Evidence for variation in human radiosensitivity: potential impact on radiological protection

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Current system of protection

- Avoid tissue injury (deterministic effects)
- Minimise risk of stochastic effects (cancer/hereditary)
  - dose limitation
  - limits derived from notional average that does not exist
• We are all different!

• Gender specific differences in risk, especially in breast (ERR incidence per Gy, 0.58 in females vs 0.35 in males)
Clinical radiosensitivity

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

- Increasing age in adults
- Smoking
- Diabetes and collagen vascular diseases
- Genetics
- No conclusion on sex, ethnicity, BMI, diet, alcohol
Radiosensitivity syndromes

Rare recessive disorders leading to cellular and sometimes clinical radiosensitivity

- Ataxia telangiectasia
- Fanconi anaemia
- Nijmegen breakage syndrome
- Cornelia de Lange syndrome
- Severe combined immuno-deficiency (SCID)
Basis of radiosensitivity syndromes

DNA repair pathways

NHEJ – SCID, Cernunnos

HR – FA, RAD51 paralogues

Damage signalling

AT, NBS, RIDDLE

Sister chromatid cohesion

Cornelia de Lange, Roberts syndrome
Radiation sensitive paediatric sub populations

- Retinoblastoma (Rb)
  - soft tissue sarcomas in radiation fields

- Neurofibromatosis type 1 (NF1)
  - second cancers associated with R/T of gliomas

- Li Fraumeni Syndrome (LFS)
  - high RR of 2\textsuperscript{nd} and 3\textsuperscript{rd} cancers related to R/T

- Nevoid basal cell carcinoma syndrome (NBCCS)
  - multiple basal cell skin cancers in radiation fields

Breast cancer mutation carrier and radiotherapy

- ATM heterozygotes – approx 2 fold elevated BC risk
  (Goldgar et al 2011, Breast Cancer Res 13: R73)

- ATM and radiotherapy – somewhat greater risk of contralateral second breast cancer
  (Bernstein et al 2010, JNCI 102: 475-483)

- Case-only studies indicates BRCA1, BRCA2, CHEK2 and ATM increase risk of secondary breast cancer (RR=2.18)
  (Broeks et al 2007, Breast Cancer Res J: R26)
How difficult can it be? (part I)

WECARE study - ~52500 women with Breast cancer
Nested association studies with ~708 CBC cases and ~1397 UBC controls
http://skiweb.mskcc.org/WeCare/front.html

- CHEK2 variant  \( \uparrow \text{RR with IR but NS} \)
- ATM, full scan  \( 1 \text{ rare variant } \uparrow \text{RR 2.8 with IR} \)
- 152 SNPs in 6 ATM targets  no associations
- BRCA1/2 variants  no associations
- 21 SNPs in BC loci  no associations
- Pregnancy factors  one strong association  \( \uparrow \text{RR 6} \)
How difficult can it be? (part II)

Nickels et al 2013, PLOS Genet 9:e1003284
34793 BC cases, 41099 controls

• 23 SNPs

• Modification of risk by 10 established environmental (non-radiation) factors

• Interaction between parity and \textit{LSP1}, OR 1.08-1.26 with ↑parity

• Interaction between alcohol \textit{CASP8}, OR 1.45 if >20g alcohol/day

• Interaction between parity and 1p11.2 SNP, OR 1.14 in parous women
• BRCA1/2 carriers at increased risk of breast cancer following multiple chest x-rays (Andrieu et al 2006, J. Clin. Oncol. 24: 3361-3366)

• BRCA1/2 and mammography
  Mixed evidence
  Screening from 35 years beneficial
  
  (Berrington de Gonzalez 2009, JNCI 101: 205-209)
Clinical implications - R/T

• Normal tissue damage limits ability to control tumour growth so predictive assays of individual sensitivity would be beneficial.

• Advice to patients on potentially modifiable risk factors could be relevant and help optimise benefits of radiotherapy.
Clinical implications - diagnostics

- Increasing use of medical diagnostics, especially CT could present problems for (the few) highly radiosensitive individuals.
- As before, predictive testing to identify such individuals could be very beneficial.
- Need to maintain justification of medical diagnostics on the basis of clinical benefit outweighing risk.
Interactions may be important

- Smoking and radon
- Exposure to radiation alone is rare in medical settings
How to utilise the knowledge?

Reliable prediction will be key

- Genetic testing
- Cellular / molecular endpoints

Requires:

Accuracy, speed, reproducibility, acceptance
The hunt for genetic predictors of R/T reaction

REQUITE

Validating Predictive Models and Biomarkers of Radiotherapy Toxicity to Reduce Side-Effects and Improve Quality of Life in Cancer Survivors

Prediction of radio-sensitivity

Radiotherapy reactions – no tests in routine clinical use, but some examples…
- Apoptosis in CD4/CD8 T-lymphocytes exposed to 8Gy found predictive of late normal tissue reactions in 399 patients (31% grade 2 toxicity, 7% grade 3). Ozsahin et al 2005 Clin. Cancer Res. 11:7426-33.

At diagnostic exposure levels?...
- γH2AX foci in 2-4mGy exposed mammary epithelial cells, more foci in cells from patients with high breast cancer risk (at least 20% on basis of family history or known mutation carrier. Colin et al 2011 Int. J. Radiat. Biol. 87:1103-1112.
CDKN1A as a marker of severe early radiation toxicity

Prediction of reaction sensitivity > 90%

But also see Finnon et al 2012, Radiother Oncol. 105: 329-36
Can expression be predictive - p53 function assay

ATM → CHK2 → p53 or P53

P21, Puma, Sesn2
Correlation with cancer risk

Implications for RP - ethics

• The ability to identify sensitive groups or individuals will need careful consideration, especially for occupational exposure.

• Possible need to consider the justice in protecting small numbers of very high risk individuals

• In the absence of routine tests, provision of information on risk modifiers and reduction/avoidance should be the main focus.

• ...and what might the legal implications be?
Requirements

- Knowledge of the range of radiosensitivity
- Reliable methods to predict
- Agreement that there may be benefits
- Robust framework in which to operate
- Acceptance
Thanks for your attention

Report available for free download at:
https://www.gov.uk/government/groups/advisory-group-on-ionising-radiation-agir