Radiation and risk of non-cancer diseases

Professor Anssi Auvinen, MD, PhD
Tampere University, Tampere, Finland
STUK – Radiation and Nuclear Safety Authority
Helsinki, Finland

DCEG Radiation Epidemiology and Dosimetry Course 2019
Overview

- Introduction
- Circulatory diseases
  - A-bomb survivors
  - Occupational low-dose studies
  - Radiotherapy studies
- Eye lens opacities (cataract)
  - A-bomb survivors
  - Occupational low-dose studies
  - Radiotherapy studies
Non-cancer diseases

- Everything but cancer
- International Classification of Diseases ICD-11
  - Infectious diseases, Neoplasms, Hematological, Immune, Endocrine, Mental/Behavioral, Sleep, Neurological, Visual, Ear, Circulatory, Respiratory, Digestive, Skin, Musculoskeletal, Genitourinary, Sexual, Pregnancy/Childbirth, Perinatal, Developmental, Signs/Symptoms, Injury/External causes
- Not covering tissue reactions (a.k.a. deterministic effects)
  - Not a topic addressed by epidemiology
What are non-cancer effects of radiation?

- Other than tissues reactions (deterministic effects)
  - Vascular disease
  - Cataract (eye lens opacities)
  - Endocrine effects
  - Nervous system effects
  - Immunological effects
  - Respiratory disease
  - Kidney disease
Radiation and circulatory disease
Three systematic reviews

- 2005 McGale & Darby: Epidemiological data do not at present provide clear evidence of a risk of circulatory diseases at doses of ionising radiation in the range 0-4 Gt
  - 26 studies, occupational and medical exposures

- 2012 Little et al: Our review supports an association between circulatory disease mortality and low and moderate doses of ionising radiation...limited by heterogeneity...if confirmed
  - 10 studies (A-bomb survivors and occupational cohorts)

- 2016 Little: The review provides strong evidence in support of a causal association between both low and high dose radiation and most types of circulatory disease
  - 20 studies (A-bomb, occupational, medical, environmental)
Paradigm change

- Earlier regarded as a high-dose phenomenon only
  - Tissue damage to the heart
- Recognised initially in radiotherapy
- Observations among A-bomb survivors a game changer
- Subsequent findings also in chronic low-dose exposure in occupational setting
Atomic bomb survivors

Shimizu BMJ 2010

Shimizu *BMJ* 2010

Takahashi et al. BMJopen 2012
### Non-neoplastic diseases and other causes

<table>
<thead>
<tr>
<th>Disease Type</th>
<th>Estimated ERR (95% CI)</th>
<th>Estimated Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood diseases</td>
<td>1.70 (0.96, 2.70)</td>
<td>238</td>
</tr>
<tr>
<td>Circulatory diseases</td>
<td>0.11 (0.05, 0.17)</td>
<td>19,054</td>
</tr>
<tr>
<td>Respiratory diseases</td>
<td>0.21 (0.10, 0.33)</td>
<td>5,119</td>
</tr>
<tr>
<td>Digestive diseases</td>
<td>0.11 (-0.01, 0.24)</td>
<td>3,394</td>
</tr>
<tr>
<td>Genitourinary diseases</td>
<td>0.14 (-0.06, 0.38)</td>
<td>1,309</td>
</tr>
<tr>
<td>Infectious diseases</td>
<td>-0.02 (-0.15, 0.13)</td>
<td>1,962</td>
</tr>
<tr>
<td>Other diseases</td>
<td>0.01 (-0.1, 0.12)</td>
<td>4,847</td>
</tr>
<tr>
<td>External causes</td>
<td>-0.11 (-0.21, 0.02)</td>
<td>2,432</td>
</tr>
</tbody>
</table>

**FIG. 1.** Estimates of excess relative risk (ERR) per Gy and 95% CI for major causes of death. 

- **a** ERR was estimated using the linear dose model, in which city, sex, age at exposure, and attained age were included in the background rates, but not allowing radiation effect modification by those factors.
- **b** Confidence interval. Horizontal bars show 95% confidence intervals.
- **c** The size of plots for site-specific cancers was proportional to the number of cases.
- **d** ERR (95% CI) of leukemia was 3.1 (1.8, 4.3) at 1 Gy and 0.15 (−0.01, 0.31) at 0.1 Gy based on a linear-quadratic model with 318 cases (not displayed in the figure).
- **e** The lower limit of 95% CI was lower than zero, but not specified by calculation.

Dose-response for vascular disease

**Hypertension**

- Relative Risk vs. Stomach dose (Sv)
- $RR_{1Sv} = 1.03$
- $P = 0.028$

**Myocardial Infarction**

- (age ATB < 40 years, 1968-1998)
- Relative Risk vs. Stomach dose (Sv)
- $RR_{1Sv} = 1.25$
- $P = 0.049$

Yamada et al. Radiat Res 2004
Risk coefficient per dose unit, by dg (incidence)

## ERR/Gy for vascular diseases (1950-2003)

<table>
<thead>
<tr>
<th>Disease category (ICD-9 code)</th>
<th>No of deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circulatory disease (390-459)</td>
<td>19,054</td>
</tr>
<tr>
<td>Heart disease (390-398, 402, 404, 410-429)</td>
<td>8,463</td>
</tr>
<tr>
<td>Ischemic heart disease (410-414)</td>
<td>3,252</td>
</tr>
<tr>
<td>Myocardial infarction (410)</td>
<td>1,735</td>
</tr>
<tr>
<td>Hypertensive heart disease (402, 404)</td>
<td>922</td>
</tr>
<tr>
<td>Rheumatic heart disease (393-398)</td>
<td>242</td>
</tr>
<tr>
<td>Heart failure (428)</td>
<td>2,983</td>
</tr>
<tr>
<td>Other heart diseases</td>
<td>1,064</td>
</tr>
<tr>
<td>Hypertensive disease without heart diseases (401, 403, 405)</td>
<td>411</td>
</tr>
<tr>
<td>Stroke (430-438)</td>
<td>9,622</td>
</tr>
<tr>
<td>Cerebral infarction (433, 434)</td>
<td>2,659</td>
</tr>
<tr>
<td>Cerebral hemorrhage (431)</td>
<td>4,060</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage (430)</td>
<td>461</td>
</tr>
<tr>
<td>Others or unspecified</td>
<td>2,442</td>
</tr>
<tr>
<td>Other circulatory disease</td>
<td>558</td>
</tr>
</tbody>
</table>

![Graph showing ERR/Gy for vascular diseases](image)

Ozasa et al. *Ann ICRP* 2015
Dose and respiratory disease mortality by period

Mainly pneumonia and influenza

Ozasa et al. *Ann ICRP* 2015
Population attributable risk (% of deaths)

Occupational studies
Mayak workers

- 22,377 workers
- Mean dose 0.51 Gy for external gamma
  - Mean alpha dose form plutonium to the liver 0.29 Gy
- Follow-up mean 20 years for incidence, 37 years for mortality
  - 5% loss to follow-up, 4% unknown cause of death
  - Ischemic heart disease 7225 incident cases and 2848 deaths
    - 5098 & 2127 cases, 2304 & 544 deaths in men and women
Heart disease incidence in Mayak workers

Moseeva 2014
Ischemic heart disease incidence: Dose-response

Azizova et al. 2015
Ischemic heart disease mortality: Dose-response

Azizova et al. 2015
Lag-time

![ERR/Gy Bar Chart]

Azizova et al. 2015
Effect size by sex

Azizova et al. 2015
## Summary of occupational cohort studies

<table>
<thead>
<tr>
<th>Study population</th>
<th>Reference</th>
<th>Cohort size (mean dose)</th>
<th>Circulatory disease</th>
<th>Ischemic heart disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuclear workers</td>
<td>Vrijheid 2007</td>
<td>275,312 (0.02)</td>
<td>0.09 (-0.4, +0.7)</td>
<td>-0.01 (-0.6, +0.7)</td>
</tr>
<tr>
<td>Chernobyl emergency workers</td>
<td>Ivanov 2006</td>
<td>53,772 (0.16)</td>
<td>0.18 (-0.03, +0.39)</td>
<td>0.41 (0.05-0.78)</td>
</tr>
<tr>
<td>Uranium miners</td>
<td>Kreuzer 2013</td>
<td>58,982 (0.05)</td>
<td>-0.13 (-0.38, +0.12)</td>
<td>-0.03 (-0.38, +0.32)</td>
</tr>
</tbody>
</table>
Mortality from circulatory disease, worker studies

Little *Mutat Res* 2016
Circulatory disease incidence, worker studies
Medical exposures
Studies of diagnostic radiation exposure

- Canadian TB fluoroscopy cohort
  - 63,707 patient, 30-year follow-up for mortality
  - Mean heart dose 0.79

- Massachusetts TB fluoroscopy cohort
  - 13,568 patients, 25-year mortality follow-up
  - Mean lung dose 0.36 Gy
Circulatory disease mortality, diagnostic x-ray studies

The graph shows the ERR/Gy for Canadian cohort and Massachusetts.

- ERR/Gy values range from -0.25 to 0.25.
- The Canadian cohort has a lower ERR/Gy compared to Massachusetts.

ERR/Gy: Risk Effect Ratio per Gray.
Radiotherapy studies

- Often predominantly very high doses >2 Gy
- Frequently in combination with cardiotoxic chemotherapy
- Childhood cancers, breast cancer, Hodgkin lymphoma
Accelerated aging?

- Physiological changes affecting several organs and processes
  - Hypertension, dyslipidemia, obesity, diabetes
- Increased morbidity and disease burden from several diseases
  - Endocrine
  - Neurological
  - Cardiovascular
- Onset at earlier age
- Increased premature mortality
- Signs, symptoms and markers of ageing (frailty)
- Induced by both radiotherapy and chemotherapy (and possibly other cancer treatments)
Cumulative mortality after childhood cancer

Second malignancy   SMR=15 (14-17) (19% of deaths)
Cardiac disease     SMR=7.0 (5.9-8.2) (7%)
Pulmonary disease   SMR=8.8 (6.8-11) (3%)

Armstrong et al. *J Clin Oncol* 2009
Heart disease mortality after left or right-sided breast cancer

Darby et al. *Lancet Oncol* 2005
Heart disease after treatment for Hodgkin lymphoma

Coronary heart disease SIR=4.5 (3.6-5.6)
Heart failure SIR=16.9 (12.8-21.8)

Cardiac events after treatment of childhood cancer

Cardiac disease incidence ERR/Gy, radiotherapy studies

- US CCS AMI
- Nordic breast cancer Ischemic heart disease
- Dutch Hodgkin lymphoma Coronary heart disease
Summary for circulatory disease
Risk by disease end-point, all 20 studies

Little 2016
Absolute risk as REID for vascular disease and cancer

From Little et al. 2012, risk if exposure-induced death (REID) for UK, expressed as $10^{-2}$/Sv
Open questions

- Consistency of results
  - Risk estimates
  - Lag/latency
- Dose-response at low exposure levels
- Mechanism(s)?
  - Direct tissue damage unlikely at low doses
  - Inflammation?
- Modifiers?
Radiation and eye lens opacities
Cataract

- Clouding of crystalline lens
  - Minimal turnover of cells
  - Progression, regression?
- Three types defined by location
  - Nuclear, cortical, posterior subcapsular
- Affects vision $\rightarrow$ cataract
- Cataracts are the leading cause of blindness worldwide
Cataract types
Radiation and the lens

- Lens among the most radiosensitive tissues in the body
- Radiation → genomic damage → abnormal proliferation and differentiation of lens epithelial cells → morphological changes
- Originally reported in A-bomb survivors in 1949
- Threshold for vision-impairing cataract 0.5 Gy (ICRP 2012)
- Eye lens dose threshold for workers 20 mSv/year over 5 yrs (>50 any single year), public 15 mSv/year revised in 2012
Major studies

- Atomic bomb survivors
- Chernobyl clean-up workers
- Mayak workers
- U.S. x-ray technologists
- (Taiwanese cohort of CT patients)
- Radiotherapy studies
Hiroshima and Nagasaki A-bomb survivors

- Ophthalmological examinations (Nakashima et al. *Health Phys* 2006)
- 730 participants, mean eye dose 0.52 Sv (DS02)
- Opacities graded using LOCS II
- OR for posterior subcapsular cataract 1.44 (95% CI 1.19-1.73)/Sv, for cortical cataract 1.30 (95% CI 1.10-1.53)/Sv
  - Decreasing risk with age at exposure
- Cataract surgery (Neriishi et al. 2007, 2012)
- 3761 AHS participants
- OR=1.39 (95% CI 1.24-1.55)/Sv, consistent with a threshold at 0.5 Gy
Dose-response for PSC and cortical opacities

(d) Posterior Subcapsular Opacities
OR/Sv=1.41 (95%CI: 1.21, 1.64)

(c) Cortical Opacities
OR/Sv=1.29 (95%CI: 1.12, 1.49)

Minamoto et al. 2004
Dose-response for cataract surgery

Neriishi et al. Radiology 2012
Chernobyl recovery workers

- 8607 workers (Worgul et al. 2007)
- Examined 12-14 years after exposure
- Information collected also on smoking, diabetes, medications
- Merriam-Focht grading of opacities
- Prevalence of PCS or cortical cataract 25%
- For PSC, OR=1.52 (1.02-2.00) @1 Sv
- Dose threshold for PSC estimated as 0.35 (0.19-0.66) Sv
Mayak workers

- Azizova et al. *Eur J Epidemiol* 2018
- Worker cohort 22,377, 22-year follow-up
  - Information on smoking (ever/never), diabetes, myopia available
- Cataract data from annual health check-ups including a standard ophthalmological examination
  - Slit lamp examination by an ophthalmologist
- Mean external gamma dose (Hp10) 0.54 Sv men, 0.44 Sv women
  - Some neutrons (0.03 Sv)
- Cataract cases 3132 cortical (cum. incidence 14%), 1239 PSC (11%)
  - 19% extracted, separate analysis (Azizova et al. 2019)
Dose-response for PSC and cortical cataract

ERR/Gy PSC 0.91 (0.67-1.20), cortical 0.63 (0.51-0.76)

nuclear 0.47 (0.35-0.60)
Dose-response for cataract removal

ERR/Sv = 0.09 (95% CI −0.02, 0.22)

Azizova et al. 2019
U.S. radiologic technologists

- 67,246 participants (Little et al. 2018)
- Median eye dose 56 mGy
- Mean follow-up 13 years
- Self-reported cataract cases and surgeries
- For cataract incidence, EHR=0.69 (95% CI 0.27-1.16)/Gy
- For cataract surgery, EHR=0.34 (95% CI -0.19, +0.97)/Gy
Dose-response for cataract incidence, radiotechs

Little et al. 2018
CT examination and cataract

- Taiwanese cohort study (Yuan et al. 2013)
- 2776 exposed people aged 10-50 years
- 27,761 non-exposed control group
- Follow-up 10 years
- Cataract extraction or 2+ health care contact with cataract dg
- Cataract incidence 0.97% vs 0.72%
- HR 1.76 (95% CI 1.18-2.63) for head/neck CT
CT and cataract incidence

Yuan et al. 2013
Number of CT examinations and cataract risk

Yuan et al. 2013
Cataract after radiotherapy for childhood cancer (1)

- 13,902 five-year survivors of childhood cancer followed up for 21 years (leukemia 34%, lymphoma 14%, CNS 12%)
- Mean lens dose 2.2 Gy (Chodick et al. Radiat Res 2016)
- Cumulative risk 3.5% (483 cases)
  - Self-reported, no information on type of cataract
- Linear dose-response eOR 0.92/Gy (95% CI 0.65-1.20), significantly elevated risk from 0.5-1.5 Gy
Dose-response for cataract after radiotherapy

Chodick et al. 2016
Cataract after radiotherapy for childhood cancer (2)

- Mean dose to the eye 2.6 Gy
- Cumulative risk 2.3% during 32-year follow-up (47 cataracts in 33 patients)
- Any radiotherapy HR=4.4 (95% CI 1.5-13)
- Chemotherapy with melphalan associated with very high risks (HR=26, 95% CI 7-97)
Summary for lens opacities

- Radiation can induce lens opacities at dose levels below tissue reactions (deterministic effects)
- Mainly posterior subcapsular but also cortical cataract
- Children more susceptible
- Is there a threshold at or below 0.5 Gy?
- Do the minor opacities progress into cataract?
- Modifiers?
  - A-bomb survivors M>F, Mayak M<F
Quiz (1)

Effect of radiation on vascular disease is comparable to cancer risk in terms of

A. Relative risk per dose unit
B. Absolute risk per dose unit
C. Lag-time (latency from exposure to manifestation of risk)
D. Weight of evidence base
Quiz (1)

Effect of radiation on vascular disease is comparable to cancer risk in terms of

A. Relative risk per dose unit
B. Absolute risk per dose unit
C. Lag-time (latency from exposure to manifestation of risk)
D. Weight of evidence base
Effect of radiation on the lens of the eye

A. Affects all types of cataracts in a similar fashion
B. Has led to a change in exposure limit to the eye
C. Is of unknown clinical relevance
D. Remains to be demonstrated in humans
Quiz (2)

Effect of radiation on the lens of the eye

A. Affects all types of cataracts in a similar fashion
B. Has led to a change in exposure limit to the eye
C. Is of unknown clinical relevance
D. Remains to be demonstrated in humans
And our musical cat, Elle