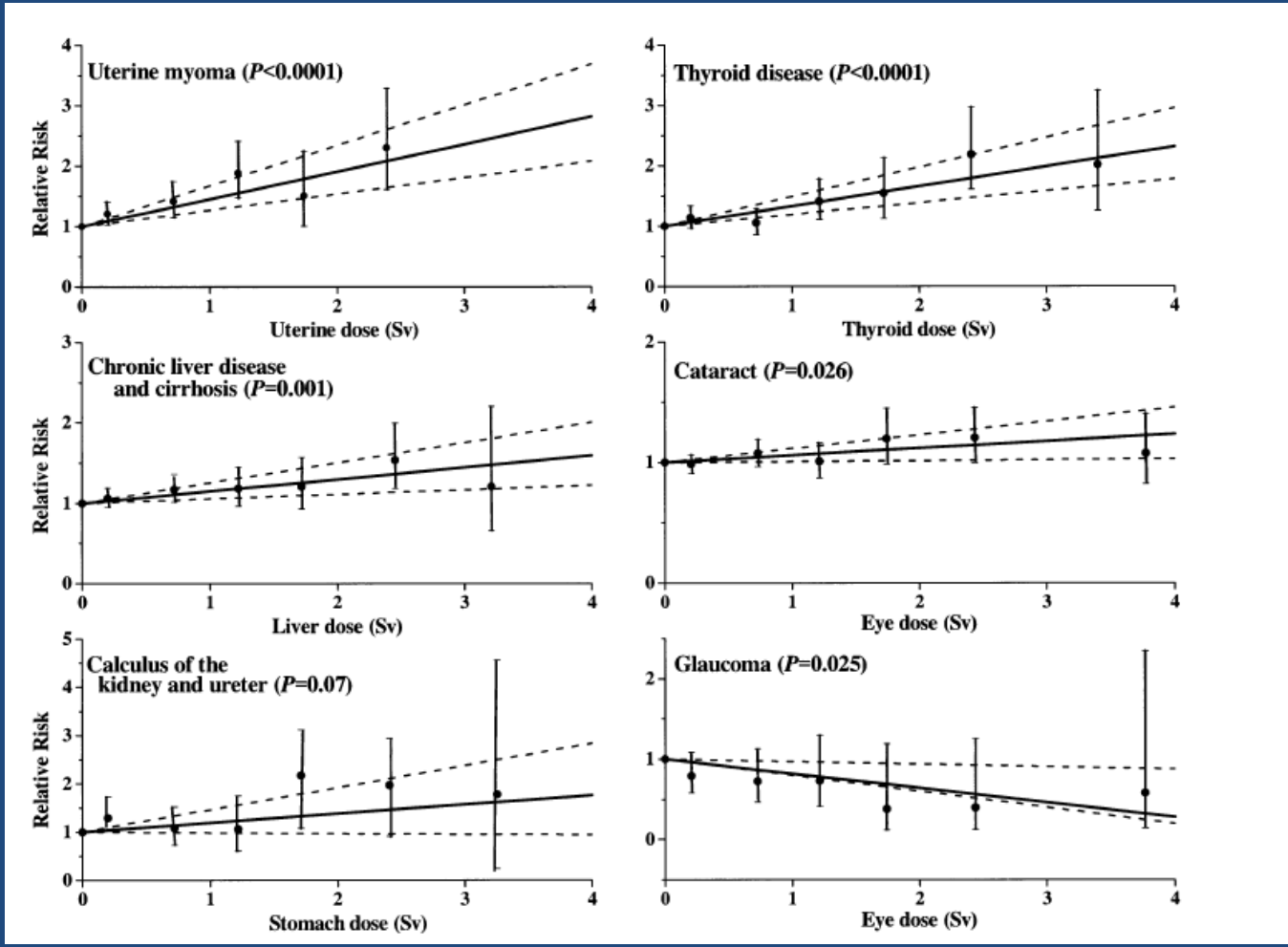
- The high ERR/Gy (0.15) for digestive disease is mainly derived from the high ERR (0.19) for liver cirrhosis
  - In part due to reduced ability to clear hepatitis B viral infection in radiation-exposed subjects
  - Possible synergistic effect of radiation and hepatitis C viral infection – prevalent in subgroups in Japan

(Fujiwara, 2002, 2003)

LSS respiratory disease risk

- The high ERR/Gy (0.18) for respiratory disease is primarily driven by the high ERR/Gy (0.18) for pneumonia in the elderly survivors
  - Possibly due to other debilitating diseases or misclassification in causes of death
  - Need clarification

AHS incidence data, 1958-98



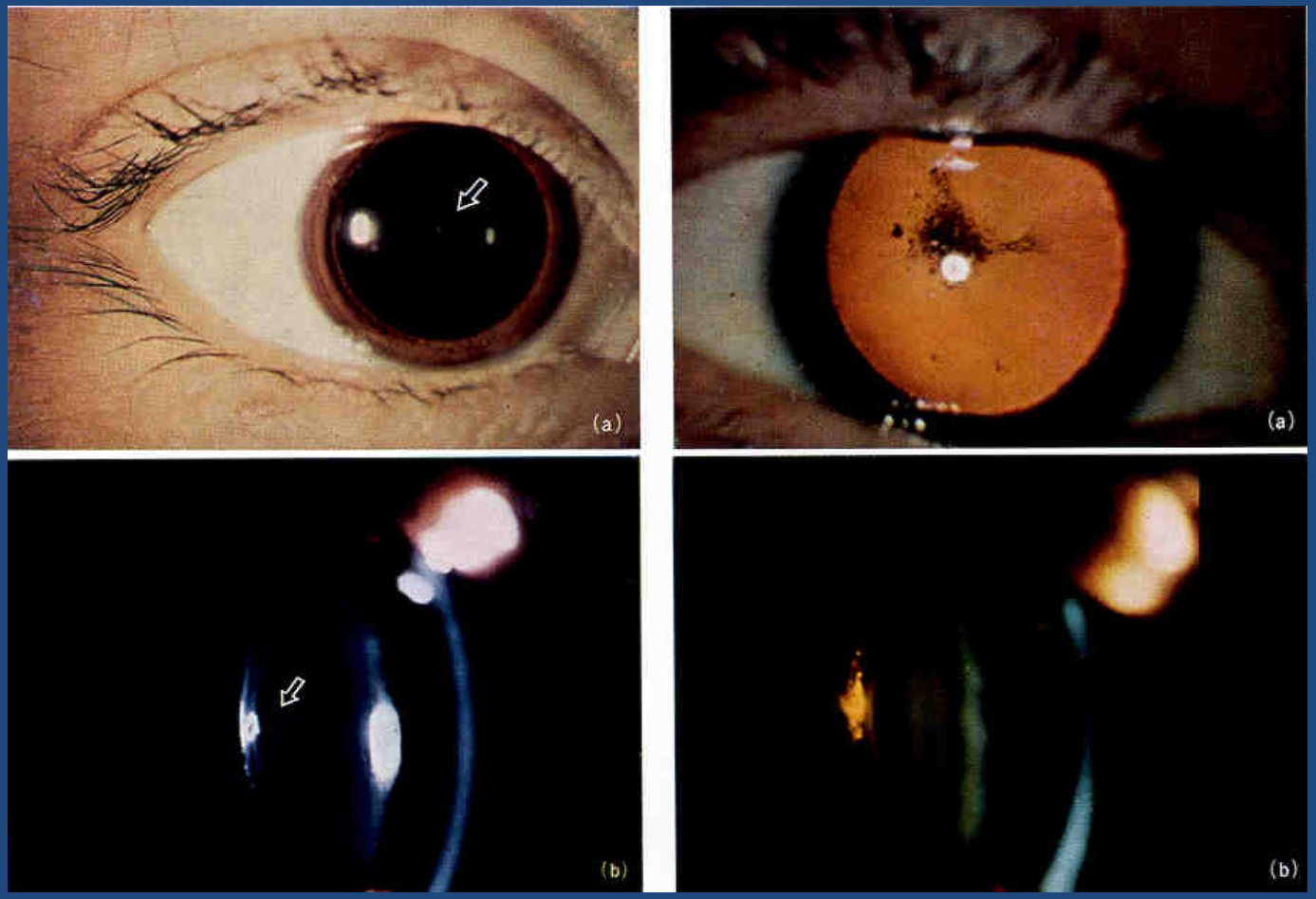
(Yamada, 2004)

AHS: Non-cancer morbidity data

	No of cases	RR at 1Sv	(95% CI)
Hypertension	5,035	1.05	(0.99, 1.00)
Thyroid disease	**964**	**1.38**	**(1.22, 1.57)**
Cataract	**3,484**	**1.11**	**(1.03, 1.19)**
Gastric ulcer	930	1.00	(0.88, 1.12)
Chronic liver disease and cirrhosis	**1,774**	**1.12**	**(1.03, 1.22)**
Cholelithiasis	959	1.00	(0.89, 1.12)
Kidney stones	323	1.16	(0.96, 1.43)
Dementia	316	1.20	(0.92, 1.59)
Glaucoma	211	0.73	(0.72, 0.89)

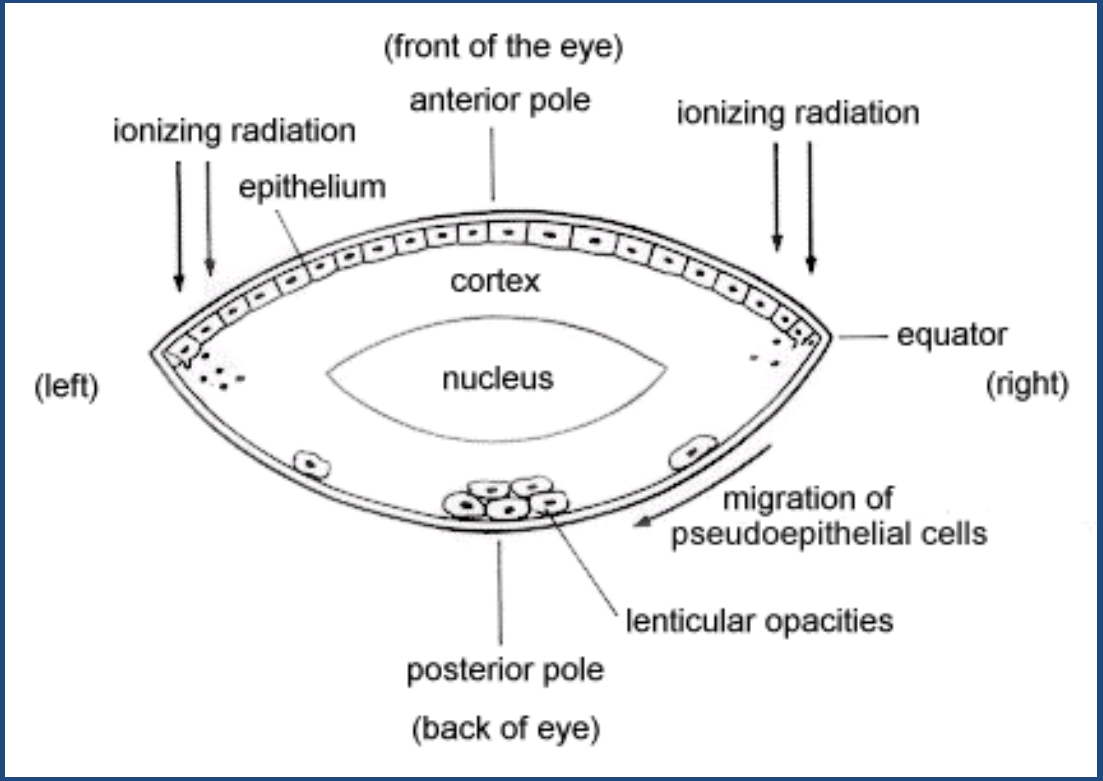
(Yamada et al, 2004, 2004)

Lens Opacities - Cataract



Posterior lenticular opacities: Possible mechanism

- Radiation especially harmful to dividing cells, at the equator
- Damaged cells move toward the rear of the lens before converging on the center
- Possible genomic involvement

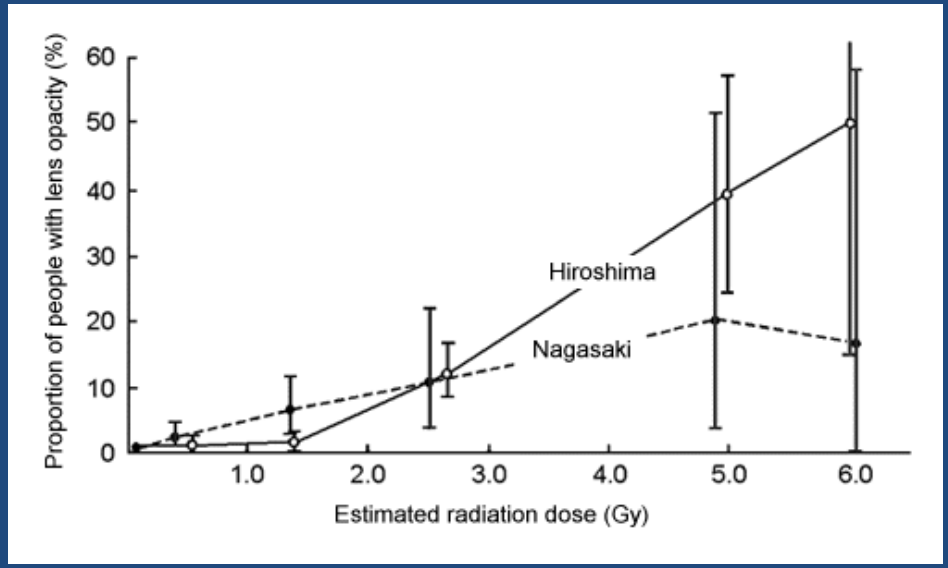


Cataract types

- Three major types
  - Cortical: involves outer, recently formed lens fiber cells
  - Nuclear: developing first in inner embryological and fetal lens fiber cells
  - Posterior subcapsular (PSC): developing from dysplasia of transitional zone epithelial cells; resulting in an opacity at posterior pole

Lens opacities in A-bomb survivors

- Early cases with very high doses observed appearing 3-4 years after the bombings
- In early 1960s, partial opacity, most often of posterior lens, detected by slit-lamp exams
  - Rarely causing visual impairment
  - Possible “threshold” dose level ~ 1.5 – 2 Sv

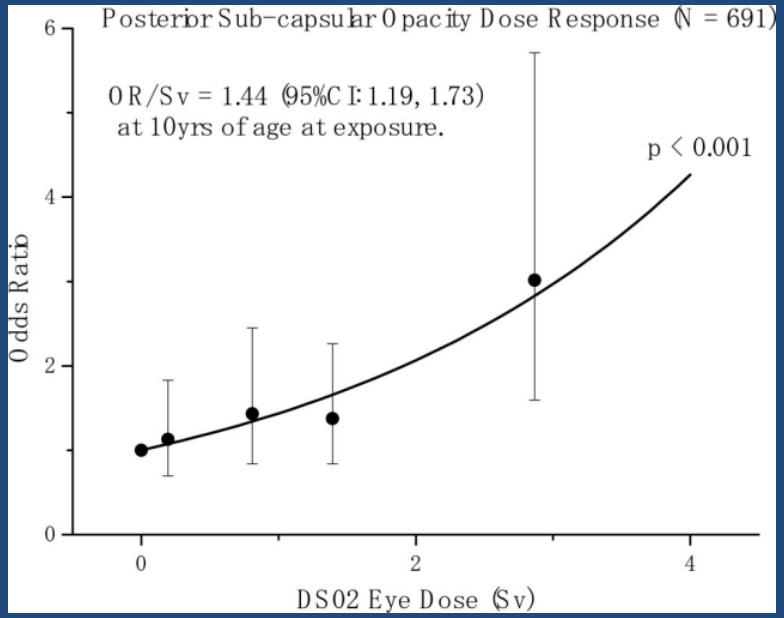


Lens opacities in A-bomb survivors: Some 50 yrs later

Ophthalmologic examinations, 2000-02 (Nakashima, 2006)

	OR at 1 Gy	p	Threshold
Cortical cataract	1.30	0.002	0.6 Gy
PSC opacities	1.44	<0.001	0.7 Gy

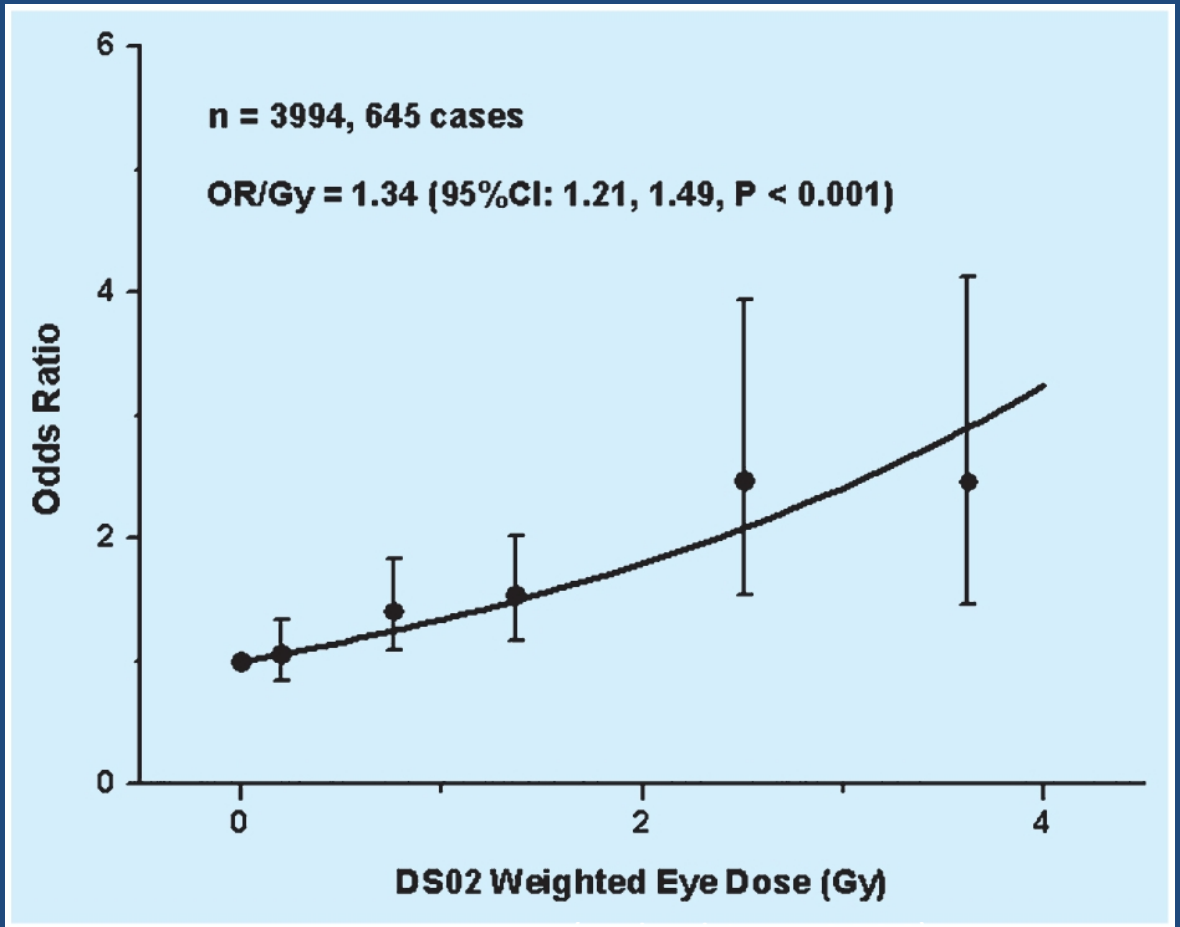
- Indication of a lower dose threshold level
- Emerging evidence of long-term effect on aging-related cataract (cortical cataract)



Postoperative Cataract, 2000-2002

OR at 1 Gy = 1.34

Best threshold estimate = 0.1 Gy – there could be no threshold



Chernobyl clean-up workers, Ukraine

8,600 clean-up workers examined for cataract 12-14 years after the accident (Worgul, 2007)

		m Gy					
Cataract	OR at 1 Gy	0-99	100-	250-	400-	600-	800+
Early PSC (Stage 1)	**1.42**	1.0	0.90	0.93	**1.20**	1.24	**1.72**
Adv opacities (Stages 2-5)	1.82	1.0	1.23	1.80	**2.56**	1.76	1.65
Cortical opacities (Stage 1)	1.51	1.0	0.89	1.00	1.07	**1.42**	**1.59**

Statement on Tissue Reactions
Approved by the Commission on April 21, 2011

(2) The Commission has now reviewed recent epidemiological evidence suggesting that there are some tissue reaction effects, particularly those with very late manifestation, where threshold doses are or might be lower than previously considered. For the lens of the eye, the threshold in absorbed dose is now considered to be 0.5 Gy.

(3) For occupational exposure in planned exposure situations the Commission now recommends an equivalent dose limit for the lens of the eye of 20 mSv in a year, averaged over defined periods of 5 years, with no single year exceeding 50 mSv.

Thyroid diseases among A-bomb survivors

Diagnosis	Cases	EOR/Gy	p
Solid nodule	464	2.01	<0.001
Malignant tumor	70	1.95	<0.001
Benign tumor	**156**	**1.53**	**<0.001**
Other	**258**	**1.67**	**<0.001**
Cyst	**244**	**0.89**	**<0.001**
Positive antthyroid antibodies	898	-0.07	0.20
Positive TPOAb	427	0.01	0.91
Positive TgAb	761	-0.04	0.52
Antithyroid antibodies-positive hypothyrodism	102	0.01	0.92
Antithyoid antibodies-negative hypothyroidism	81	0.17	0.31

(Imaizumi , 2006)

TPOAb + anti-thyroid peroxidase antibody; TgAb = anti-thyroglobulin antibody

Summary - 1

- There is emerging evidence that radiation exposure at low, diagnostic doses can increase several types of non-cancer diseases.
- Radiation-related risks of non-cancer diseases are relatively low but can be substantial when baseline disease rates are high, and thus have important public health implications. This concern is particularly great for circulatory disease.

Summary - 2

- The risk of circulatory disease at doses below 0.5 Gy is currently statistically uncertain, but there are indications that the risk in that dose range is consistent with that expected from data at higher doses – suggesting a non-threshold dose response.
- The age and time patterns of the radiation-related circulatory disease risk are currently not well understood. However, the indications are that the risk is prolonged and high among those exposed when young.

Summary - 3

- There is also increasing evidence of increased risk of cataract in several forms at doses lower than a previously considered threshold level (2+ Gy).
- Further follow-up of the LSS and other cohorts are expected to provide data to improve the understanding of the non-cancer dose response and risk patterns at low doses.
- The possibility of low dose radiation effects on non-cancer disease risks should be explicitly considered in developing radiation protection standards and more efforts should be made to identify possible mechanisms for these effects.