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

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22 October 2015
ICRP Symposium 2015, Seoul, South Korea

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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

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The obvious

- 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)

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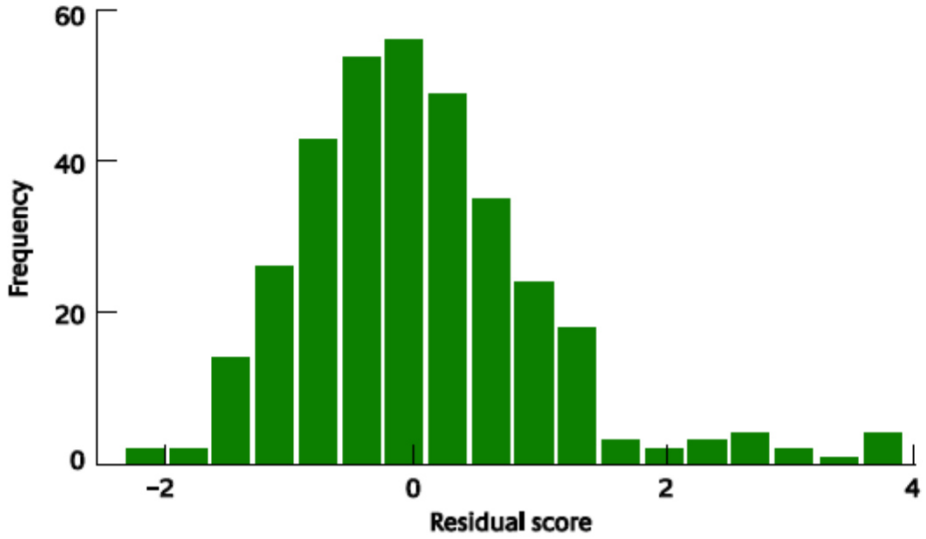
Clinical radiosensivity



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

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

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Clinical radiosensitivity factors

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

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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)

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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

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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 2nd and 3rd cancers related to R/T
- Nevoid basal cell carcinoma syndrome (NBCCS)
  - multiple basal cell skin cancers in radiation fields

See Kleinerman RA (2009) Paediatr. Radiol. 39 Suppl 1: S27-S31

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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)

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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	↑RR with IR but NS
• ATM, full scan	1 rare variant ↑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 ↑RR 6

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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 *LSP1*, OR 1.08-1.26 with ↑parity
- Interaction between alcohol *CASP8,* OR 1.45 if >20g alcohol/day
- Interaction between parity and 1p11.2 SNP, OR 1.14 in parous women

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Diagnostic exposure

- 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)

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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.

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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.

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Interactions may be important

- Smoking and radon
- Exposure to radiation alone is rare in medical settings

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How to utilise the knowledge?

Reliable prediction will be key

- Genetic testing
- Cellular / molecular endpoints

Requires:

Accuracy, speed, reproducibility, acceptance

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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

Collecting blood from 5300 cancer patients undergoing R/T, Oct 2013 – Sept 2018. Around 1800 recruited so far…

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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.*

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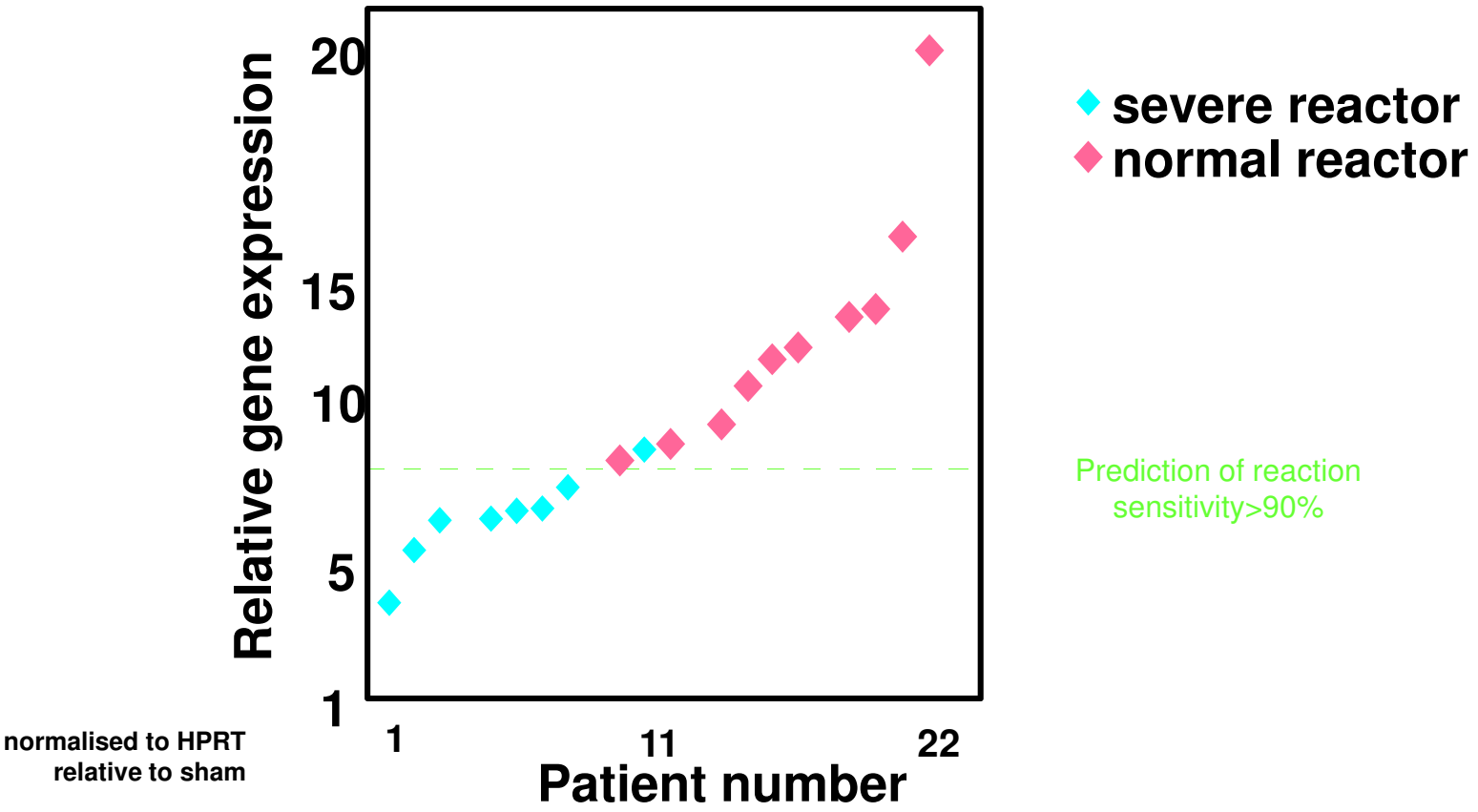
CDKN1A as a marker of severe early radiation toxicity



Badie et al 2008, Br. J. Cancer 98: 1845-51
But also see Finnon et al 2012, Radiother Oncol. 105: 329-36

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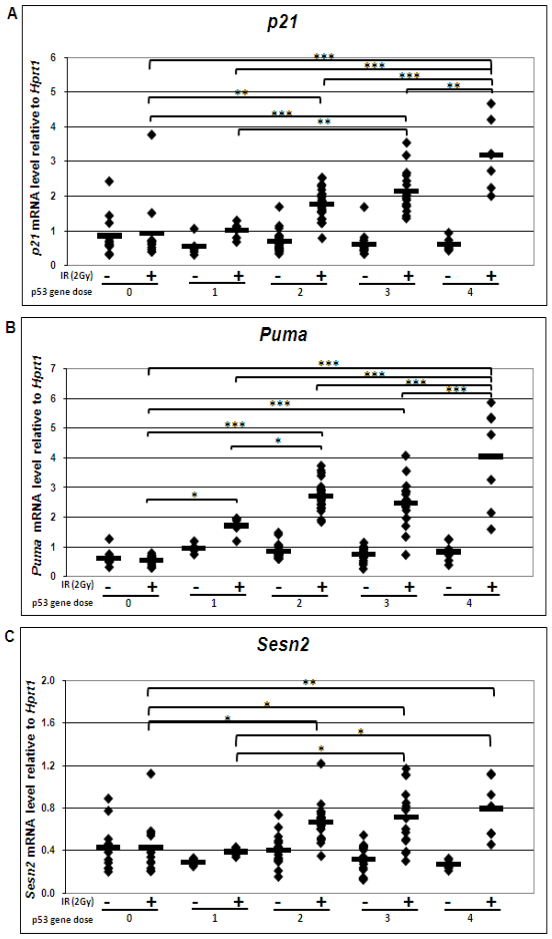
Can expression be predictive - p53 function assay



ATM

↓

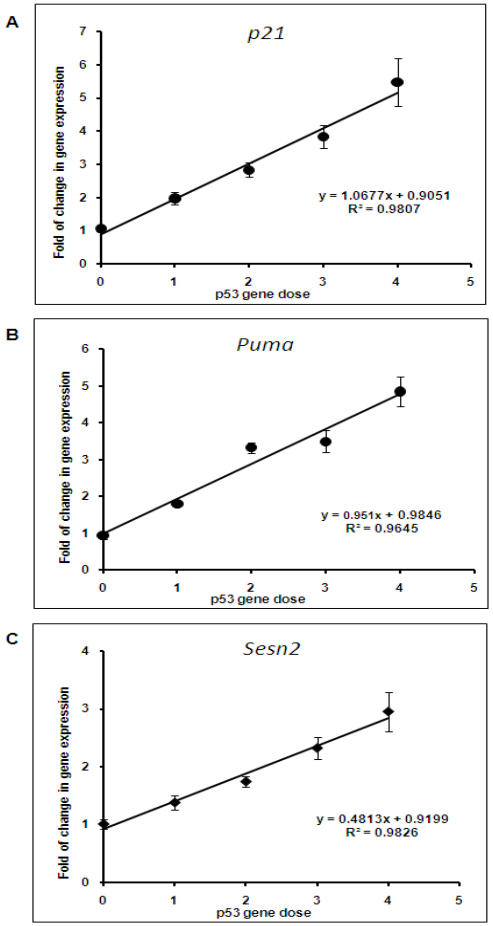
CHK2

↓

~~p53~~ or p53

↓

P21, Puma, Sesn2



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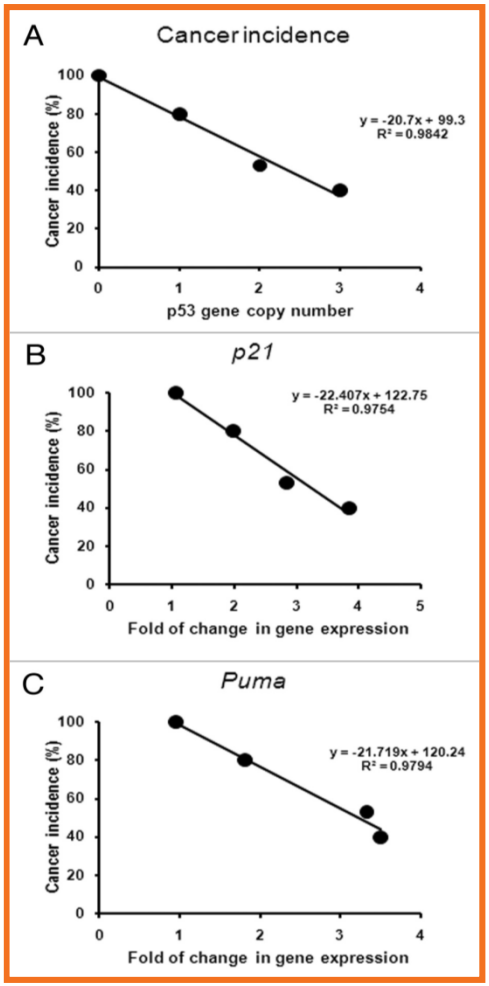
Correlation with cancer risk



Kabacik et al (2011) Cell Cycle 10: 1152-1161

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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?*

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Requirements

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

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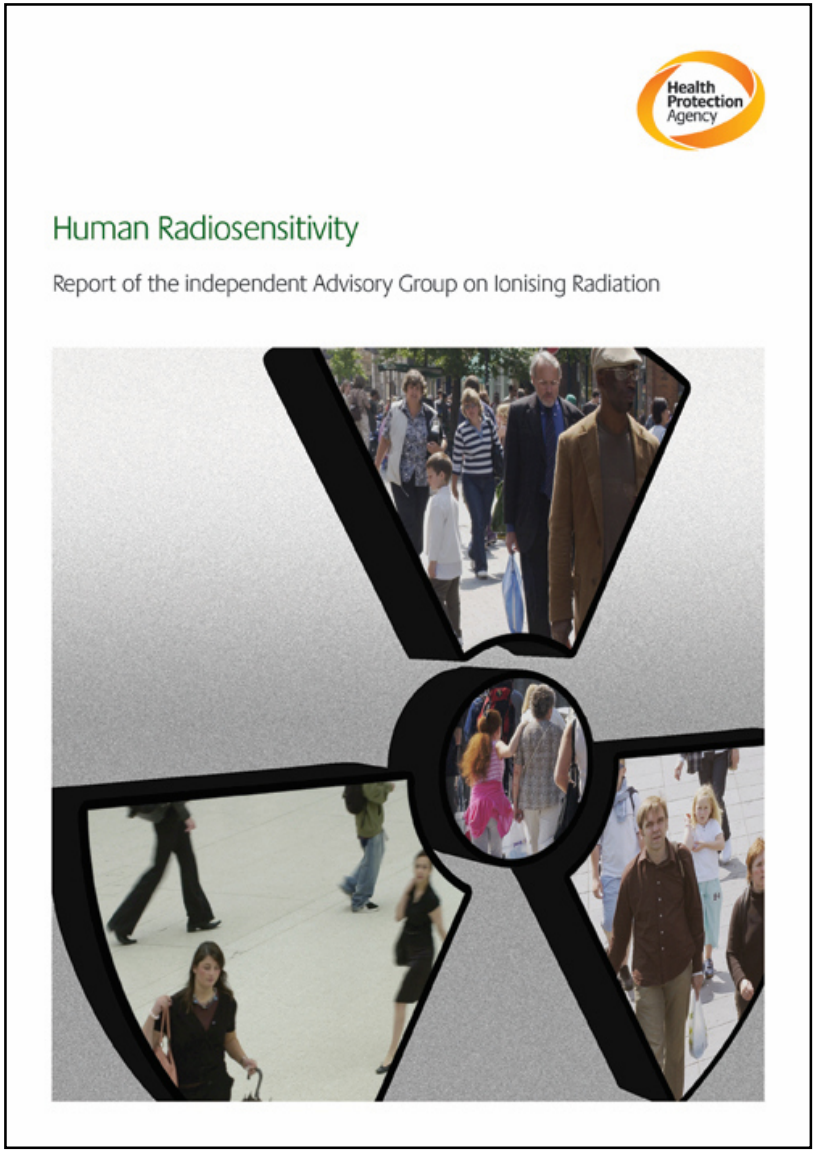
Thanks for your attention



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