HelmholtzZentrum münchen
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Implications of cardiovascular disease risk for radiation protection?

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HELMHOLTZ ASSOCIATION

Implications of cardiovascular disease risk for radiation protection?

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1. 2012 Statements of ICRP and SSK

Statement of the ICRP

Although uncertainty remains, medical practitioners should be made aware that the absorbed dose threshold for circulatory disease may be as low a 0.5 Gy to the heart and to the brain.

ICRP Publication 118: ICRP Statement on Tissue Reactions (2012)

Statement of the SSK

Die Hinweise auf mögliche Risikoerhöhungen für Herz-Kreislauferkrankungen nach Strahlenexposition mit einer Dosis von einigen hunderrt Milligray sollten, obwohl ein Nullrisiko nicht ausgeschlossen werden kann, aus Vorsorgegründen und angesichts bestehender wissenschaftlicher Unsicherheiten bei der Erarbeitung von gesetzlichen Regelungen einbezogen werden

Translation:
The elaboration of regulations of radiation exposures with a few hundred milligray should take into account indications of a possible increase of cardiovascular disease risk, although there are scientific uncertainties and a vanishing risk cannot be excluded

Herz-Kreislauferkrankungen nach zulässigen beruflichen Strahlenexpositionen

Verabschiedet in der 256. Sitzung der Strahlenschutzkommission am 19./20. April 2012

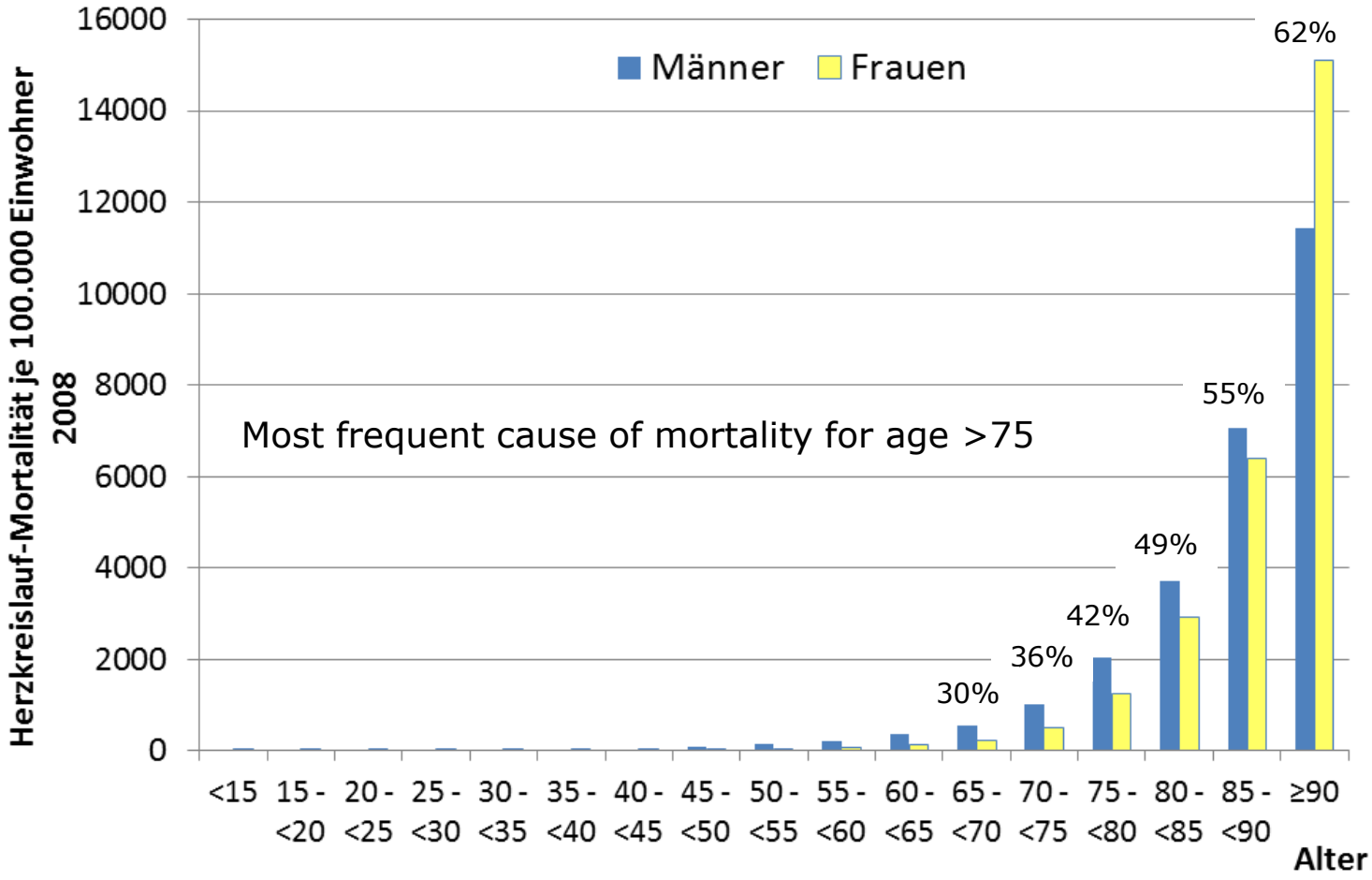
2. Mortality from cardiovascular diseases

Baseline proportion (%) of deaths due to circulatory disease

Circulatory disease	France (2007)	Germany (2006)	Japan (2009)	Spain (2005)	UK (2003)
Ischemic heart disease	5	19	6	10	19
Other heart disease	7	13	11	11	5
Cerebrovascular disease	5	9	11	10	12
Other circulatory disease	3	8	3	5	4
All	21	49	31	36	40

After Little et al, Environmental Health Perspectives (2012)

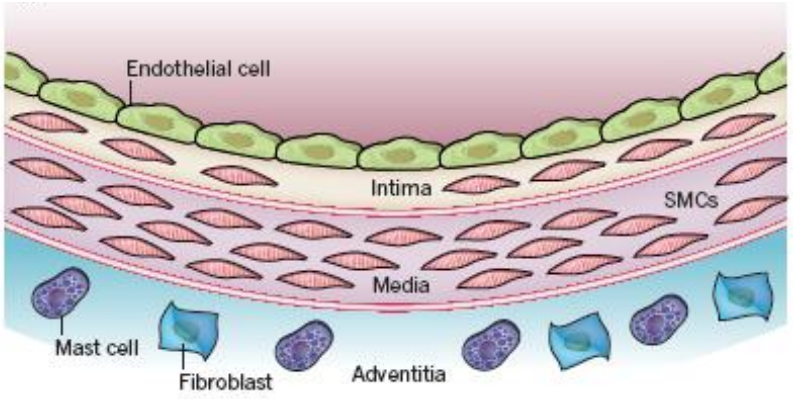
Age- and sex-specific mortality of cardiovascular disease
Age-specific proportion of deaths



www.statistischesbundesamt.de (2011)

3. Pathogenesis of cardiovascular disease

Schematic presentation of the wall of a human muscular artery



Three layers

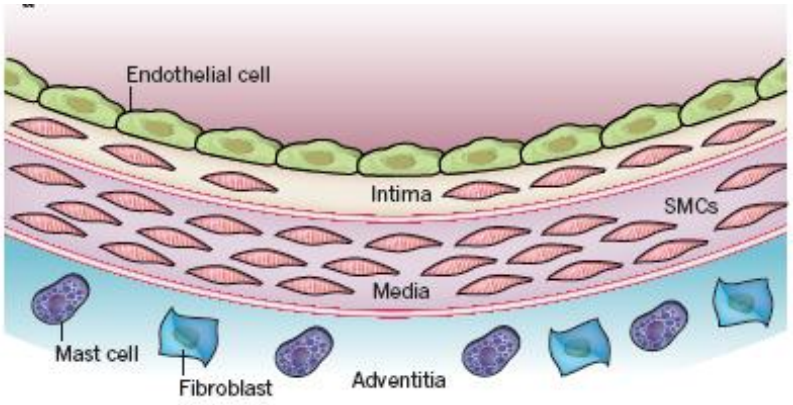
Tunica intima (0.007-0.14 mm): Monolayer of endothelial cells + basement membrane containing smooth muscle cells (SMCs)

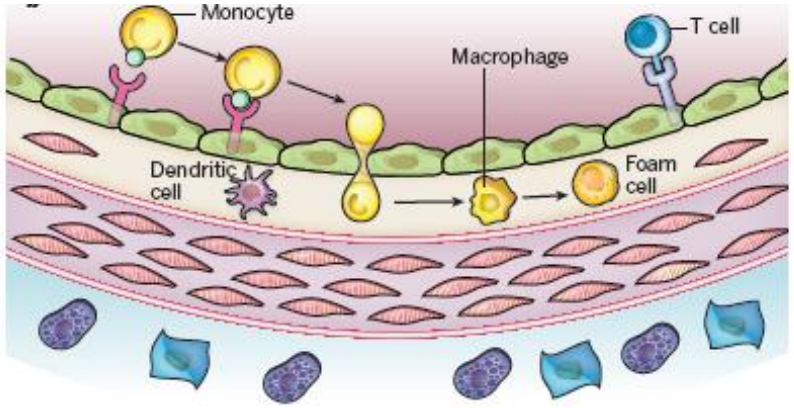
Tunica media (0.35 - 1.4 mm): SMCs embedded in a complex extracellular matrix

Adventitia: containing mast cells, nerve endings and microvessels

Libby, Nature (2011)

Initial steps of artherosclerosis





Inflammatory reactions caused, e.g., by shear forces at bifurcations or high blood pressure, lead to expression of adhesion molecules for leucocytes

Changed permeability of the endothelium allows infiltration of LDL in intima

Adhesion of leukocytes (mostly monocytes)

Migration of the monocytes into the intima

Maturation into macrophages

Uptake of lipid yielding foam cells

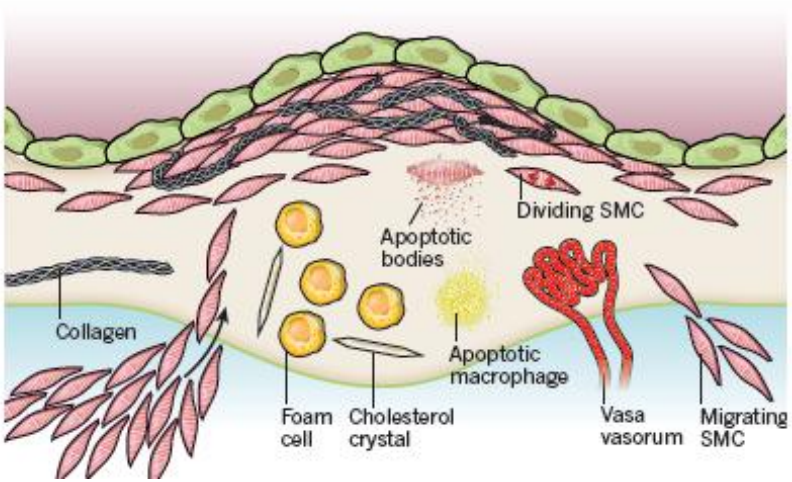
Excretion of inflammatory signalling molecules into intima

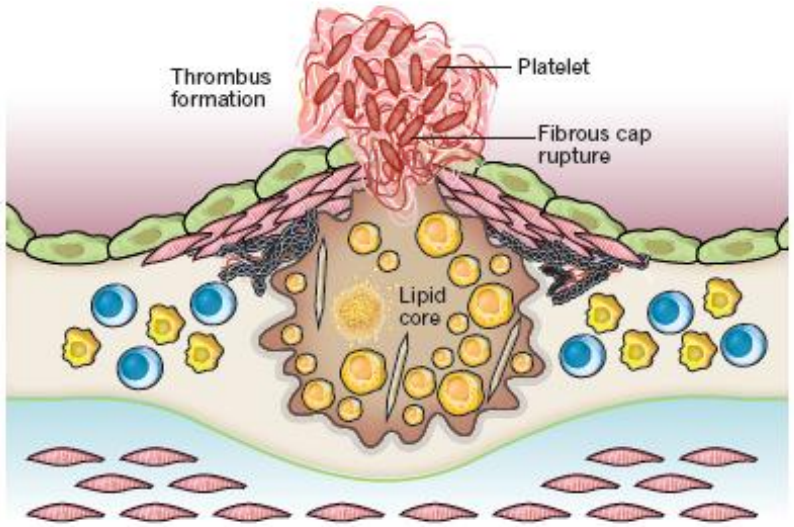
Libby, Nature (2011)

Disruption of atherosclerotic plaque

Fracture of the plaque's fibrous cap
Blood coagulation components coming into contact with tissue factors in the plaque's interior
Formation of thrombus extending into vessel lumen and impeding blood flow

Libby, Nature (2011)





Myocardial microcirculation

Besides atherosclerosis in medium and large blood vessels, disturbances of myocardial microcirculation may play an important role for heart diseases

Karch, Cardiovasc Pathol (2005)

4. Low/moderate-dose radiation effects

Mitochondrial impairment in mouse hearts

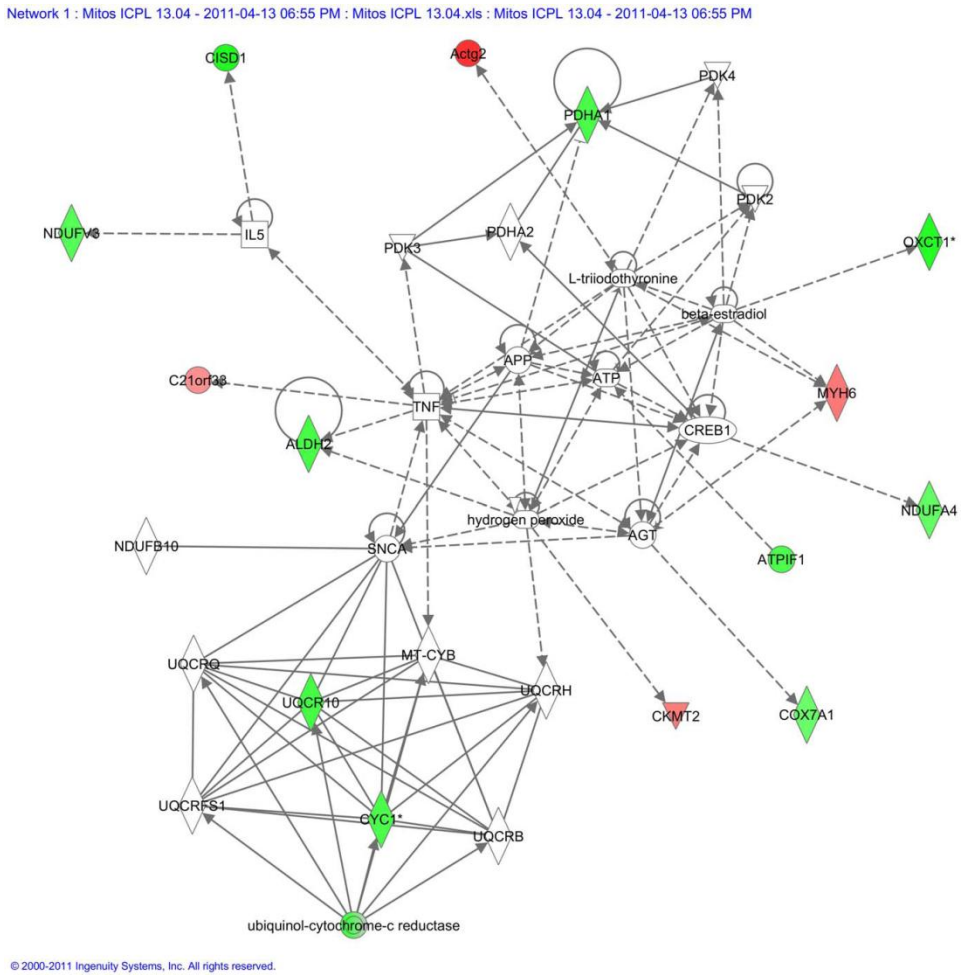
C57BL/6N mice

At age of eight weeks exposed to local irradiation of the heart either with a dose of 0.2 Gy or sham-irradiated

Cardiac mitochondria isolated four weeks after exposure

Proteins of the pyruvate metabolism and proteins involved in cytoskeletal structure were changed

Barjaktarovic et al, PLoS ONE (2011)



Protein interaction network of differentially regulated proteins

Atherosclerotic lesions in mice

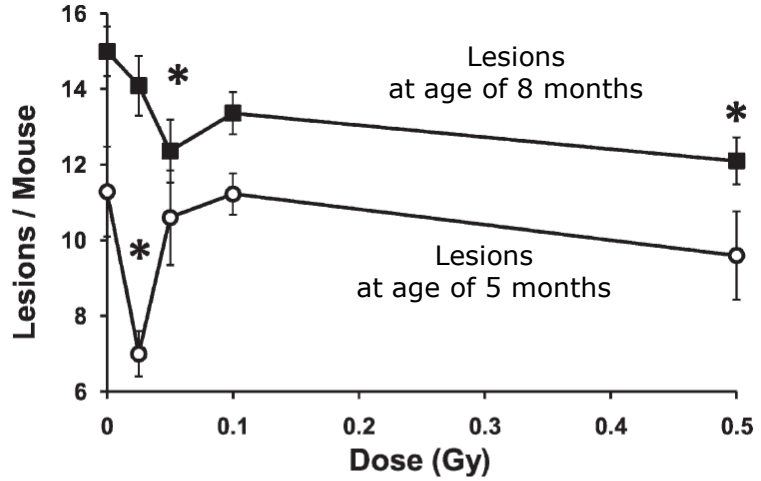
Whole body exposure of ApoE-/- mice

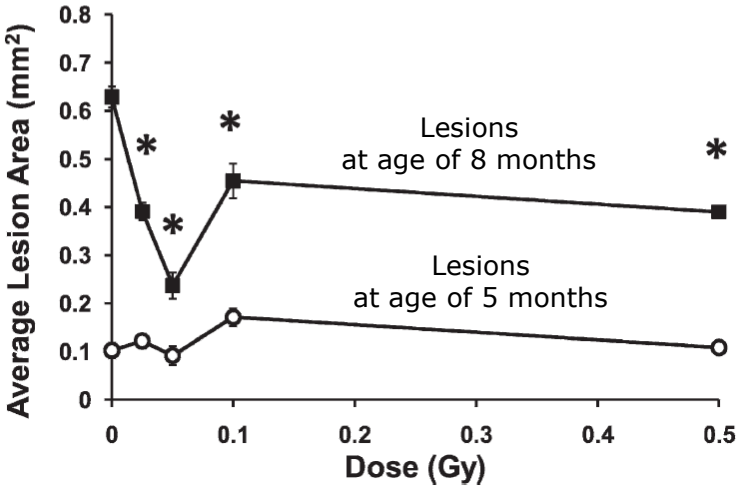
Indications of protective action after exposure with low/moderate dose

- for the lowest dose rate that has been used in the experiment (1 mGy/min)
- for the lowest stage of disease (age) at time of exposure used in the experiment (age of 2 months)

Mitchel et al, Radiat Res (2011)

Exposure at age of 2 months
with 1 mGy/min





Mechanisms at low/moderate dose

Mechanisms of a **possible** change of cardiovascular disease rates after exposure with low/moderate dose are not understood

5. Radiation risks in the Life Span Study (LSS)

5.1 All cardiovascular diseases
Whole cohort

86 611 survivors of atomic bombings of Hiroshima and Nagasaki
19 054 deaths due to cardiovascular disease, 1950-2003
9712 of these in age group 30-49!

Evaluation with LNT:
ERR per unit dose = **0.11 (95%CI: 0.05; 0.17) / Gy**
EAR per unit dose = 5.5 (95%CI: 2.7; 8.4) cases per 10^4 PY Gy

210 of the cases associated with radiation

Shimizu et al, BMJ (2010)

5.1 All cardiovascular diseases
Risk factors in sub-cohort

36 468 survivors responded to mail survey in 1978
7 907 deaths due to cardiovascular disease, 1950-2003

Risk factor	Smoking	Diabetes mell.	BMI > 25	College/university
Relative risk	1.4	1.6	1.1	0.75

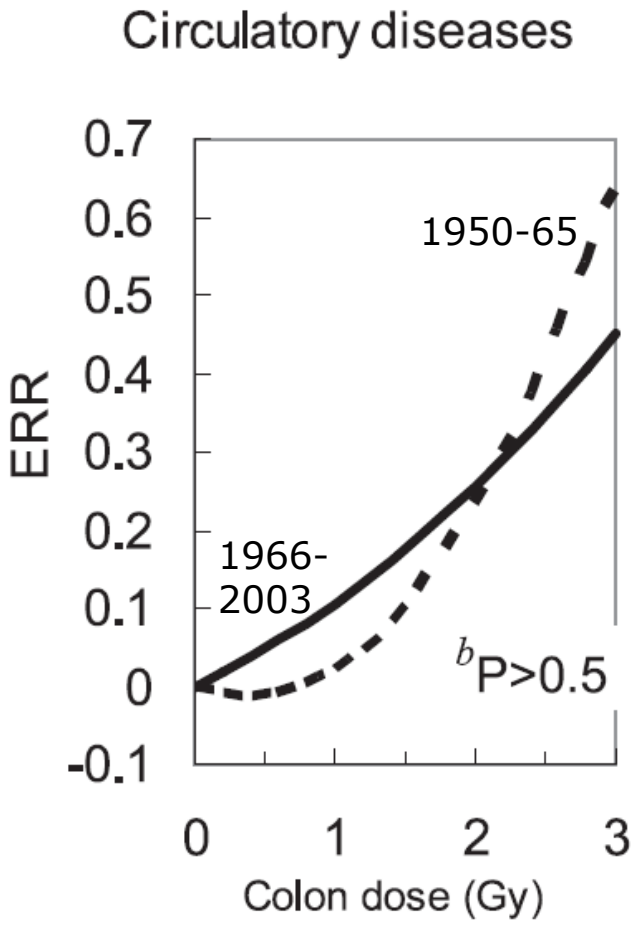
ERR per dose (non adjusted) = 0.10 / Gy
ERR per dose (adjusted) = 0.096 / Gy

Shimizu et al, BMJ (2010)

5.1 All cardiovascular diseases
Effect of healthy survivors?

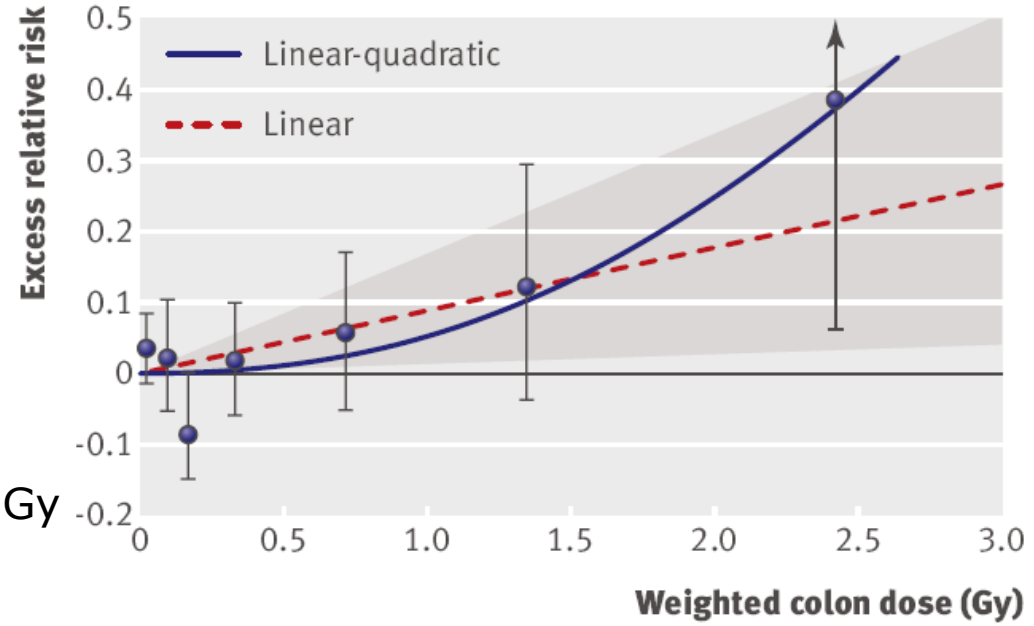
Difference of dose response
for deaths in 1950 - 1965
compared to 1966 - 2003
is not significant

Osaza et al, Radiat Res (2012)

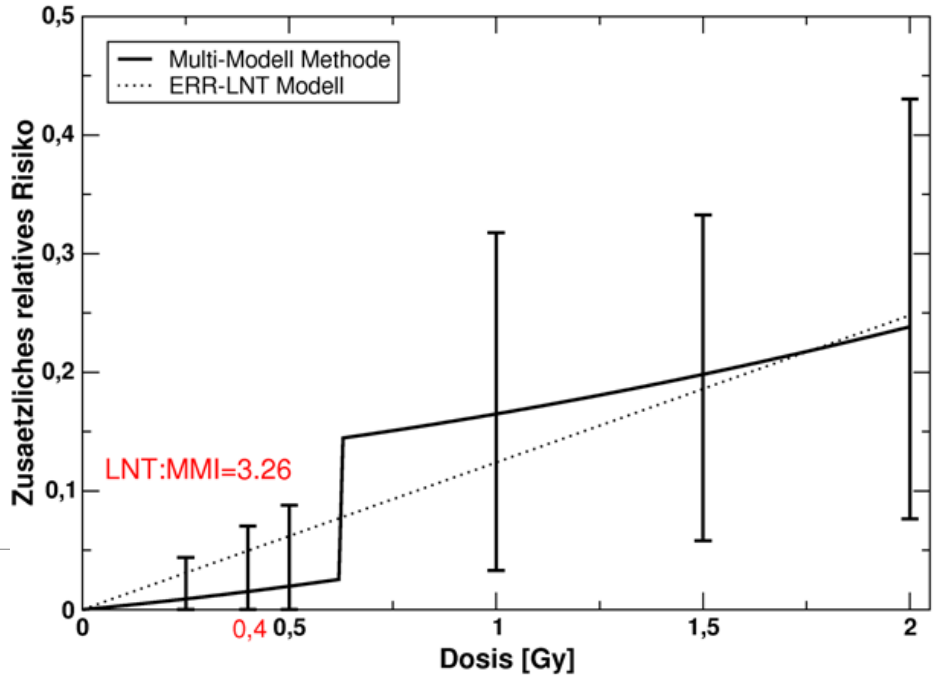


5.2 Cerebrovascular diseases

9622 deaths in 1950 - 2003
Evaluation with LNT:
ERR per dose =
0.09 (95%CI: 0.01; 0.17) / Gy
Best fit: pure quadratic model
Threshold model: D_{thr} = 0.5 (<0; 2) Gy
Shimizu et al, BMJ (2010)



3954 deaths in 1968 - 1997
Evaluation with LNT:
ERR per dose =
0.12 (90%CI: 0.03; 0.22) / Gy
Multi-model inference: at 400 mGy risk lower than LNT by factor of 3.3
Schöllnberger et al,
Radiat Environ Biophys (2012)



5.3 Other cardiovascular diseases

8463 deaths from heart diseases in 1950 – 2003

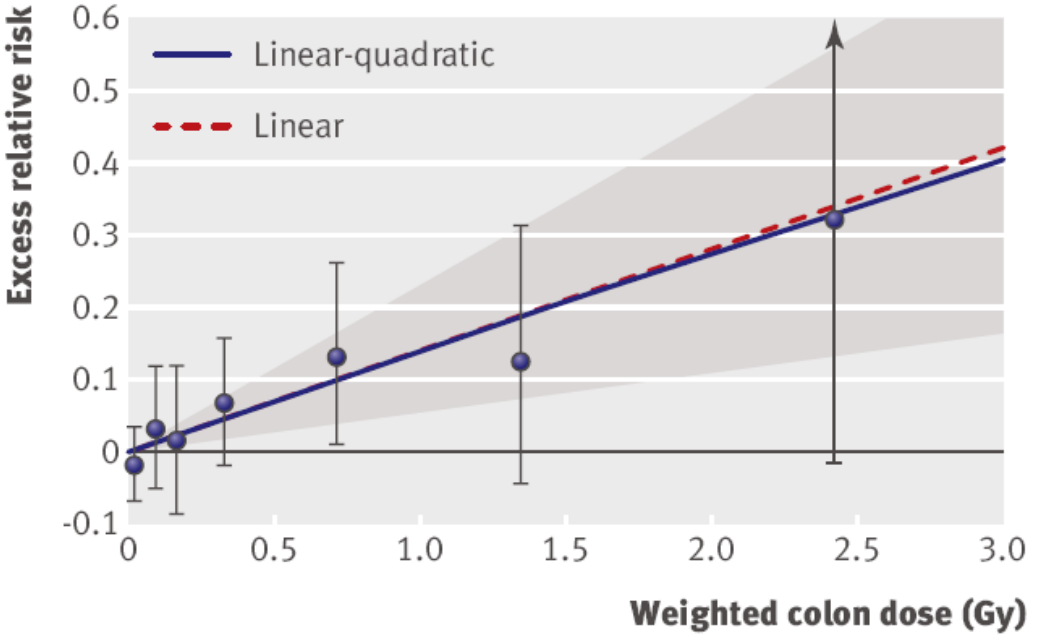
Evaluation with LNT:

ERR per dose =

0.14 (95%CI: 0.06; 0.23) / Gy

No evidence for non-linearity

Shimizu et al, BMJ (2010)



4477 deaths from cardiovascular diseases excluding CVD in 1968 – 1997

Evaluation with LNT:

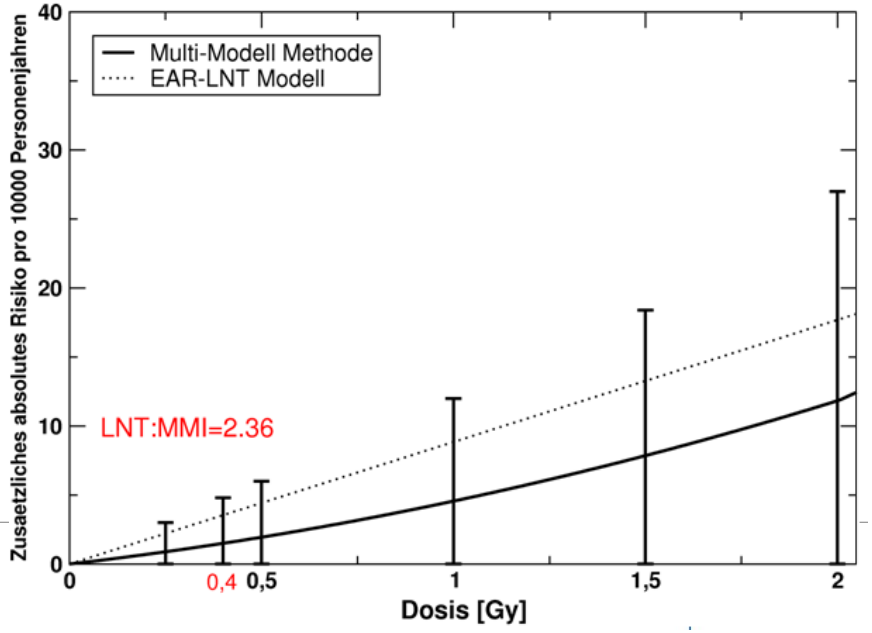
ERR per dose =

0.17 (95%KI: 0.08; 0.27) / Gy

Multi-model inference: at 400 mGy risk lower than LNT by factor of 2.4

Schöllnberger et al,

Radiat Environ Biophys (2012)



6. Radiation risks of protracted exposures

6.1 All cardiovascular diseases

Cohort	Reference	ERR per dose (Gy^{-1})
LSS	Shimizu 2010	**0.11 (0.05; 0.17)**
BNFL workers	McGeoghegan 2008	0.65 (0.36; 0.98)
Chernobyl liquidators	Ivanov 2006	0.18 (-0.03; 0.39)
German uranium miners	Kreuzer 2006	-0.26 (-0.6; 0.05)
NRRW-3	Muirhead 2009	0.25 (-0.01; 0.54)
Semipalatinsk	Grosche 2011	0.02 (-0.32; 0.37)
Workers in nuclear industry (15 countries)	Vrijheid 2007	0.09 (-0.43; 0.70)
9 studies excluding LSS	Little 2010	0.11 (0.07; 0.14)

Overall: No evidence for ERR per dose after protracted exposures being different from that in the LSS

6.2 Cerebrovascular diseases

Cohort	Reference	ERR per dose (Gy^{-1})
LSS / Incidence	Yamada 2004	0.07 (-0.08; 0.24)
LSS / Mortality	Shimizu 2010	0.09 (0.01; 0,17)
Chernobyl liquidators	Ivanov 2006	0.45 (0.11; 0.80)
BNFL workers	McGeoghegan 2008	0.43 (-0.10; 1.12)
EdF workers	Laurent et al. 2010	17.4 (0.2; 43.9)
Eldorado uranium miners	Lane 2010	-0.29 (<-0.29; 0.27)
German uranium miners	Kreuzer 2006	-0.09 (-0.6; 0.8)
Mayak workers / incidence	Azizova 2011	0.41 (0.32; 0.50)
Mayak workers / mortality	Azizova 2011	0.03 (-0.06; 0.12)
NRRW-3	Muirhead 2009	0.16 (-0.42; 0.91)
Semipalatinsk	Grosche 2011	-0.06 (-0.65; 0.54)
Workers in nuclear industry (15 countries)	Vrijheid 2007	0.88 (-0.67; 3.16)

6.2 Cerebrovascular diseases
Risk different from the risk of other cardiovascular diseases?

Cerebrovascular disease risk to be compared with **0.11 (0.05; 0.17) Gy^{-1}**

LSS / Mortality	Shimizu 2010	0.09 (0.01; 0,17)
9 studies (excluding BNFL workers, Mayak workers mortality, Semipalatinsk)	Little 2012	0.21 (0.02; 0.39)
8 studies (further excluding Mayak incidence)	Little 2012	0.12 (0.02; 0.23)

Little: ERR per unit dose = 0.45 (0.34; 0.56) Gy^{-1} for Mayak incidence (Azizova 2010)
However: Azizova et al., Radiat Environ Biophys (2012):
Incidence, Main analysis: 0.41 (0.32; 0.50)
Incidence, Stratifying for internal dose: 0.35 (0.25; 0.44)
Mortality, Main analysis: 0.03 (-0.06; 0.12)

Overall: Currently no evidence for ERR per dose for cerebrovascular diseases being different from that for other cardiovascular diseases

6.3 Dose-response relationship

BNFL workers, all cardiovascular diseases: No evidence for deviation from LNT

Mayak workers, CVD: No evidence for deviation from LNT

Mayak workers, IHD: Indication for ERR per unit dose being lower at a few hundred milligray than in LNT analysis

Workers in nuclear industry (15 countries): Indication for ERR per unit dose being lower at low doses than in LNT analysis

Chernobyl liquidators: Indication of dose rate effect

Overall: Mixed evidence for or against ERR per unit dose at low doses being lower than in LNT model or even being zero

7. Potential population mortality risks from low/moderate-dose exposures

Analysis of mortality 1950-2003 among 86 611 survivors (LNT model)

19 054 deaths from cardiovascular diseases

ERR per unit dose = 0.11 (95%CI: 0.05; 0.17) Gy^{-1}

210 cases associated with radiation exposure

Shimizu et al, BMJ (2010)

10 929 deaths from solid cancer

ERR per unit dose = 0.47 (95%CI: 0.38; 0.56) Gy^{-1}

527 cases associated with radiation exposure

Osaza et al, Radiat Res (2012)

Analysis of ICRP: Early and late effects of radiation in normal tissues and organs – Threshold doses for tissue reactions in a radiation protection context (2012)

Based on a meta analysis of AGIR (2010) with the LNT model (!)
it is estimated that 1% of people exposed to 500 mGy
will develop an additional cardiovascular disease.
This dose level is defined a threshold.

Analysis of Little et al., EHP (2012)

Based on a meta analysis with the LNT model
it is estimated that at low/moderate dose
excess mortality risk from all cardiovascular diseases
is similar to that from cancer.
For an exposure to 100 mGy
it ranges from 0.25% in France to 0.85 % in Russia.

8. Implications for radiation protection?

Summary

LNT model for LSS: Number of excess mortalities from cardiovascular diseases is lower than that from cancer by a factor of about 2.5.

There is no evidence for ERR per unit dose in moderate dose, low-dose rate studies being different from that in the LSS

There is no evidence for ERR per unit dose for cerebrovascular diseases being different from that for all cardiovascular diseases

There is some evidence that risk at a few hundred milligray is lower than that obtained by the LNT model (Multi-model inference: factor of 2 to 3)

It can not be excluded that there no excess cardiovascular risk at doses of a few hundred milligray

Evaluation

Present dose limit for occupationally exposed workers of 100 mSv in five years is based on cancer and hereditary effects

For life time doses corresponding to this dose limit, there is some evidence for a small additional risk from excess cardiovascular diseases

Although this might not be a reason to change the dose limit, the awareness of the probable cardiovascular risk should be clearly stated

This will improve the **credibility** of radiation protection

Acknowledgements

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Thank you for your attention !