TASK GROUP 111
Factors Governing the Individual Response of Humans to Ionising Radiation

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Mandate

Tissue reactions and stochastic effects after exposure to ionising radiation are variable between individuals. Factors and mechanisms governing individual responses to ionising radiation are complex and not well understood. These responses can be measured at different levels of biological organization following varying doses of radiation by analysing different endpoints such as cancers, non-cancer diseases and mortality in the whole organism; normal tissue reactions after exposures; and cellular endpoints such as chromosomal damage and molecular alterations. There are many factors that, to different degrees, influence the responses of individual people to radiation. In addition to the obvious factors of radiation quality, dose, dose rate and the tissue (sub)volume irradiated, determining factors include, among others, age and sex, life style (e.g. smoking, diet, and possibly body mass index), environmental factors, genetics and epigenetics, stochastic distribution of cellular events and systemic comorbidities such as diabetes or viral infections. Genetic factors are commonly thought to be a substantial contributor to individual response to radiation. The inheritance of an abnormally responsive phenotype among a population of healthy individuals does not follow a classical Mendelian, monogenic heredity pattern. Rather it is considered to be a multi-factorial, complex trait.

LITERATURE REVIEW

NO consideration of the implications for RP

Human health effects under consideration

- Clinical studies, including those concerning normal tissue reactions, cancers and non-cancer diseases such as circulatory diseases, cognitive dysfunction and cataract.
- Epidemiological studies.
- Animal experiments and cellular assays to mimic / model and explore the 3 human situations.

Potential Contributors to Variation in Response

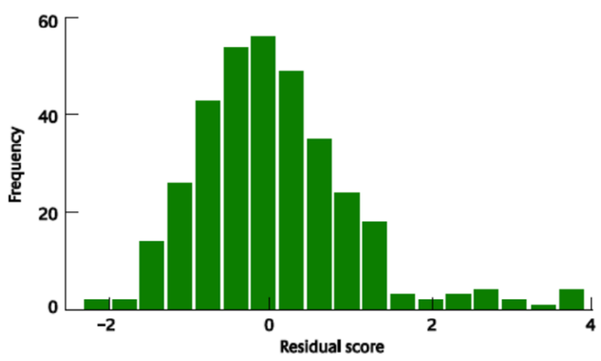
- Age and sex
- Genetic factors
- Epigenetic modifications
- Abnormal DNA damage signaling and repair kinetics
- Lifestyle factors e.g., smoking
- Co-exposures e.g., chemicals
- Underlying health conditions e.g., diabetes
- Stochasticity of responses

Measuring Radiosensitivity

Whole Organism	• Assays such as $LD_{50/30}$
Clinical radiosensitivity	• Consequence of radiotherapy • e.g. skin erythema, lung fibrosis
Susceptibility to Radiation Carcinogenesis	• Risk differences in populations • Epidemiology studies
Tissue radiosensitivity	• By specific tissues/organs • Epidemiology/clinical studies
Cellular radiosensitivity	• e.g. cell killing, chromosomal damage, DNA damage

Clinical Radiosensitivity: Severity of Normal Tissue Reactions

1010 breast cancer patients: residual score standardized and accounts for patient and treatment related factors



Preliminary conclusions

- Some evidence that sex, increasing age, rheumatoid arthritis, prior surgery and chemotherapy affect the frequency of normal tissue reactions. Smoking generally increases the frequency of normal tissue reactions but in the lung protects against radiation-induced normal tissue reactions.
- The risk of radiation cataract tends to be higher in females, and in those of younger age at the time of exposure. Animal studies and limited human studies have indicated that genetic factors play a role. Some evidence indicates that co-morbidities (e.g., diabetes and glaucoma) and co-exposures (UV, antioxidants) modify risk. However, no firm conclusions can yet be drawn.
- There is some suggestive evidence that younger age at exposure and concurrent chemotherapeutic (e.g., anthracycline and vinca alkaloids) exposure increase the risk of radiation induced circulatory diseases. The majority of evidence for these modifiers comes from high dose (radiotherapy) studies.
- There is a clear age dependency of radiation-induced brain injury associated with cognitive dysfunction. Other factors (such as sex, lifestyle and environmental factors) have no or significantly less influence on the development of neurocognitive disorders after exposure of the brain to ionizing radiation.
- Epidemiological and animal data indicate that younger age at exposure and female sex are associated with a higher relative risk for all solid cancers. However, there is variation between cancer sites. For breast cancer in females, the most sensitive age is the peri-pubertal period; human and animal studies are consistent in this finding.
- In the case of leukaemia, absolute risk is higher at younger ages and in males.
- Both epidemiological and some experimental animal evidence suggest that smoking increases the relative and absolute risk of radiation cancer in the lung.
- Animal studies provide some indication that excess body weight is associated with increased solid cancers and leukaemias.
- For breast cancer in animal studies hormonal factors (long-term estrogen exposure) increase risk.
- Animal studies provide some evidence that co-exposure to chemical agents is generally additive to radiation cancer risk, and radioprotectors and free radical scavengers reduce radiation cancer risk.
- Variation in cancer risks in inbred strains provides good evidence that genetic factors modify radiation cancer risks. The use of genetically modified mouse strains indicates that deficiencies in genes that modify background cancer incidence also modify radiation cancer incidence.
- There is clear evidence that rare homozygous mutations in some DNA repair genes, such as ATM, have a large effect on normal tissue radiosensitivity. The combined effect of multiple common polymorphisms will be smaller.
- In principle, tests measuring individual radiosensitivity, such as those proposed based on apoptosis or ATM foci, could lead to improved patient protection in radiotherapy but there are no internationally validated assays routinely available.

← *Image: Barnett et al 2011, Int. J. Radiat. Oncol. Biol. Phys. 82: 1065-1074*