Workshop on Individual Response to Ionizing Radiation
Session 2 – Factors influencing the risk of late and stochastic effects
13:00–13:30, 1 September 2022, Stockholm, Sweden

# Individual risk of radiogenic non-cancer effects


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There is no conflict of interest to declare.

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## Terminology in this talk

Radiogenic non-cancer effects
- late heath effects that occur (e.g., >10 years after exposure to <1 Gy) in directly exposed human individuals, but exclude cancer
- some of which are classified as tissue reactions

Tissue reactions (formerly "non-stochastic" or "deterministic" effects)
- injury in populations (substantial numbers or proportions) of cells characterized by a threshold dose and an increase in the severity of the reaction as the dose is increased further

Threshold dose
- dose causing an effect in 1% of exposed individuals
- nominal (independent of age, sex and population etc)
- depends on post-irradiation time and sensitivity of the detection methods

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## The need to (re)consider non-cancer effects

With longer follow-up, increased risks have been reported, at dose below 1 Gy, for tissue reactions that have been listed as radiation health hazards but at dose much lower than previously thought (e.g., cataracts), newly listed tissue reactions (e.g., DCS), and for unlisted non-cancer effects on the "radar".

Consideration of such non-cancer effects would be needed not only for radiation protection of workers and public, but also patients
- Given that the dose threshold generally decreases with increasing post-irradiation time, the longer the post-radiotherapeutic survival of patients, the broader the spectrum of normal tissue complications of concern
- Such consideration is also important in justifying radiotherapy for non-cancer diseases (life saving vs late occurring normal tissue complications), e.g., for COVID-19 pneumonia and refractory ventricular tachycardia.

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## Today's topics

Non-cancer effects of concern at lifetime dose <1 Gy

- ophthalmological diseases (e.g., cataracts, normal-tension glaucoma)
- diseases of the circulatory system (cardio- and cerebrovascular diseases)
- neurological diseases (e.g., Parkinson's disease, dementia)

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## Cataracts

- a clouding of the normally transparent lens of the eye
- the primary cause of visual impairment globally (the seventh cause in Japan)
- curable (typically by a day surgery)

- tissue reaction with threshold of 0.5 Gy to the lens (causing 1% incidence of VICs with >20 years follow-up) independent of dose rate
- significantly increased radiation risk for cataracts has been observed for all three types of cataracts, with PSC cataracts most strongly associated than cortical and nuclear cataracts
- significantly increased radiation risk for cataract surgery has been observed only in atomic bomb survivors: cataract surgery is an imperfect surrogate for VICs and is less specific than high-grade cataracts, but is better than low-grade cataracts

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## Recent evidence at low dose, low dose rate

US Radiologic Technologists (USRT) Cohort

- mean dose 0.06 Gy, ~70,000 participants
- significantly increased risk for self-reported cataracts below 0.1 Gy (but with a non-significant increase below 0.05 Gy)

EHR/Gy = 1.16 (95% CI: 0.11, 2.31)
EAR/$10^4$ PY Gy = 82 (95% CI: 25, 139)

Little … Hamada et al. Eur J Epidemiol 2018
Little … Hamada et al. Occup Environ Med 2018

High natural background radiation (HNBR) area in China

- mean dose 0.2 Gy, ~500 participants
- significantly increased risk for PSC opacities ($OR_{0.1\ Gy}$ = 1.73 (95% CI: 1.05, 2.85)) with no threshold and cortical opacities ($OR_{0.1\ Gy}$ = 1.26 (95% CI: 1.00, 1.60)) with threshold of 0.14 Gy (90% CI: 0.11, 0.16)

Su et al. J Radiat Res 2021

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## Why is the lens so radiosensitive?

ICRP Publications 1 (1958) & 41 (1984)

- Bone marrow, gonads and the lens are among the most radiosensitive tissues in the body, and the lens is the most radiosensitive ocular tissue.

High sensitivity of the lens to low-LET radiation may involve excess proliferation and abnormal differentiation of LECs, oxidative stress, and denaturation of lens proteins.

The lens is much more sensitive to high-LET radiation than other tissues. Its mechanisms may involve low oxygen, cellular quiescence, and high nitrogen.

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# Individual factors for cataracts

There are indications for potential factors listed below, but no firm conclusions can yet be drawn

- sex (e.g., higher sensitivity in females)
- age (e.g., higher sensitivity in younger individuals)
- genetics (e.g., ATM, Rad9, BRCA1, PTEN, p53, p21, Ptch1, and ERCC2/XPD)
- comorbidity (e.g., diabetes, glaucoma)
- coexposures (e.g., UV, nutrients, antioxidants)

INTERNATIONAL JOURNAL OF RADIATION BIOLOGY
https://doi.org/10.1080/09553002.2022.2074166
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**Individual response of the ocular lens to ionizing radiation**

Stephen G. R. Barnard[a] and Nobuyuki Hamada[b]



# Predictive assays for cataracts

ATM? (the role suggested from studies in mice, HNBR and AHS)

Mechanisms for consideration

- early onset PSC with threshold via excess LEC proliferation?
- late onset PSC with no threshold via LEC cell death or inactivation?
- late onset cortical or nuclear cataracts via accelerated lens aging?
- A cloudy lens formed from a damaged single lens stem cell?

Post-exposure monitoring of opacification (real time and almost non-invasively)

- e.g., with slit-lamp biomicroscopy, retroillumination, Scheimpflug imaging, and optical coherence tomography
- detection sensitivity depends on diagnostic modalities



# Other ocular diseases on the "radar"

Glaucoma

- optic neuropathies causing optic nerve damage and visual field defects
- the secondary cause of visual impairment globally (the primary cause in Japan)
- basically incurable
- Increased radiation risk for normal-tension glaucoma has been observed in atomic bomb survivors and Russian Mayak workers

Kiuchi et al Radiat Res 2013, Sci Rep 2019
Azizova … Hamada et al. Cancers 2022

Diabetic retinopathy

- ocular complication of diabetes
- the quinary cause of visual impairment globally (the secondary cause in Japan)
- increased radiation risk has been observed only in AHS

Minamoto Int J Radiat Biol 2004



# Diseases of the circulatory system

- tissue reaction with threshold of 0.5 Gy to the heart and the brain (causing 1% incidence of CVD and CeVD with >10 years follow-up) independent of dose rate (given the same 0.5 Gy thresholds, the circulatory system can be as highly radiosensitive as the lens, but mechanisms of such high radiosensitivity remain unclear)
- significantly increased radiation risk has been observed in various cohorts, in particular for IHD and CeVD, at dose <0.5 Gy
- hypertensive in Japan vs atherosclerotic in Western countries
- inconsistency between incidence and mortality
- the dose response relationship remains unclear, with the possibility of LDEF <1 and DREF <1
- targets (organs/tissues, cells) remain unidentified: e.g., heart, major arteries (e.g., carotid), kidneys and pancreas,

Little. Mutat Res 2016
Little… Hamada et al. Radiat Res 2020
Little & Hamada. Radiat Res 2022

# Individual factors for DCS

There are indications for several potential factors, but no firm conclusions can yet be drawn

- In the LSS, ERR decreases with increasing age at exposure, with borderline significant decreasing trends with attained age, but risk does not substantially differ with sex, or time since exposure
- genetic factors may include ATM, p53, p21, TGF-β1 and TNF-α
- coexposure factors may include cardiotoxic chemotherapeutic agents (e.g., vinca alkaloids like vincristine, and anthracyclines like doxorubicin)

ICRP TG 111 is looking into it

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# Predictive assays for DCS

ATM? (the role suggested from studies in mice)

Mechanisms for consideration

- mechanisms can vary among subtypes
- there is no strong evidence suggesting existence of threshold, and DCS risks are largely consistent across a wide range of dose, suggesting that the same targets and mechanisms may commonly operate over all levels of dose
- role of clonal hematopoiesis (clonal expansion of somatic mutations in hematopoietic stem cells)?

Post-exposure monitoring of atherosclerosis (real time and almost invasively)

- e.g., measurement of carotid intima-media thickness

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# Neurological diseases on the radar

Parkinson's disease

- increased incidence risk in Russian Mayak workers

  ERR/Gy = 1.02 (95% CI: 0.59, 1.63)

  Azizova … & Hamada. Int J Epidemiol 2020
- increased mortality risk in US Million Person Study cohorts

  $ERR_{0.1\ Gy}$ = 0.30 (95% CI: 0.08, 0.56): pooled analysis

  $ERR_{0.1\ Gy}$ = 0.19 (95% CI: 0.04, 0.36): meta-analysis

  Boice et al. Int J Radiat Biol 2022, Lopes et al. Brain Sci 2022

Dementia

- increased mortality risk in US female nuclear workers and in INWORKS

  Sibley et al. Am J Ind Med 2003, Gillies et al. Radiat Res 2017

Impact of childhood exposure remains unknown

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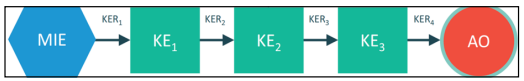
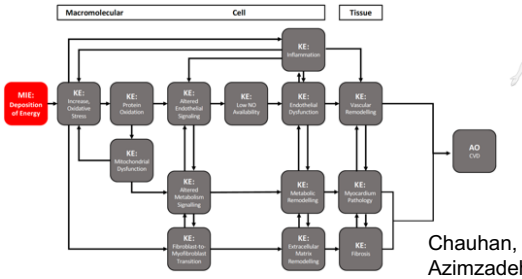
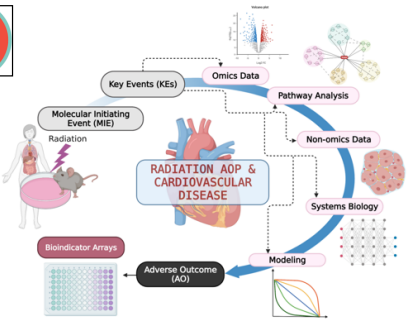
# AOP approach to integrate epi and bio

The proposed approach is to develop biologically based dose response (BBDR) models. Determination of BBDR model parameters needs identification of key events (bioindicators) with the AOP approach. The qualitative AOPs will be useful to identify knowledge gaps and priority research areas, and the quantitative AOPs to develop BBDR models and perhaps also to identify individual factors.




Chauhan, Hamada et al. Int J Radiat Biol 2021
Azimzadeh … & Hamada. Int J Radiat Biol 2022
Chauhan … Hamada et al. Int J Radiat Biol 2022

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## Wrap-up

For cataracts and DCS, there is a growing body of evidence with some mechanistic developments, but no firm conclusions can yet be drawn regarding individual factors.

Other late non-cancer effects on the radar at the level of dose below 1 Gy include normal-tension glaucoma, Parkinson's disease and dementia. These observations, if confirmed in other cohorts, have significant implications for radiation protection.

The individualized approach may be useful for patients, astronauts and emergency workers.

Continued studies would be needed to better understand potential inter-individual differences in radiation responses for non-cancer effects.

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