Factors Influencing Risk

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Factors Influencing Risk.

- Genetic considerations.
- Age at Exposure.
- Gender.
- Fractionation and protraction of exposure.
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- Genetic considerations.
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Genetic Factors.

• There are now two clear instances from human epidemiological studies which imply the existence of a radiosensitive sub-population.
Scoliosis, Multiple Diagnostic X-rays and Breast cancer.

- Mean Age at Diagnosis…..11yr (0-19)
- Mean No. of radiographs 26.8 (0-332)
- 3000 women diagnosed with scoliosis.
- Mean # Years Exposed …6.1 (0-55)
- Mean Total Breast Dose (cGy)… 12.1 (0-111)

Scoliosis, Multiple Diagnostic X-rays and Breast cancer.

- Borderline significant radiation dose-response for breast cancer in the whole cohort (ERR/Gy=2.86).

- Dose-response much greater) for a sub-set of women with a family history of breast cancer in first or second degree relatives. (ERR/Gy=8.37)

Israeli study of Children Epilated for the Treatment of Tinea Capitis

- More than 20,000 children involved.
- A sub-set included 525 large families, with 5 or more children.
- Overall, about 1% of those irradiated developed meningioma, but it was not random.
- Marked clustering in some families, with multiple children developing the malignancy.

Sadetsky et al. The Lancet Oncology, 2007
Family #1
(Origin: Morocco)
Family #2
(Origin: Morocco)

Leukemia 22 years
Breast Cancer
Conclusion.

• While there are instances from human epidemiological studies which imply the existence of a radiosensitive sub-population.

• The genes involved have not been identified.

• This is worth studying.
The Plan: Use Mice Heterozygous for Various Candidate Genes and Score:-

• Oncogenic Transformation in embryo fibroblasts as a surrogate for carcinogenesis.

• Ocular cataracts, as an in vivo endpoint relevant to NASA.
In Vitro Cell Transformation

++ AT wildtype
+- AT heterozygote
-- AT homozygote

Normal
Transformed
Atm and mRad9

Transformation Incidence %

Transformation Apoptosis

% Apoptosis
Atm and BRCA1

Transformation Incidence %

- Atm+ BRCA1++
- Atm+ BRCA1+-
- Atm+ BRCA1+-
- Atm+ BRCA1+--
- WT

Apoptosis %

- Atm+ BRCA1++
- Atm+ BRCA1+-
- Atm+ BRCA1+--
- WT
0.5 Gy of $^{56}$Fe 1000 MeV/n
0.5Gy of $^{56}$Fe 1000 MeV/n
ATM Heterozygote

ATM Homozygote

Wild-type

4 Gy
Cataract grade: 2.0

Time after irradiation (weeks)

Cataract prevalence
Wild-type

0 1 0 2 0 3 0 4 0 5 0 6 0 7 0 8 0 9 1.0

Time after irradiation (weeks)

0.0 0.1 0.2 0.3 0.4 0.5

Cataract prevalence

0.5 Gy

Cataract grade: 1.0

ATM Homozygote

ATM Heterozygote

Wild-type

0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0

Cataract prevalence

0 10 20 30 40 50 60 70

Time after irradiation (weeks)
Genes Identified

- **ATM** 66 exons 150 kb
- **BRCA1** 24 exons 5.6 kb
- **Rad9** 9 exons 10.0 kb
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Attributable Lifetime Risk

- Attributable Life-Time Risk % per Sv
- Age at Time of Exposure
Cancer Incidence
Population average (male): 8.6%/Sv
Population average (female): 12.8%/Sv

BEIR VII
Gender averaged ERR’s at age 70 for exposure at age 10 or 40
All Solid Cancers. Variation with Age at Exposure.

- **BEIR VII;** Log-Linear trend to decrease for 0-30yrs, no further change after age at exposure 30yr.

- **Preston et al (2007)** Excess risks declined with age at exposure less than 40 years, but increased with age at exposure late in life.

- Lung cancer is the only one to consistently increase with age
All Solid Cancers

![Graph showing ERR per Gy vs Age at Exposure](image)

- Log-linear
- BEIR VII
- Spline

**P-spline = 0.03**
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Gender specific ERR’s at age 70 for exposure at age 30
Effect of Gender on Risk.

- Overall, women have higher ERR’s than men.
- The largest gender effects on ERR’s are for lung & bladder; baseline rates affected by smoking.
- When gender-specific cancers are excluded, excess absolute risks are essentially equal.
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**DDREF**

- **NCRP (1978)** 2 to 10 (animal studies)
- **BEIR III (1980)** 2.25 ($\alpha/\beta$ ratio)
- **BEIR V (1990)** 2 to 10 (best estimate 4)
- **UNSCEAR (1977)** 2.5 (leukemia at high & low doses)
- **UNSCEAR (1986)** 2 to 10
- **ICRP (1990)** 2
- **BEIR V11 (2006)** 1.5 ($\alpha/\beta$ ratio)
The Effect of Dose Protraction.

- We now have cancer risk estimates from several nuclear worker studies involving protracted exposures over many years to compare with the acute exposure of the A-bomb survivors.
- The 15-nation study (Cardis et al 2005.)
- The NRRW study from the UK. (Muirhead et al 2009)
IARC 15 Country Study (Cardis et al. 2005)

- 600,000 nuclear workers
- Average cumulative dose = 19.4 mSv
- All cancers (except leukemia) ERR = 0.97 (0.14 to 1.97)/Sv
- Leukemia ERR = 1.93/Sv (NS)
IARC 15 Country Study (Cardis et al. 2005)

Cohorts

- Canada
- Sweden
- UK - all
- USA - Hanford
- USA - NPP
- USA - ORNL
- All combined

NPP=Nuclear Power Plants
ORNL=Oak Ridge National Laboratory

Excess relative risk/Sv

Cardis, E et al. BMJ 2005;331:77
IARC 15 Country Study
Criticised for two reasons.

- Result driven by the Canadian contribution.
  (Few workers, many cancers!)
- The predominance of lung cancers suggest a confounding effect of smoking.
- For both of the above reasons, the ERR/Sv may be exaggerated.
UK National Registry of Radiation Workers

• 175,000 workers: long follow-up
• Healthy worker effect – i.e. all causes of death lower than general population
• ERR / Sv for solid cancer mortality similar to A-bomb survivors (0.275)
• Cancer risk increased with cumulative dose; Mean dose 24.9 mSv

Muirhead et al
BJC 2009
## ERR/Sv for Cancer Mortality

<table>
<thead>
<tr>
<th></th>
<th>Leukemia excluding CLL</th>
<th>Solid cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>A – bomb survivors</td>
<td>1.4</td>
<td>0.26</td>
</tr>
<tr>
<td>15 – nation study</td>
<td>1.93*</td>
<td>0.97</td>
</tr>
<tr>
<td>UK – NRRW analysis</td>
<td>1.7*</td>
<td>0.275</td>
</tr>
</tbody>
</table>

A - bomb survivors, BEIR VII Report  
15 nation study, Cardis et al. 2005  
UK – NRRW analysis, Muirhead et al., 2009  
* Not Statistically Significant
The Effect of Dose Protraction.

• Comparing nuclear worker studies with the A-bomb data lead us to conclude that the reduction of cancer risks by dose protraction is surprisingly small.

• However, the confidence intervals are so wide that they easily accommodate a DDREF of 1.0, 1.5, 2.0, or even larger (or 0.5 for that matter!!)
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A Recent History of Radiation Protection in the United States.
Dose Limits, 1950’s ICRP

Based on genetic effects

1956; Dose limit for radiation workers reduced to 0.1R/week \((5\text{R/yr})\)

1/10 for the general public
Dose Limits, 1950’s ICRP

Based on genetic (heritable) effects:
1956; Dose limit for radiation workers reduced to 0.1R/week (5R/Yr)
1/10 for the general public

This is essentially unchanged to this day
(Except it is now called 50mSv!)
Mutations, spontaneous or induced, are usually harmful. This is a wrong assumption.

Any dose entails some risk. (i.e. no threshold)

Number of mutations is proportional to dose; a linear extrapolation from high doses provides a valid estimate of low dose effects. This is the linear no-threshold (LNT) model.

The effect is independent of the rate at which the radiation is delivered or the spacing between exposures. It is not valid for Drosophila, it is valid for mice.
Radiation-Associated Deaths in the Life-Span Study

Excess Deaths per Year

- Solid Cancer
- Noncancer
- Leukemia

Years:
- 1945
- 1965
- 1985
- 2005
Because of the increasing number of solid cancers in the A-bomb survivors:

- ICRP (1991) added the requirement that occupational exposure averaged over 5 years should not exceed 20mSv/year.
- NCRP (1993) added the cumulative limit of 10mSv x age.
- Both retained the 50mSv in one year.
Heritable Effects

Carcinogenesis

Reassessment (multifactorial diseases)

Drosophila data

Mouse data available

Level of Concern

Date

% of Detriment due to genetic component (ICRP)

- 1955 ............ 100%
- 1977 ............ 25%
- 1991 ............ 18%
- 2007 ............ 4%
NCRP “recommends”. NRC “regulates”

- NRC never adopted the cumulative limit (age x 10mSv) recommended by NCRP.
- The NRC limit is 50mSv per year, and every year! More than is allowed in any other Western country that follows ICRP.
## Population Averaged Cancer Risk %/Sv

<table>
<thead>
<tr>
<th></th>
<th>Incidence</th>
<th>mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>8.6</td>
<td>4.6</td>
</tr>
<tr>
<td>Female</td>
<td>12.8</td>
<td>6.2</td>
</tr>
<tr>
<td>Combined</td>
<td>10.8</td>
<td>5.4</td>
</tr>
</tbody>
</table>

Calculated from BEIR V11 Data including a DDREF of 1.5
Cancer Risks for a Radiation Worker Receiving the Maximum Permissible Dose from age 18-65 years

<table>
<thead>
<tr>
<th>Rule</th>
<th>Total Dose</th>
<th>Cancer Incidence</th>
<th>Cancer Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRC</td>
<td>2.35 Sv</td>
<td>19.0</td>
<td>10.8</td>
</tr>
<tr>
<td>50 mSv/yr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCRP</td>
<td>0.65 Sv</td>
<td>6.1</td>
<td>3.3</td>
</tr>
<tr>
<td>50 mSv/yr + 10 mSv x age</td>
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