Individual radiosensitivity – an overview

……or "*what we don't know about individual susceptibility*"

Mike Atkinson

Individual radiation sensitivity

- What is radiation sensitivity ?
-Does radiation sensitivity predict cancer risk ?
-Does radiation sensitivity predict non-cancer end points ?
-What does sensitivity contribute to dose response curves ?
-How can we include this in modelling risk ?
-What is the relevance to radiation protection ?

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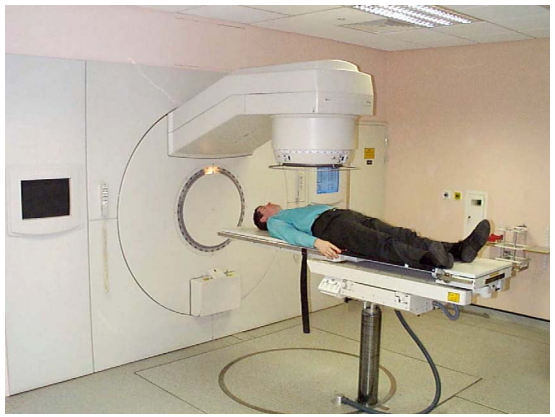
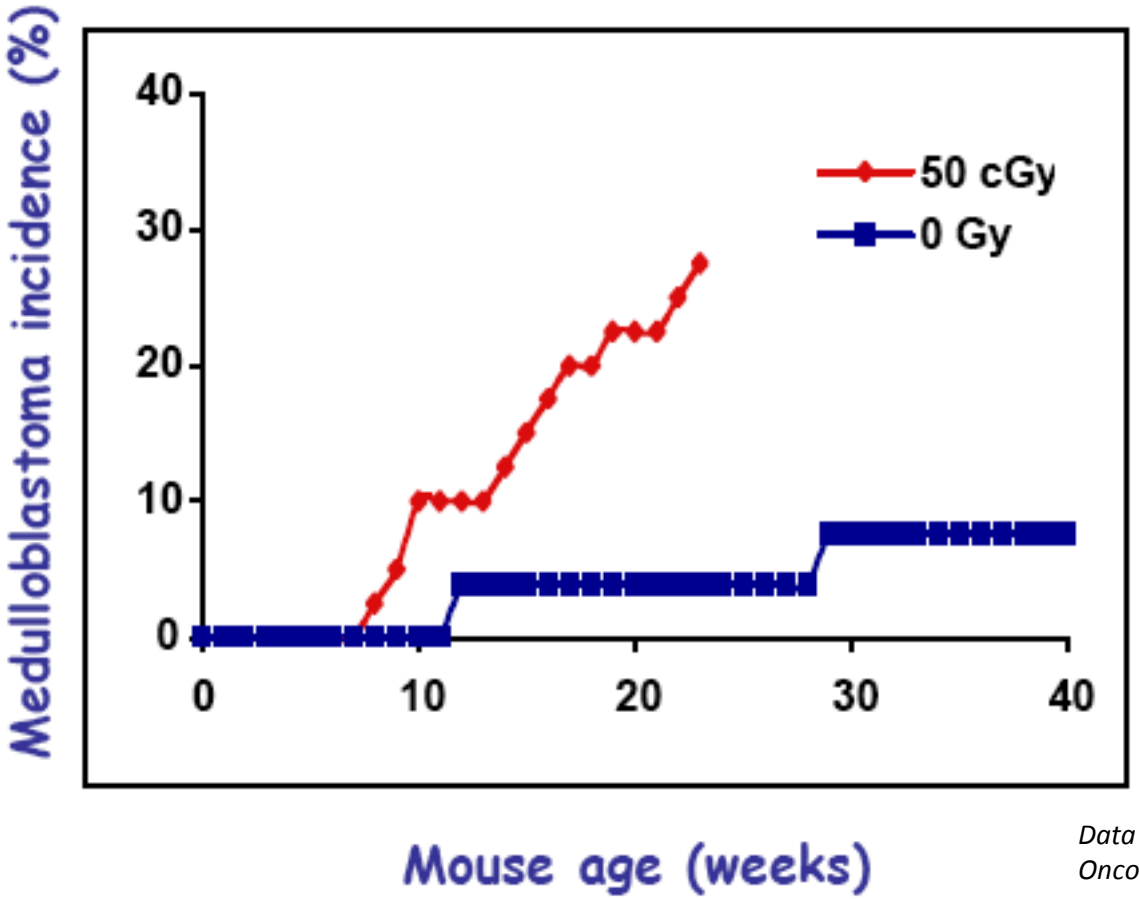
Acute radiosensitivity

Clinical experience of acute radiation reaction (1-10%)



Chronic radiation sensitivity (cancer)

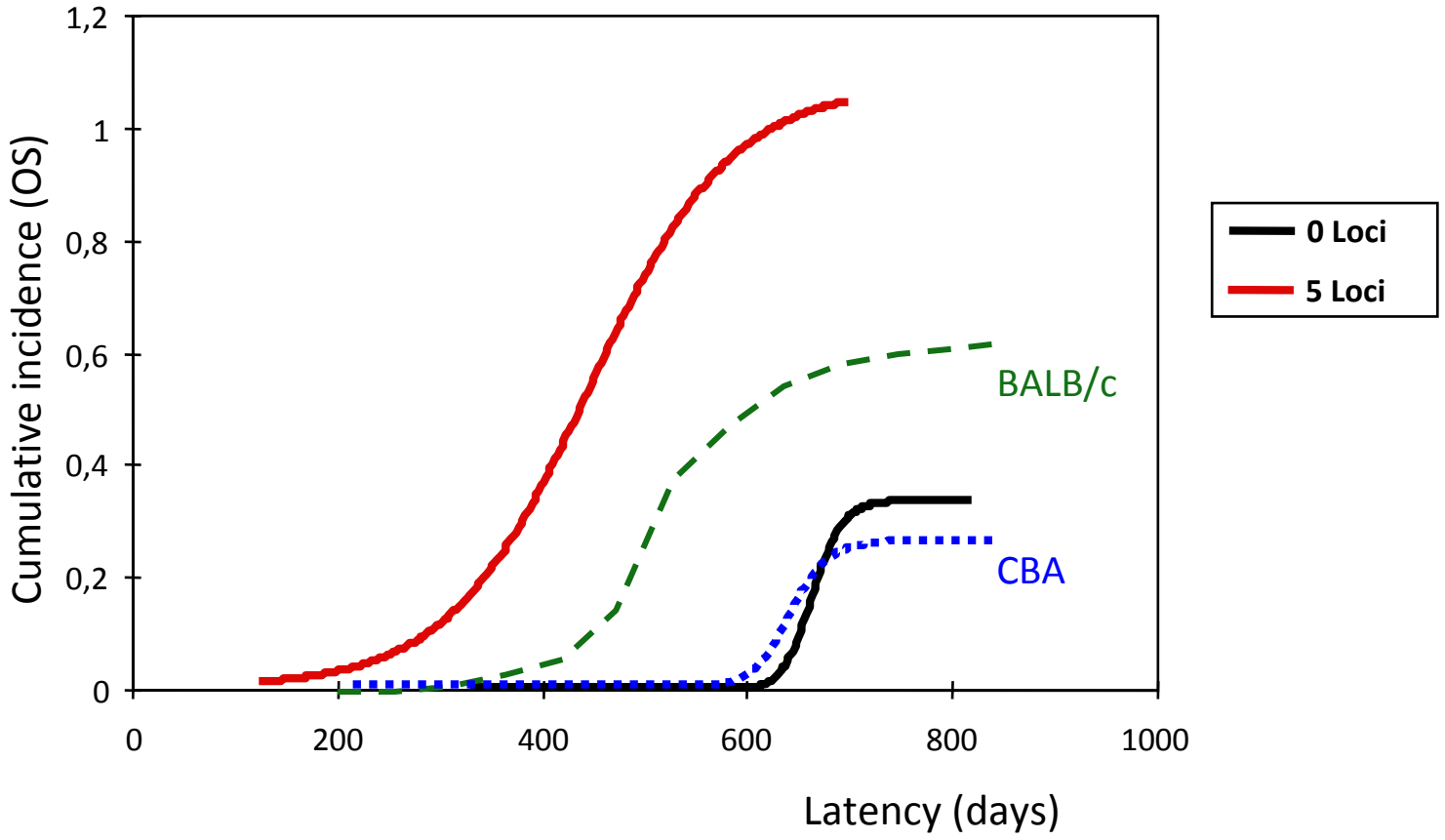
"Severe" genetic disposition (under 0.01%)



Data from Pazzaglia et al
*Oncogene **25**:1165-1173 (2006)*

Chronic radiation sensitivity (cancer)

"low penetrant" genetic disposition (unknown 10-50%??)



Sensitivity can be defined on many scales:-

- Induction of a specific lesion in a cell (DNA DSB, disruption of a mitochondrion)

- Change to a tissue or organ (inflammation, cell death)

- Change to an individual (cancer, cardiovascular disease)

Note that a shift from “deterministic” to “stochastic” events accompanies the change of scale, but no shift in dose response relationship is considered.

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- Is there a genetic basis ?
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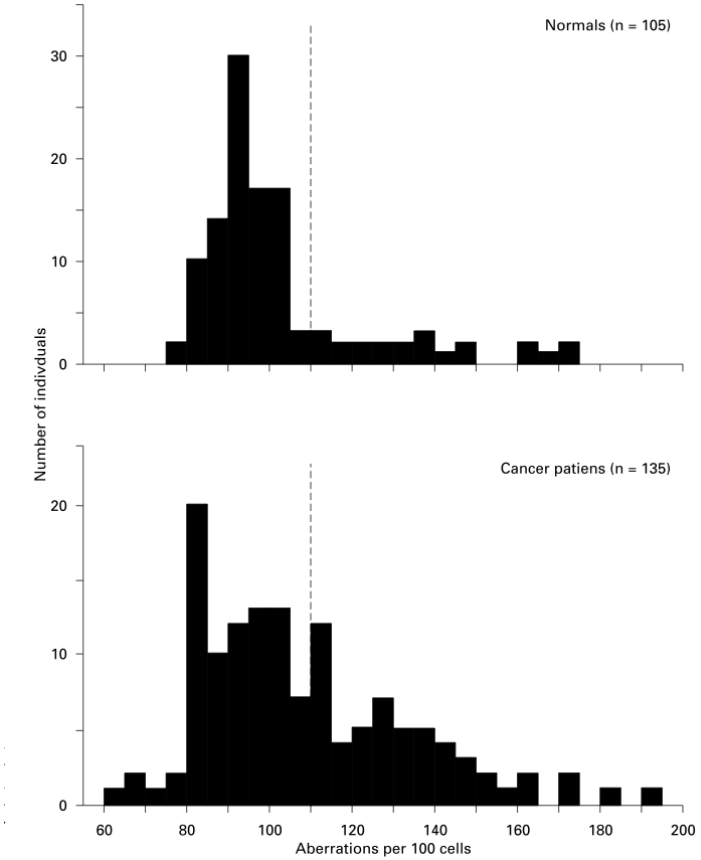
Meta-analysis of 64 individual studies

*Berwick & J Natl Cancer Inst 2000; **92**: 874–97 :*

Primarily comparing DNA damage induced by stressor (radiation, CTX etc) in a cancer case with the same challenge in a non-cancer control.

OR in range 1.4 to 75.3

Cause or effect ??????



*Scott Cytogenet Genome Res 2004; **104**: 365–70*

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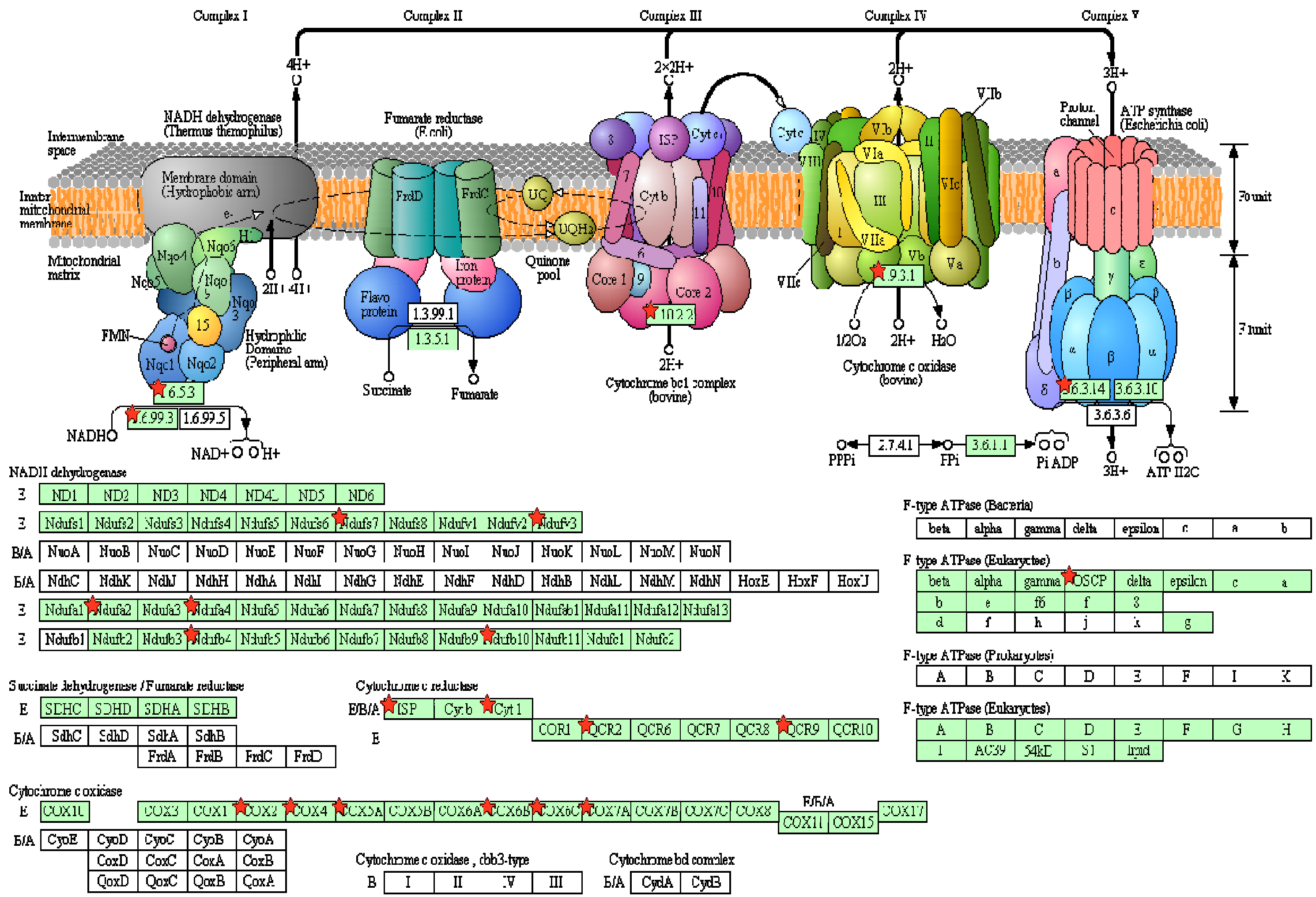
- Non-cancer effects are not clonal. Therefore an initial single cell lesion from radiation hit may not explain the effects.

- Current assays of radiation sensitivity directly or indirectly assay only DNA damage at a single cell level.


Complex I
Complex II
Complex III
Complex IV
Complex V
4H+
2×2H+
2H+
3H+
Intermembrane space
Inner mitochondrial membrane
Mitochondrial matrix
NADH dehydrogenase (Thermus thermophilus)
Membrane domain (Hydrophobic arm)
Hydrophilic Domain (Peripheral arm)
FMN
NADH
NAD+
H+
1.6.99.3
1.6.99.5
1.6.5.3
Fumarate reductase (E.coli)
FrdD
FrdC
Flavo protein
Iron protein
1.3.99.1
1.3.5.1
Succinate
Fumarate
Quinone pool
UQ
UQH2
Cyt c
ISP
Cyt b
Core 1
Core 2
1.10.2.2
2H+
Cytochrome bc1 complex (bovine)
1/2O2
H2O
1.9.3.1
Cytochrome c oxidase (bovine)
Proton channel
ATP synthase (Escherichia coli)
F0 unit
F1 unit
3.6.3.14
3.6.3.10
3.6.3.6
PPPi
2.7.4.1
PPi
3.6.1.1
Pi ADP
ATP H2O
NADH dehydrogenase
E ND1 ND2 ND3 ND4 ND4L ND5 ND6
E Ndufs1 Ndufs2 Ndufs3 Ndufs4 Ndufs5 Ndufs6 Ndufs7 Ndufs8 Ndufv1 Ndufv2 Ndufv3
B/A NuoA NuoB NuoC NuoD NuoE NuoF NuoG NuoH NuoI NuoJ NuoK NuoL NuoM NuoN
B/A NdhC NdhK NdhJ NdhH NdhA NdhI NdhG NdhE NdhF NdhD NdhB NdhL NdhM NdhN HoxE HoxF HoxU
E Ndufa1 Ndufa2 Ndufa3 Ndufa4 Ndufa5 Ndufa6 Ndufa7 Ndufa8 Ndufa9 Ndufa10 Ndufab1 Ndufa11 Ndufa12 Ndufa13
E Ndufb1 Ndufb2 Ndufb3 Ndufb4 Ndufb5 Ndufb6 Ndufb7 Ndufb8 Ndufb9 Ndufb10 Ndufb11 Ndufc1 Ndufc2
Succinate dehydrogenase / Fumarate reductase
E SDHC SDHD SDHA SDHB
B/A SdhC SdhD SdhA SdhB
FrdA FrdB FrdC FrdD
Cytochrome c reductase
E/B/A ISP Cyt b Cyt1
E COR1 QCR2 QCR6 QCR7 QCR8 QCR9 QCR10
Cytochrome c oxidase
E COX10 COX3 COX1 COX2 COX4 COX5A COX5B COX6A COX6B COX6C COX7A COX7B COX7C COX8 COX17
E/B/A COX11 COX15
B/A CyoE CyoD CyoC CyoB CyoA
CoxD CoxC CoxA CoxB
QoxD QoxC QoxB QoxA
Cytochrome c oxidase, cbb3-type
B I II IV III
Cytochrome bd complex
B/A CydA CydB
F-type ATPase (Bacteria)
beta alpha gamma delta epsilon c a b
F-type ATPase (Eukaryotes)
beta alpha gamma OSCP delta epsilon c a
b e f6 f 8
d f h j k g
F-type ATPase (Prokaryotes)
A B C D E F I K
F-type ATPase (Eukaryotes)
A B C D E F G H
1 AC39 54kD S1 Irad

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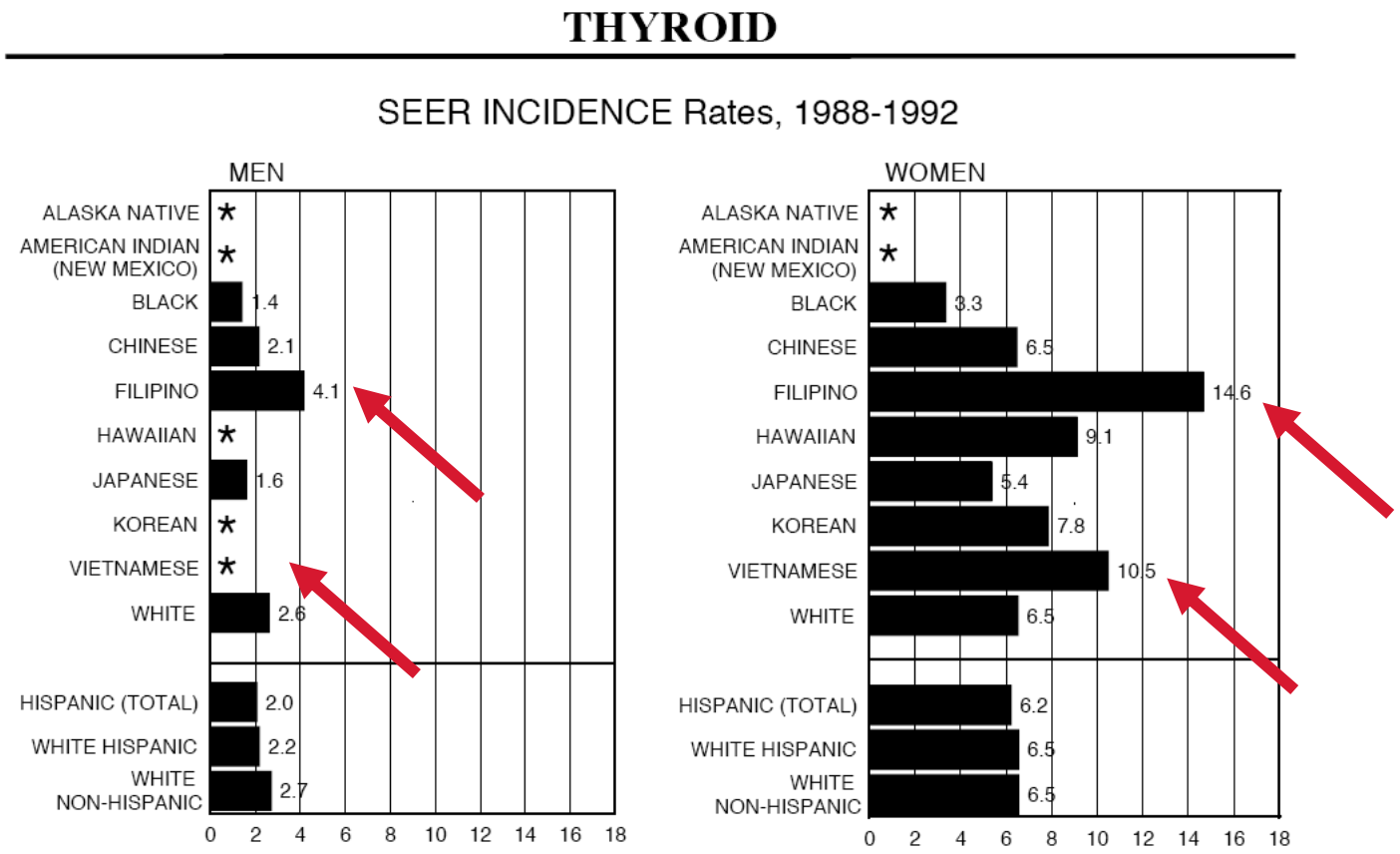
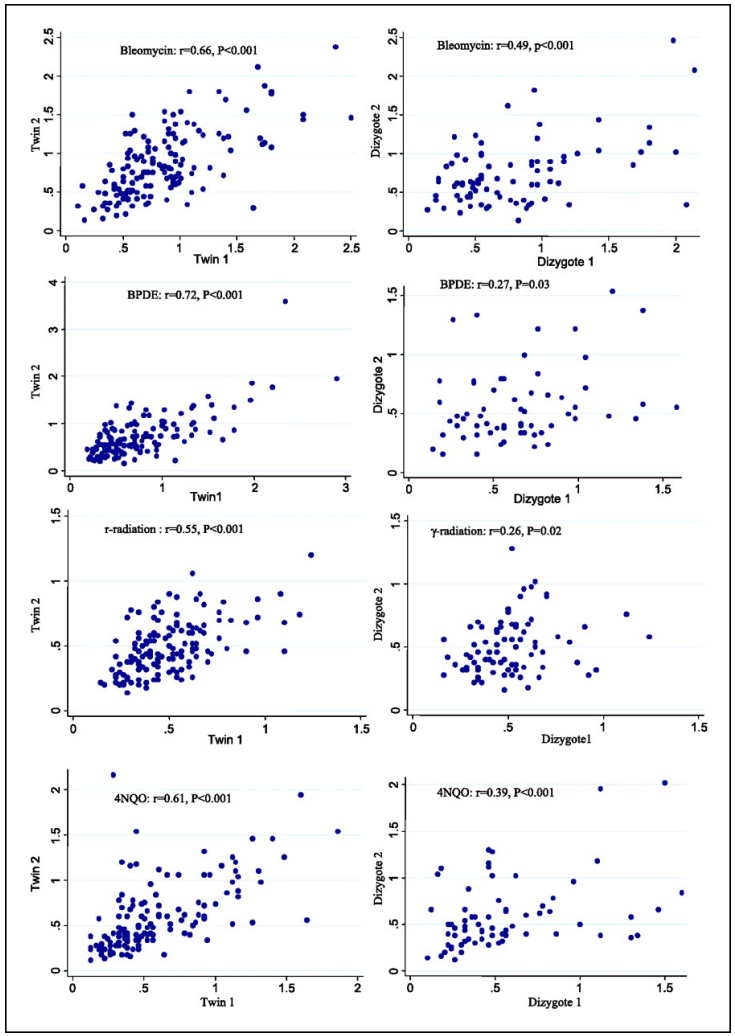
Differences in thyroid cancer rates



is this due to gender, environment or genetic effects?

Data from SEER

Is sensitivity genetically determined ?



Intraclass correlation of mutagen sensitivity (mean breaks per cell) between twin 1 and twin 2 in MZ twins (left) and between person 1 and person 2 in dizygotes (right), as calculated by use of ANOVA.

Heritability for agents such as bleomycin and benzopyrene between 40 and 60%

Wu X et al. Cancer Res 2006;66:5993-5996

DNA repair gene activity and radiation-induced cancer

Table II. Effect Modification of Occupational and Personal Radiographic Dose Response Relationships With Breast Cancer by DNA Repair Polymorphisms, U.S. Radiologic Technologists Study

						Occupational radiation effect modification				Diagnostic radiation effect modification			
Gene	Entrez SNP ID[1]	AA or nt variant ID[2]	Genotype	Cases (%) (*n* = 859)	Controls (%) (*n* = 1083)	*EOR*/Gy[3]	95% Confidence interval		*p*-value[4]	*EOR*/unit breast dose score[3]	95% Confidence interval		*p*-value[4]
BRCA1	rs4986850	D652N	*GG*	698 (85)	916 (85)	1.2	<0	5.1	>0.5	0.1	<0	2.7	0.02
			GA/AA	122 (15)	165 (15)	2.3	<0	13.4		9.4	1.4	25.7	
PRKDC	rs1231202	*IVS15 + 6C > T*	*CC*	753 (91)	971 (90)	1.6	<0	5.6	0.2	2.9	0.3	6.8	0.03
			CT/TT	77 (9)	105 (10)	<0[5]	<0	4.4		<0	<0	1.5	
PRKDC	rs8178097	*IVS34 + 39T > C*	*TT*	738 (89)	964 (90)	1.6	<0	5.5	0.3	2.6	0.2	6.3	0.05
			TC/CC	89 (11)	110 (10)	<0	<0	8.2		<0	<0	2.1	
PRKDC	rs10109984	*IVS31 − 634T > C*	*TT*	305 (37)	375 (35)	1.2	<0	7.2	>0.5	9.1	3.0	19.3	0.002
			CT	383 (46)	522 (49)	2.5	<0	8.2		<0	<0	1.8	
			CC	145 (17)	177 (16)	<0	<0	5.2		<0	<0	4.5	
WRN	rs2230009	V114I	*GG*	720 (87)	960 (89)	0.6	<0	4.0	0.04	1.0	<0	4.1	>0.5
			GA/AA	109 (13)	119 (11)	10.9	1.1	32.9		2.2	<0	13.4	

Bhatti et al Int J Cancer 122:177 2008

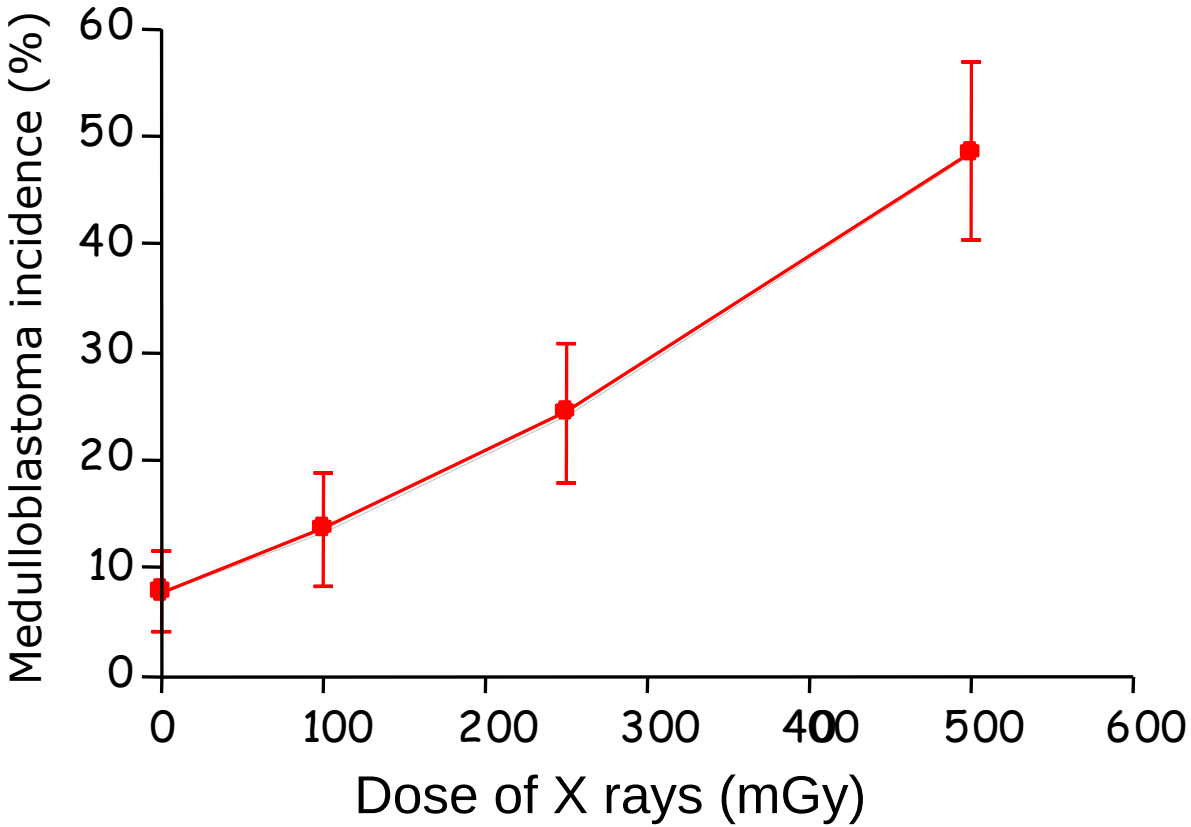
Some individuals are inherently more susceptible to radiation-induced cancers

Familial cancer syndromes (germ-line mutations) predispose to an increased sensitivity to radiation-induced (secondary) cancers:-

- Gorlin (BN) syndrome (Patched1 gene)
- Retinoblastoma (RB1 gene)
- Li-Fraumeni (p53 gene)

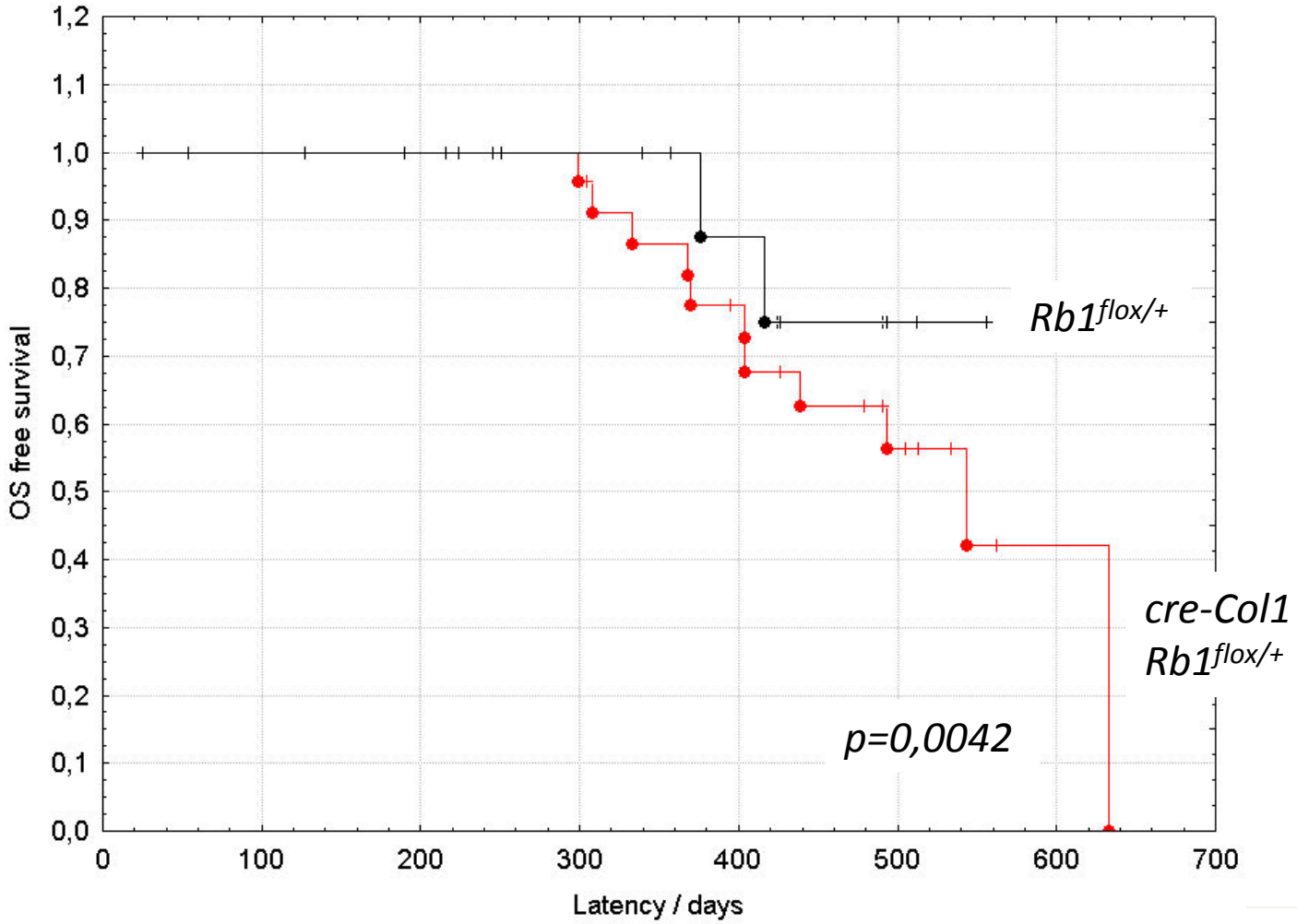
DNA repair genes are also candidates (ATM, BRCA1, DNA-PKcs etc.)

Medullloblastoma formation in Ptc1+/- mice irradiated with 250kV X-rays at postnatal day 1



Constitutive deletion of one copy of Rb1 in the osteoblast lineage (cre-Col1:Rb1$^{flox/+}$) confirms radiation sensitivity

Osteosarcoma induction in Th^{227}-injected mice



Role of environment, diet and lifestyle on sporadic cancer susceptibility

Studies of cancer incidences in migrant populations:-

- Japanese in Hawaii and Brasil
- Vietnamese and Pacific islanders in mainland US.

Overall in subsequent generations the rates of stomach and colon fall to US average.

Incidence of mammary and prostate approach US norm and rate of lung cancer remains unchanged.

Although not complete explanation, diet and lifestyle have some contribution BUT WHAT ABOUT RADIATION?

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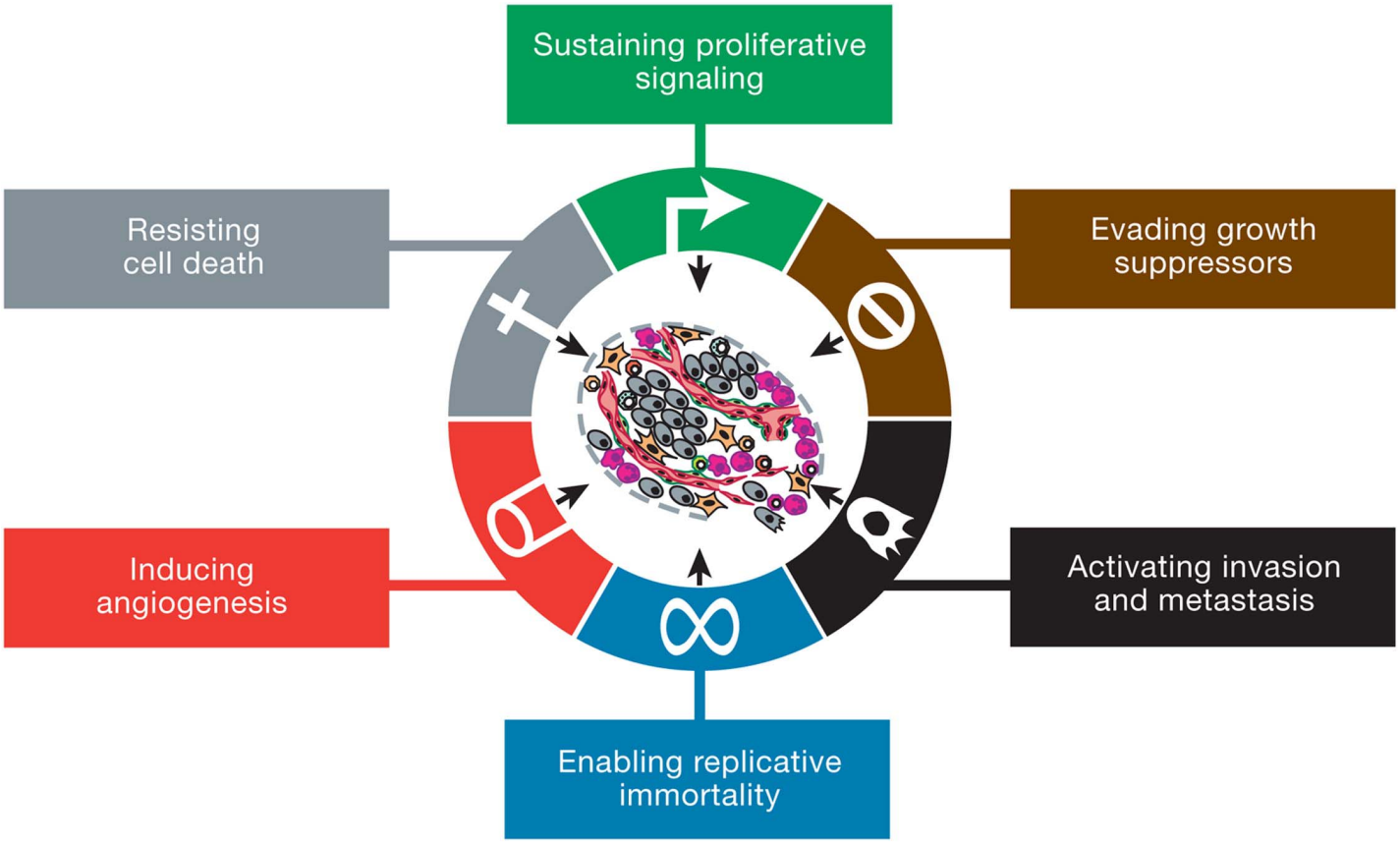
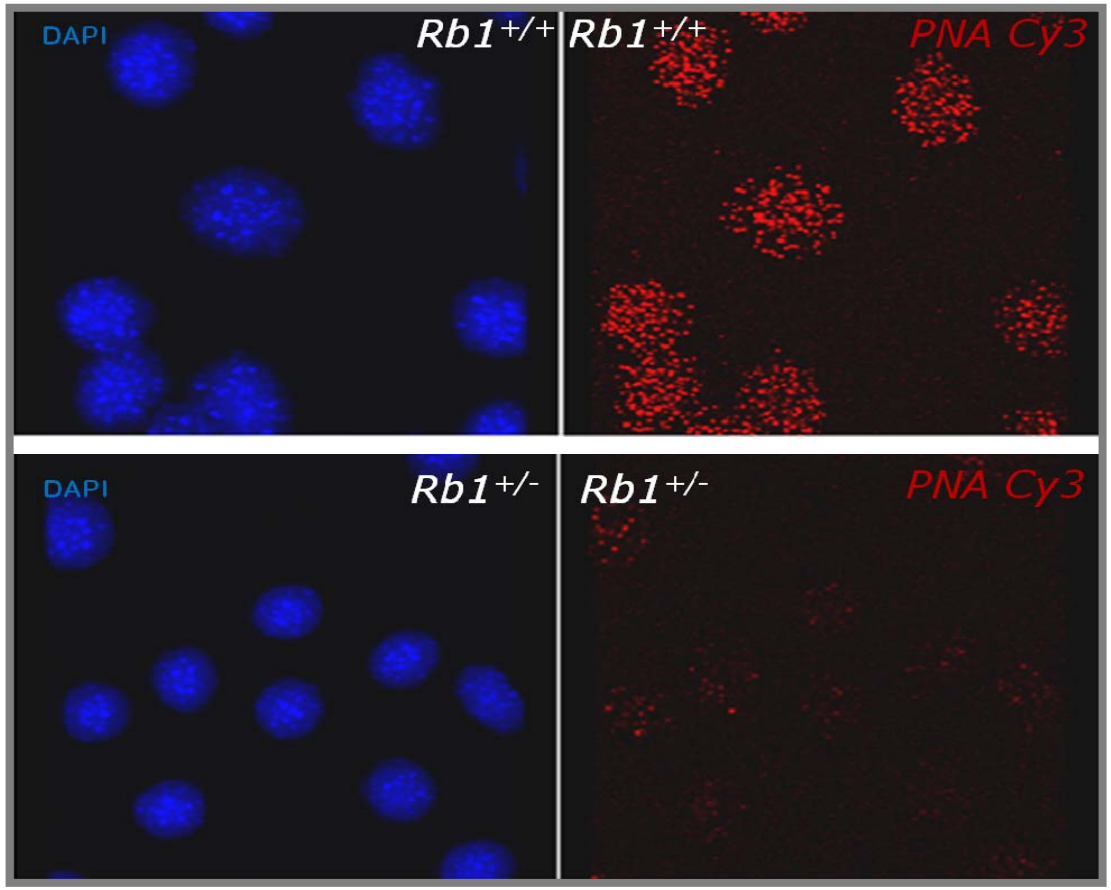


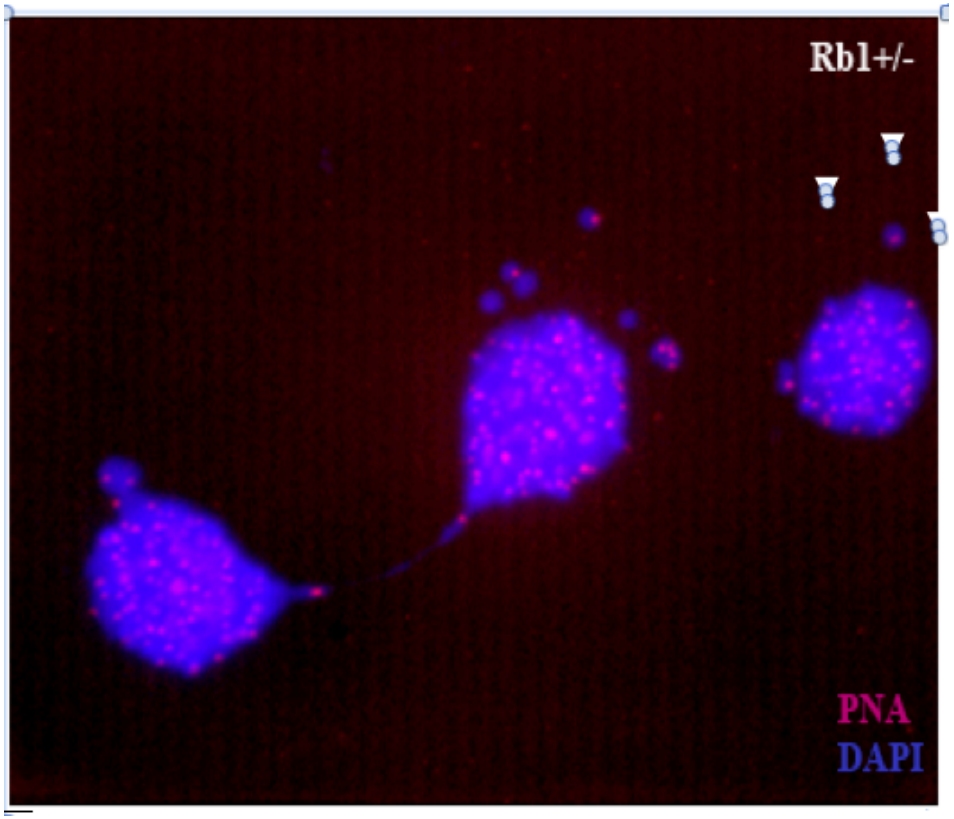
Pathways take precedence over individual gene functions

From: Hanahan D., Weinberg RA. (2011) Cell 144:646-74

Susceptibility may drive genomic instability

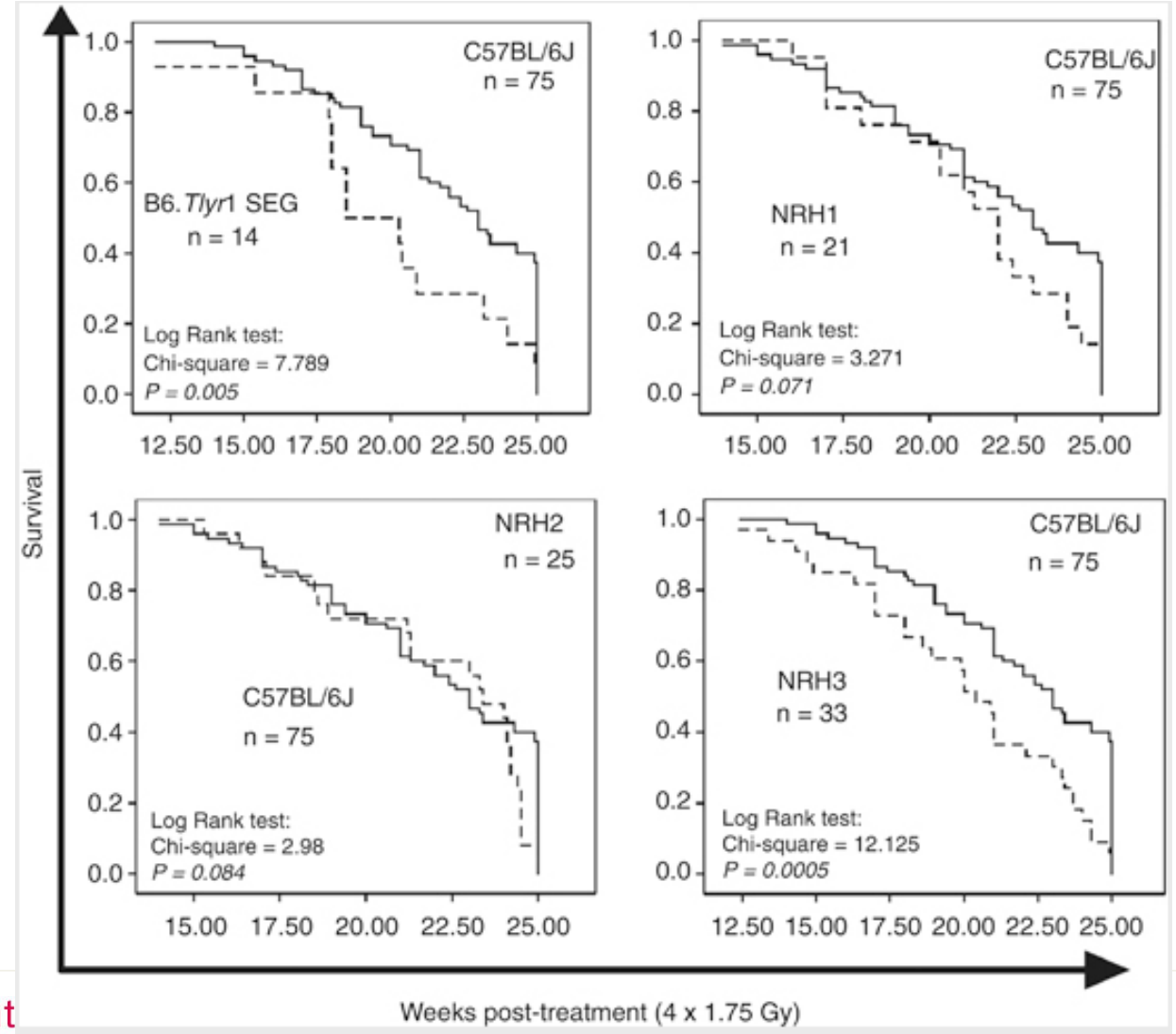
Telomere content assay in untreated osteoblasts *in vitro after repeated passaging*





Telophase bridges contain PNA-telomere signals, suggesting BFB

Susceptibility may modulate cell-cell interaction



Santos et al Oncogene 29 5265 2010

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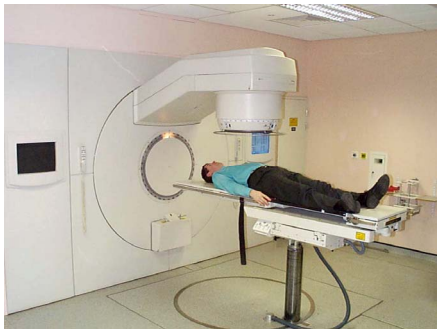
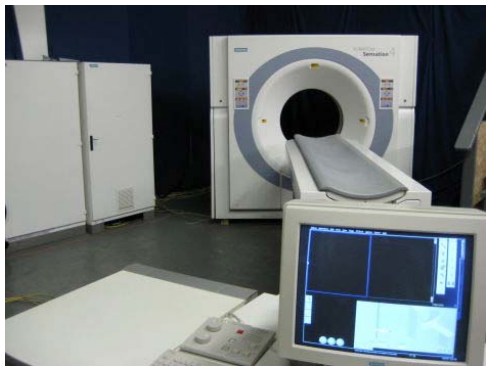


Negative health effects



2mGy

0,1Gy

2Gy

Positive health effects

What experiments are needed ?

Assessment of risk,.....in the dose region from fractions of mGy to a few tens of mGy, would be greatly facilitated by knowledge of the ***shapes of the dose-response relationships*** *for radiation induced cancers in humans.*

*.....**not** available and **not** likely to be obtained by direct observations.*

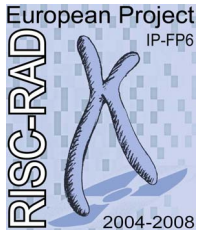
UNSCEAR 1986

Key questions

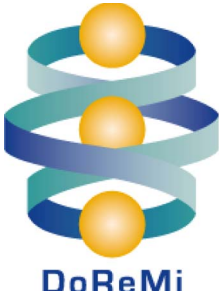
- Are non-cancer effects influenced by individual sensitivity ?
- How many genes with high penetrance ?
- How many genes with low penetrance ?
- Can we include sensitivity in pathways and model them ?
- Relative contributions of gene-environment interaction ?


EURATOM


SEVENTH FRAMEWORK
PROGRAMME


European Project
IP-FP6
RISC-RAD
2004-2008


GENRISK


DoReMi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