Risks associated with protracted low dose radiation exposure

Bijan Modarai
Professor of Vascular Surgery

Academic Department of Vascular Surgery
Guy’s & St Thomas’ NHS Foundation Trust, King’s College London
Disclosures

Cook Medical: Proctoring, Speaker’s fees, Grant support

Getinge: Educational grant support
- Cataracts
- Skin erythema
- Epilation
- Sterility
- Accelerated arterial disease
- Inflammation
- Cancer (Leukaemia, solid tumours)
Life Span Study

- 1945 – Hiroshima and Nagasaki
- Acute high dose exposure
- Cohort of 120,000 survivors
- Followed since 1950

Ozasa et al. J Epidemiol 2018
Significance of low dose radiation

- ICRP safe dose limits informed by Life Span
- 100mSV: Raised leukaemia and solid cancer risk
- Linear, no threshold model: Any dose can be carcinogenic
- Risk of cancer increases with increasing dose

Richardson et al. BMI 2015
Leureud et al. Lancet Haematol 2017
Area of uncertainty: Low dose effects

- a: Linear, no threshold
- b: Threshold dose
- c: Lower risk
- d: Higher risk
### Representative dosage

<table>
<thead>
<tr>
<th>Type of exposure</th>
<th>Dose/Dose rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical diagnostics</td>
<td>0.01-25mSv</td>
</tr>
<tr>
<td>Dose limit for radiation worker</td>
<td>20mSV/year</td>
</tr>
<tr>
<td>Background radiation</td>
<td>1-10mSv/year</td>
</tr>
<tr>
<td>Complex endovascular case</td>
<td>50uSv</td>
</tr>
</tbody>
</table>
Background radiation exposure

- Medical exposure: 20%
- Cosmic rays: 13%
- Food/water: 8%
- Others (all man-made sources): 1%
- Radon (natural internal exposure): 43%
- Earth gamma radiation (natural external exposure): 15%

165,924 MILES FLOWN
14 DAYS IN THE AIR
29 CITIES VISITED
17 COUNTRIES VISITED
13.3 x FROM POLE TO POLE

5uSv/hr

Vaiserman et al. Dose Response 2018
Radiation Hormesis: Low dose radiation has beneficial effects?!

- Adaptive immune response
- Antioxidant generation
- Apoptosis
- Repair induction
Interventional Caseload 2008-2018: Dosimetry Estimate

Total vascular cases: 1071

Estimated total dose
- 20uSv/case: 21mSv
- 40uSv/case: 42mSv
- 60uSv/case: 64mSv

Note: Excludes GI cases (gastrostomies, balloon dilatations, stents insertions, PTCs), nephrostomies-ureteric stents, bleed/other embolisations, tunneled lines, dialysis access, IVC filters
Leukaemia cases: 1- 204mSV exposure

Radiologist, PC=9.1% BUT compensated

Cumulative radiation exposure dose was not believed to correctly reflect the actual exposure.
The need for better epidemiological studies

- Stringent study design
- Well defined population
- Adequate sample size
- Control for confounding factors
- Rigorous follow up

- HIGH QUALITY DOSIMETRY
HEALTH EFFECTS OF CHRONIC LOW DOSE RADIATION EXPOSURE:
MORE QUESTIONS THAN ANSWERS!
- Lymphocytes
- Spermatogonia
- Haematopoietic Cells
- Intestinal epithelium
- Skin
- Nerve cells
- Muscle tissue
- Bone
- Collagen

Most sensitive

Least sensitive
Low-dose or low-dose-rate ionizing radiation–induced bioeffects in animal models

Feng Ru Tang¹,*, Weng Keong Loke² and Boo Cheong Khoo³

- Increased incidence of lung tumours
- DNA damage
- Shortened life span
- Risk synergic with other toxic agents (e.g. tobacco smoke)

Feng et al. J Radiation Research 2017
Experimental studies on the biological effects of chronic low dose-rate radiation exposure in mice: overview of the studies at the Institute for Environmental Sciences

- 0.05mGy/day to 20mGy/day
- 0.05mGy/day – radiation worker equivalent
- Neoplasm Increased (0.05mGy/day)
- Shortened life (1mGy/day)
- Chromosome aberrations (1mGy/day)
- Decreased tumour immunity (20mGy/day)

Braga-Tanaka et al. Int J Rad Biol 2018
Operators: Evidence of DNA damage during EVAR

Radiation Energy transfer to the cell

DNA break

Induction of DNA repair pathway (e.g. phosphorylation of H2AX)

Generation of toxic factors e.g. ROS, TGFβ, IL-6, TNF

Error prone: Chromosomal aberrations

GENOMIC INSTABILITY

CANCER
Markers of chronic exposure:
Dicentric/Acentric chromosomal fragments
Markers of chronic exposure: Micronuclei

Tichy et al. PLOS 2018
Zeegers et al. Genome Integrity 2017
Effects of ionising radiation on micronucleus formation and chromosomal aberrations in Chinese radiation workers

Qing-Zeng Qian,1,* Xiang-Ke Cao,2 Fu-Hai Shen,1 and Qian Wang1

<table>
<thead>
<tr>
<th>Groups</th>
<th>Cases (N)</th>
<th>MN Numbers (N)</th>
<th>MN numbers (N)</th>
<th>MN rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed group</td>
<td>1392</td>
<td>1 392 000</td>
<td>3395</td>
<td>2.44\textsuperscript{a}</td>
</tr>
<tr>
<td>Control group</td>
<td>143</td>
<td>143 000</td>
<td>246</td>
<td>1.72</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exposure time (y)</th>
<th>Cases (N)</th>
<th>MN</th>
<th>MN number (N)</th>
<th>MN rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>723</td>
<td></td>
<td>1597</td>
<td>2.21</td>
</tr>
<tr>
<td>10–20</td>
<td>532</td>
<td></td>
<td>1316</td>
<td>2.47\textsuperscript{a}</td>
</tr>
<tr>
<td>&gt;20</td>
<td>137</td>
<td></td>
<td>482</td>
<td>3.52</td>
</tr>
</tbody>
</table>

Qian et al. Radiat Prot Dosimetry 2016
“Genetic susceptibility to radiation-induced cancer involving strongly expressed genes is judged to be too rare to appreciably distort estimates of population risk; the potential impact of common but weakly expressing genes remains uncertain”
Biological assessment/Biodosimetry

- Current methods laborious
- Large number of cells
- Next gen/high throughput sequencing
Bystander: Cell–Cell interaction

- ROS
- TGFB
- IL-6
- TNF
- IL-8
Antioxidants?

Cancer staging: 99mTc MDP bone scans

Anti-oxidant formulation:
- 1.2g N-acetylcysteine,
- 600mg lipoicacid
- 30mg betacarotene

Reduced DNA damage (gamma H2AX)

0.25Gy → HUVECs in vitro

Anti-oxidant formulation:
- Resveratrol (45%), Extramel (2.15%), Seleno-L-methionine (2%), Curcuma longa (42%), reduced L-glutathione (6%), and vitamin C (2.4%)

Reduced ROS

Reduced DNA damage (gamma H2AX)
The mainstay of radioprotection

ALARA
Summary

- We live in a world of ever increasing radiation exposures
- Health effects of occupational exposure unknown
- Better radiation epidemiology needed
- Biological and physical dosimetry
- Assume all radiation is dangerous
- Insist on maximal protection