Overview on radiation quality dependence on the molecular, chromosome, cellular and tissue level

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TECHNISCHE UNIVERSITÄT DARMSTADT

EURADOS

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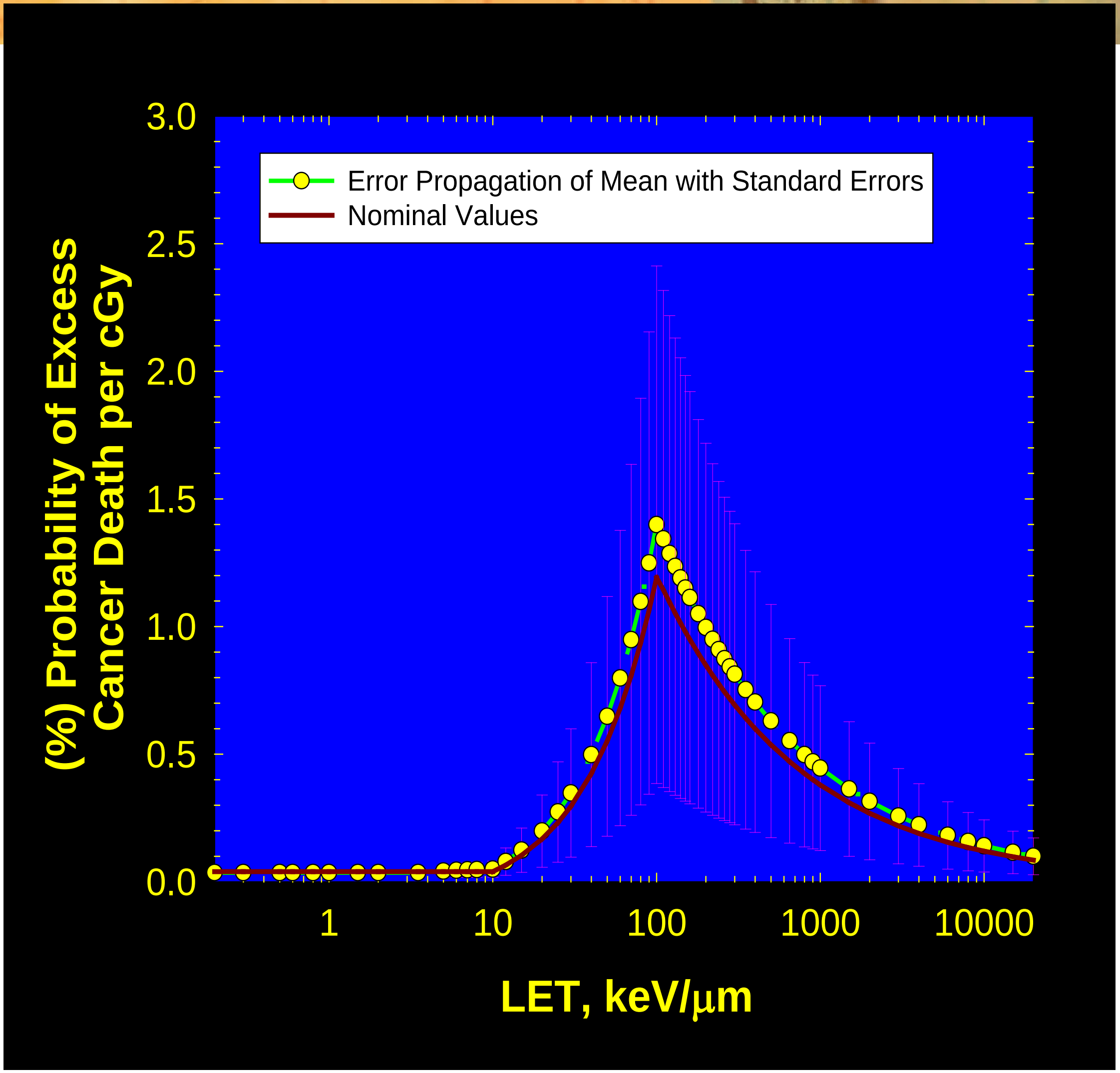
Uncertainties on radiation quality

- Dose Equivalent

  H = Flux x LET x Q(LET)

- Risk = R_0 x H
- NCRP recommended approach of propagation of uncertainties in individual risk factors
  - **epidemiology, dose-rate, quality factor, and physical uncertainties**
- Uncertainty on quality factors are enhanced by the lack of epidemiological data



NCRP report 153, 2006

A little help from epidemiology?

- Very limited data from astronauts and radiotherapy patients treated with protons or heavy ions
- Some cohorts available for alpha particles from internally deposited radionuclides
- Lung cancer and ^{222}Rn (underground miners and houses)
- Liver cancer and leukemia in patients given injections of Thorotrast for cerbral arteriography (1930-1940)
- Bone cancers in patients and workers exposed to radium by injection or ingestion
- Lung cancer in Mayak workers exposed to inhalation of ^{239}Pu

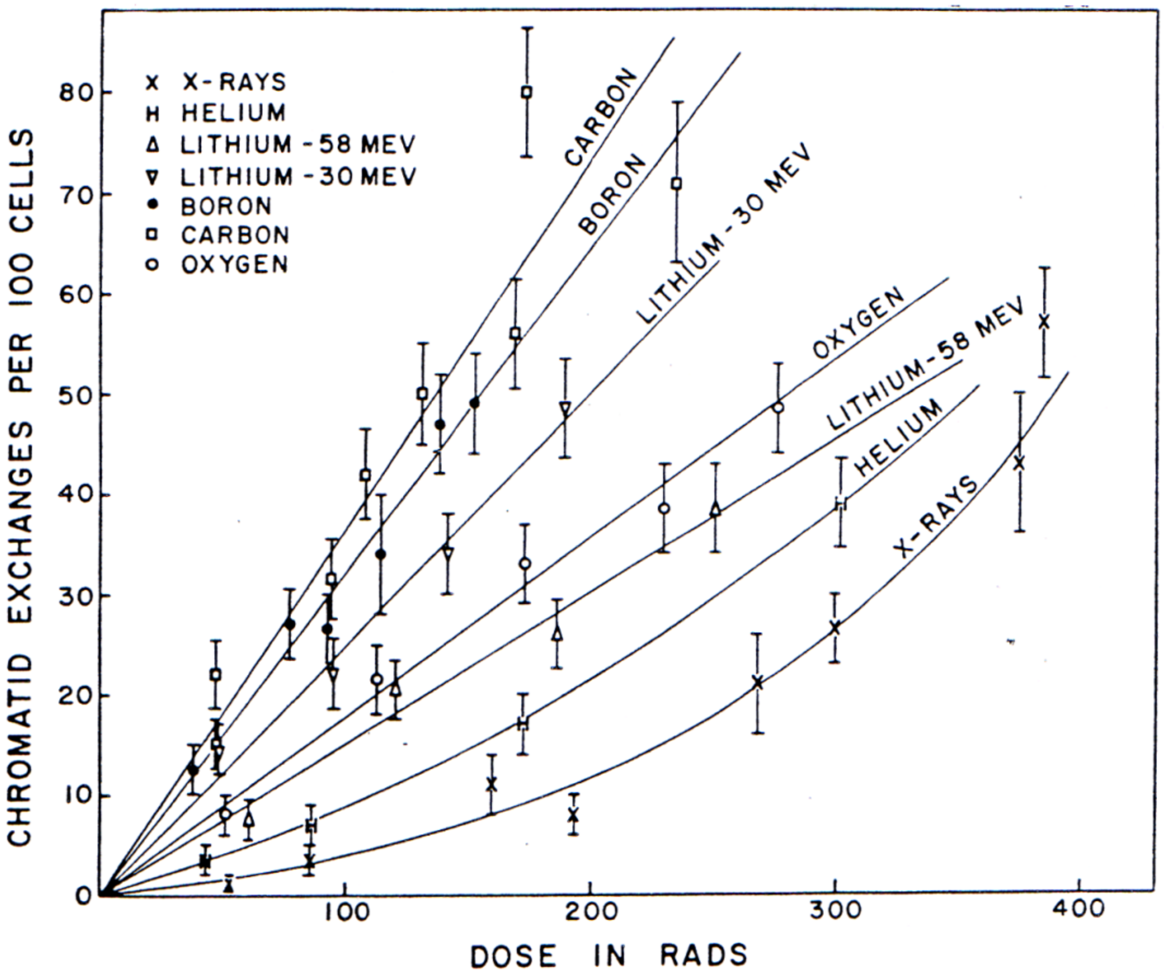
Cancer	Nuclide	Risk (Sv^{-1})[a]	Eternal radiation risk (Sv^{-1})[b]
Lung	^{222}Rn	2.5×10^{-3}	6.8×10^{-3}
	^{239}Pu[c]	10×10^{-3}	
Liver	^{232}Th[d]	$2–4 \times 10^{-3}$	3×10^{-3}
Leukaemia	^{232}Th[d]	$7–9 \times 10^{-4}$	$5–8 \times 10^{-3}$
Bone	^{224}Ra	6×10^{-5}[e] (5×10^{-4})[f]	$1–4 \times 10^{-4}$

[a] Assuming an RBE of 20 for alpha-particles.
[b] Based on data for the A-bomb survivors.
[c] Preliminary dosimetry.
[d] Thorotrast—colloidal ^{232}Th oxide preparation.
[e] Based on dose to 10 μm depth target cell layer on endosteal (inner) bone surfaces.
[f] ICRP estimate based on uniform bone dose.

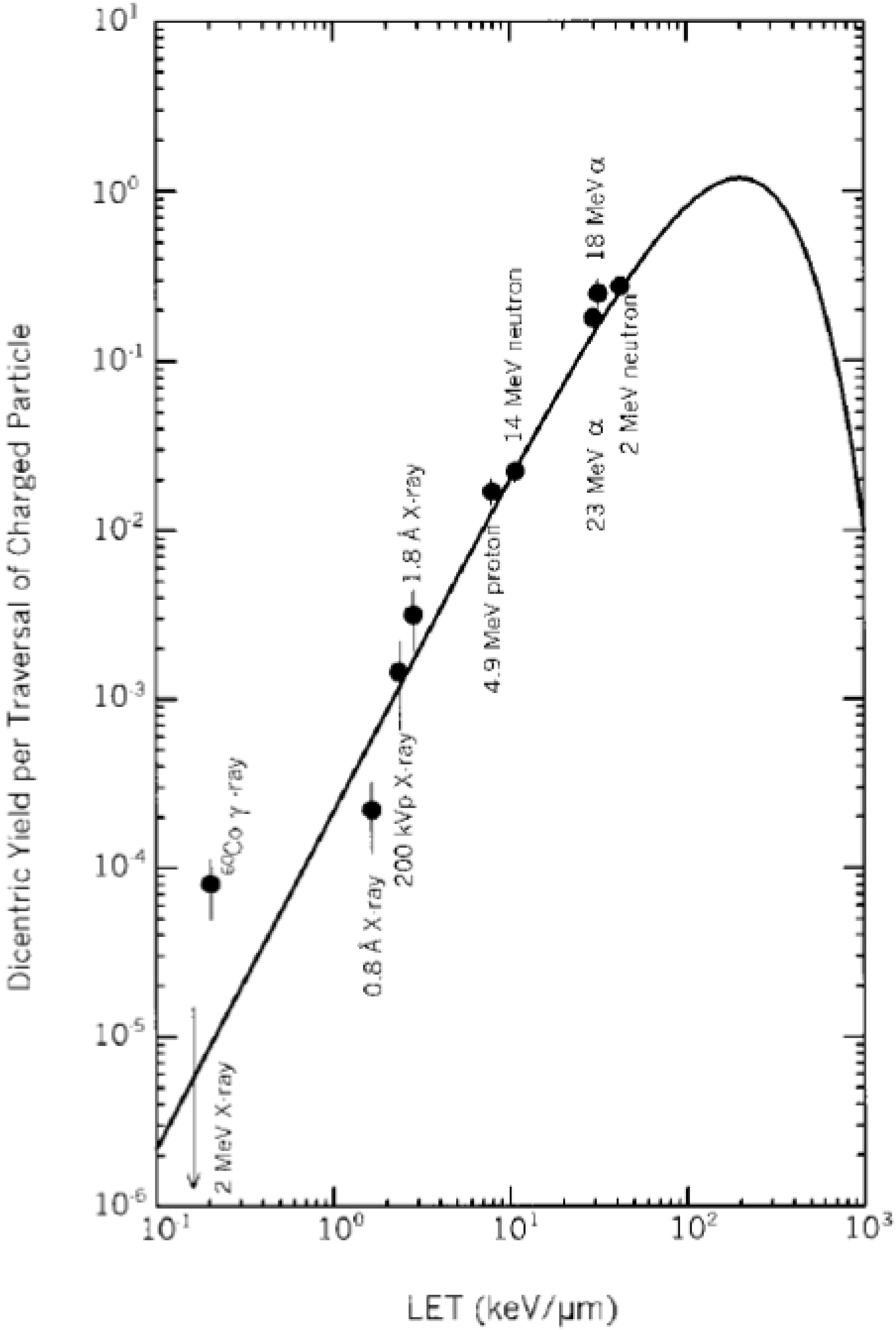
Limited data affected by high uncertainties – in general, the ICRP-103 w_R=20 for α-particles seems to be overestimated

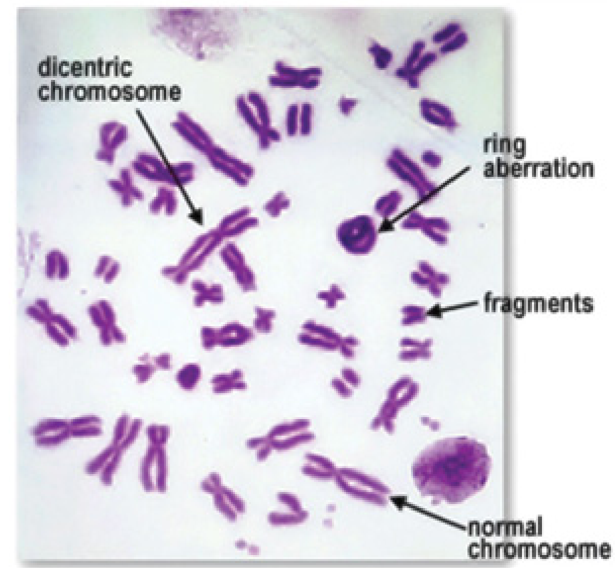
Harrison and Muirhead, *Int. J. Radiat. Biol.* 2003; and UNSCEAR

w_R often based on chromosome aberration data



Skarsgard et al. *Radiat Res Suppl.* 7 (1967).

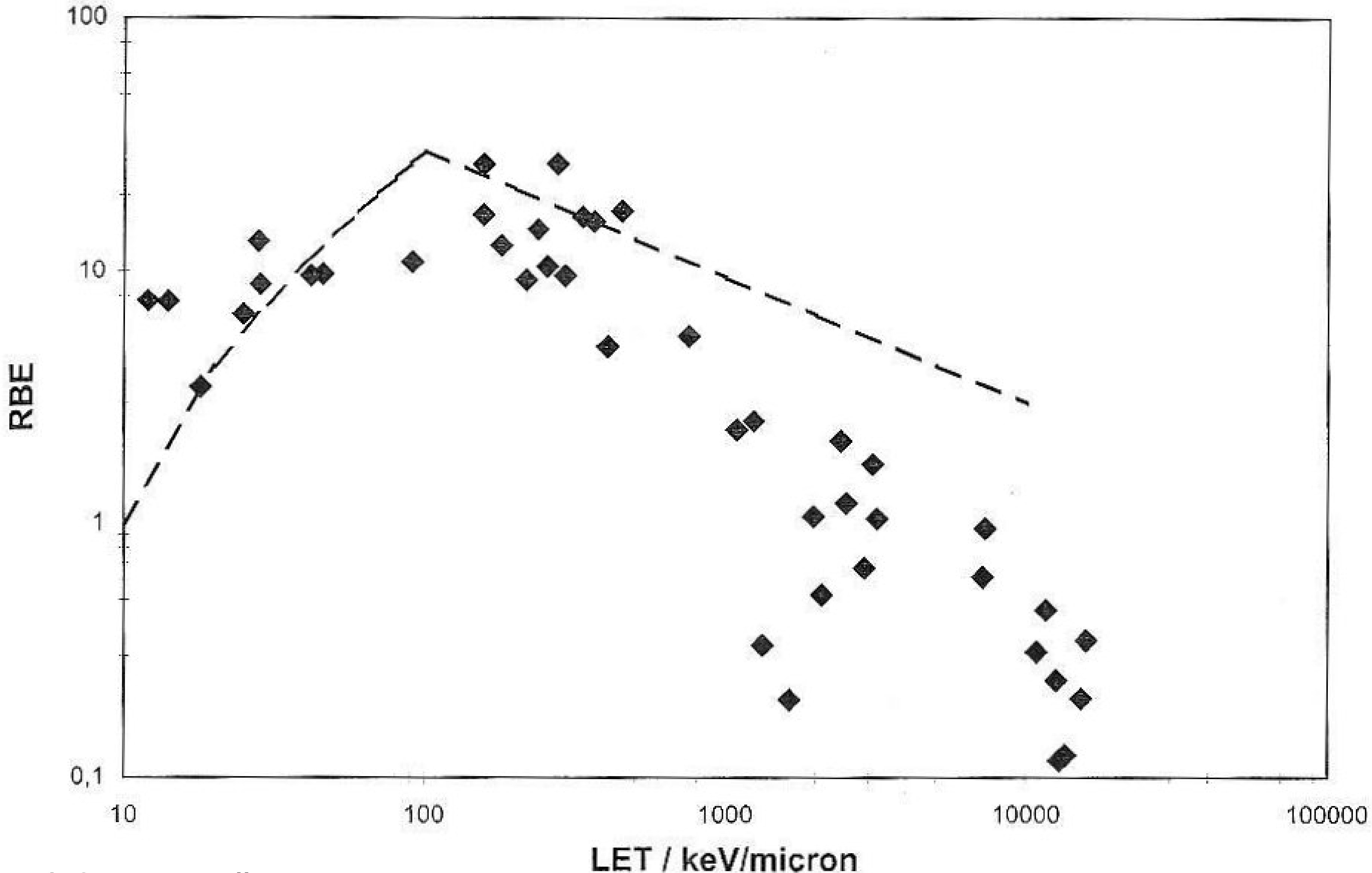




The relationship between LET and the dicentric yield per traversal of the cell nucleus by a charged particle at the low dose limit. For X- and γ -ray, the charged particle is a recoil- or photo-electron induced by the photon.

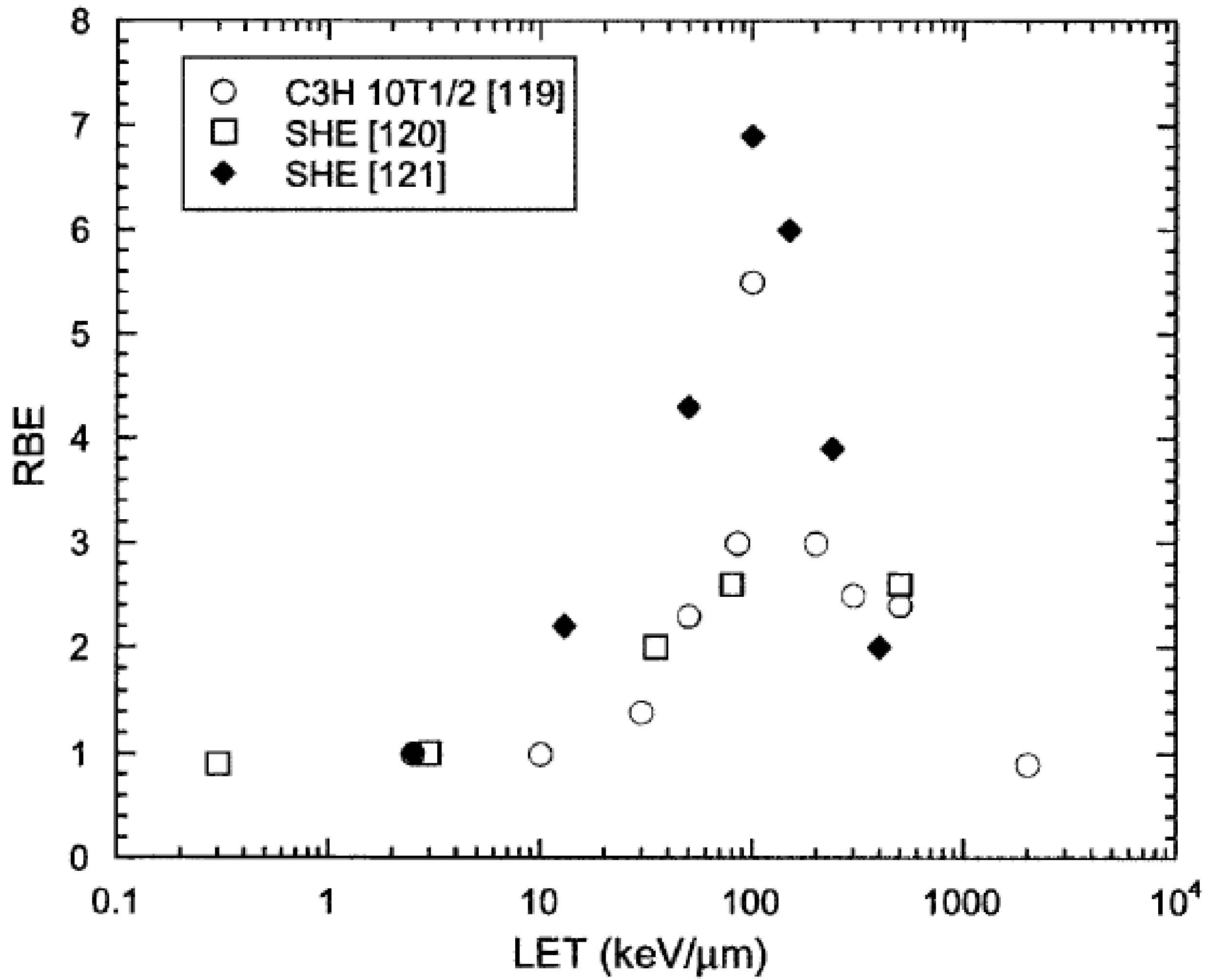
Takatsuji *et al., J. Radiat. Res*. 1999

...or *hprt* mutations in hamster cells..



Kiefer, *J. Radiat. Res*. 2002

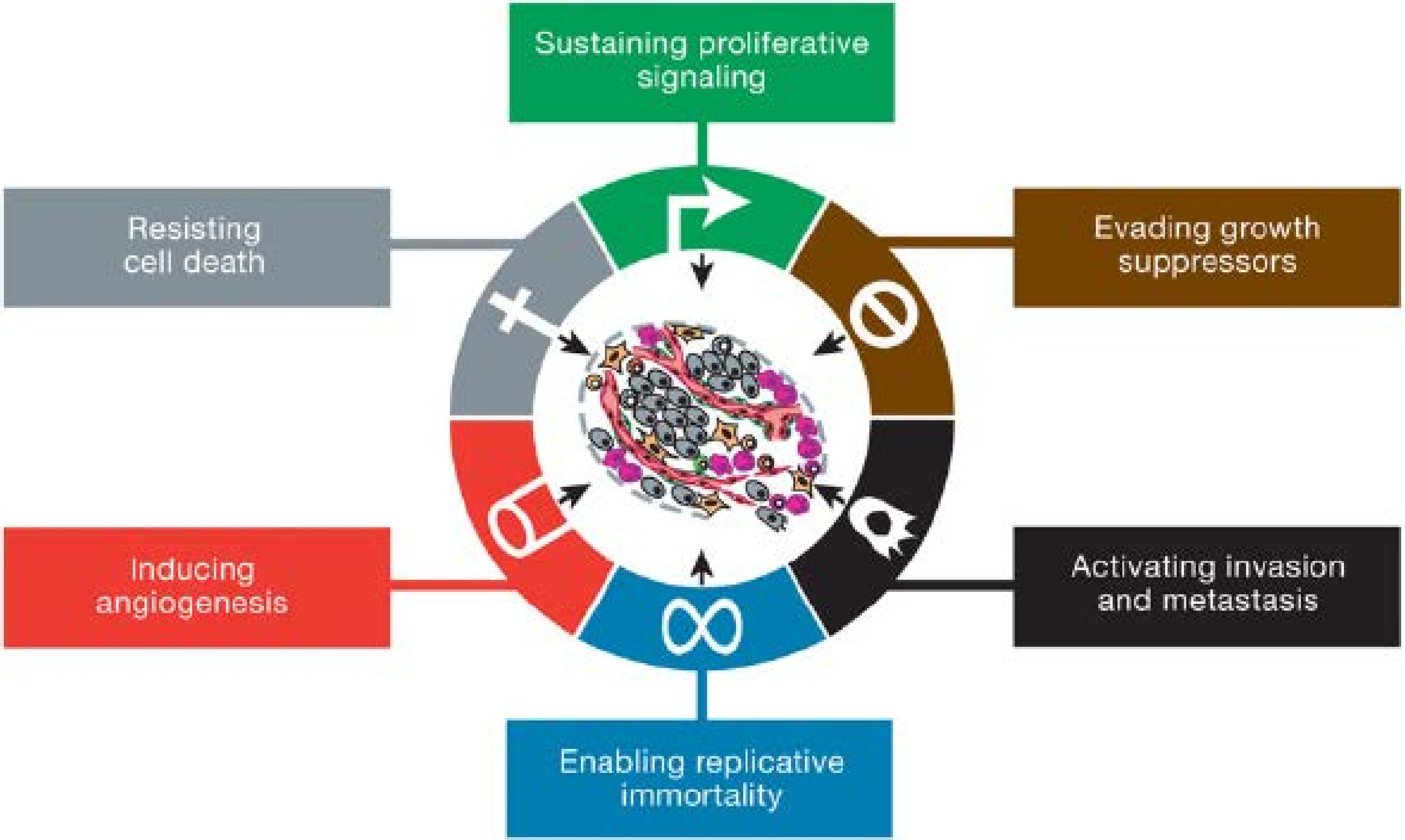
..or in vitro neoplastic transformation of rodent cells



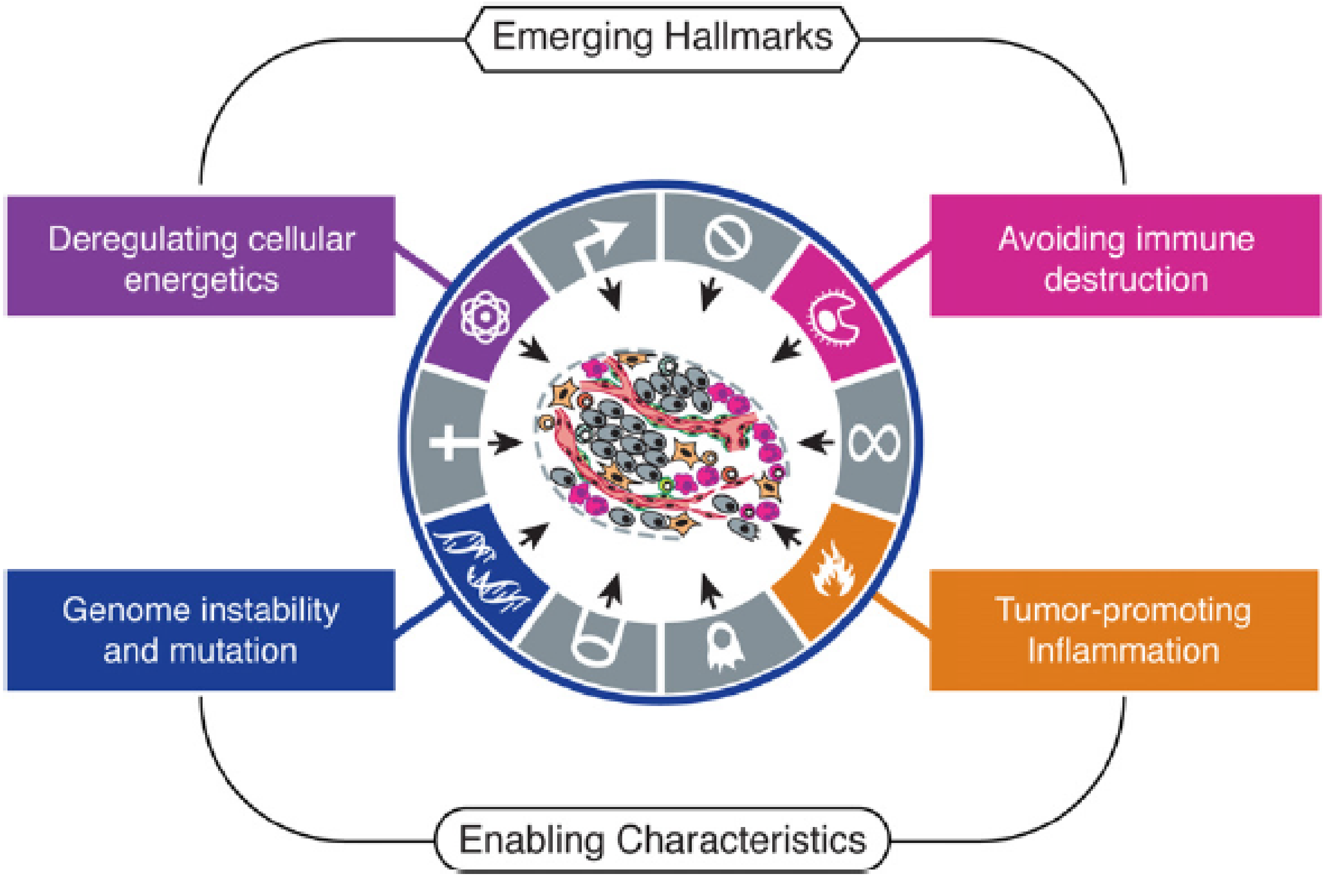
Experiments from LBNL and HIMAC

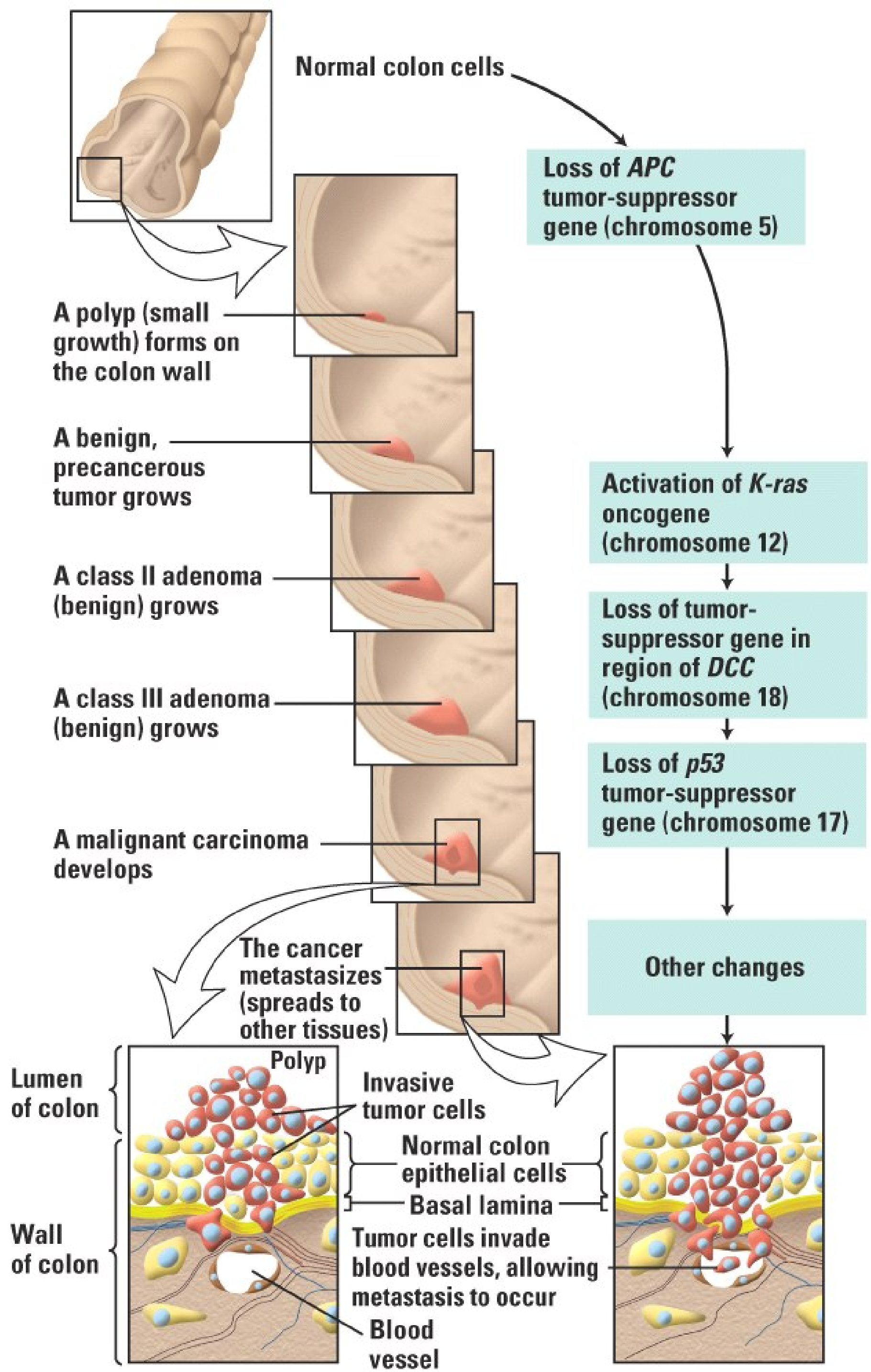
but how relevant are in vitro models?

The hallmarks of cancer
(Hanahan & Weinberg, *Cell*, 2000)



The hallmarks of cancer (Hanahan & Weinberg, *Cell*, 2011)





Multistep carcinogenesis

Tumor initiation and progression results from stepwise accumulation of DNA mutations or epigenetic factors (inflammation).

Several characters of malignant neoplasm are the result of multiple genetic defects.

Initial steps reversible(e.g. dysplasia), but final Malignant transformation is irreversible.

(Fearon & Vogelstein, *Cell* 1990)

Animal studies

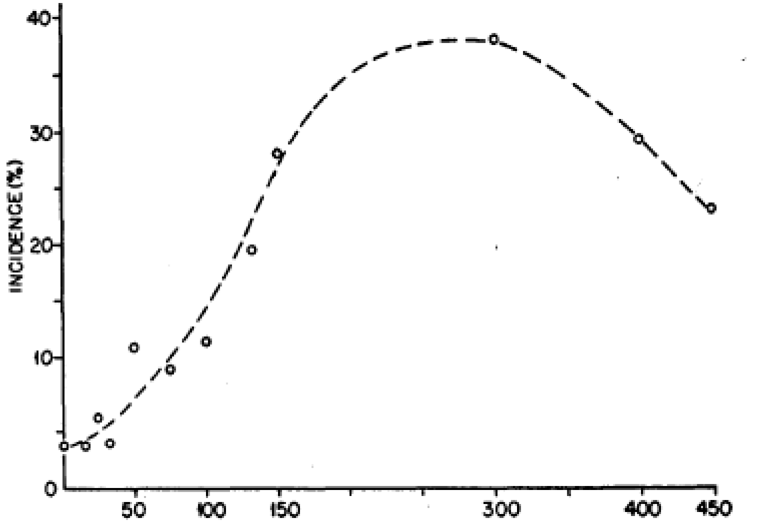
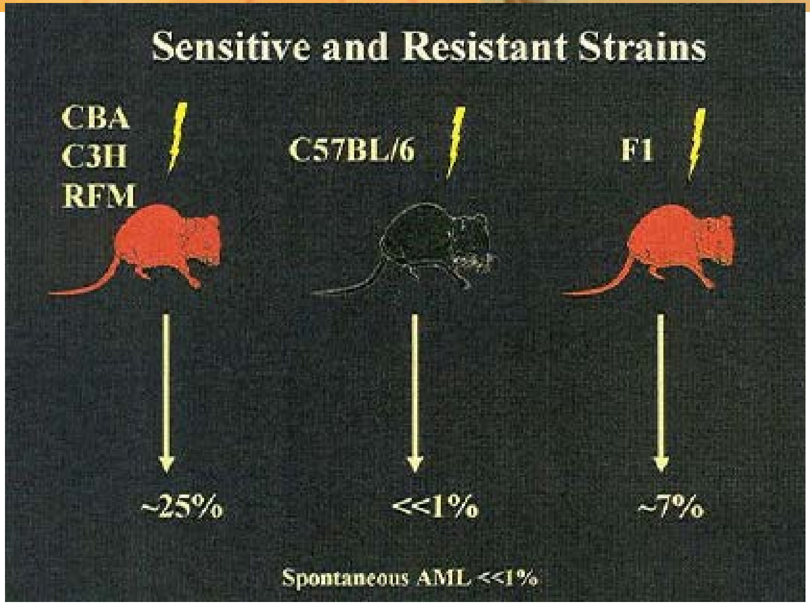
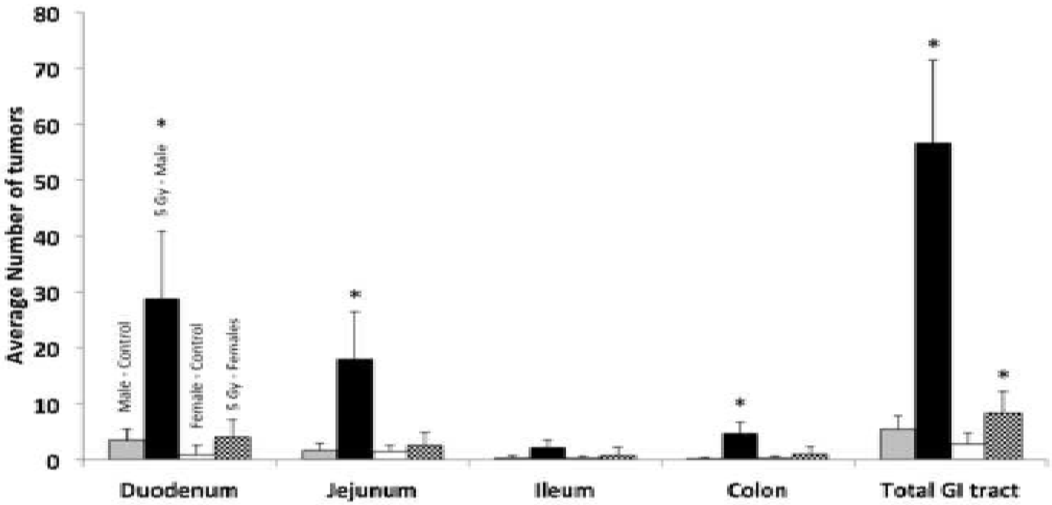


Figure 19–3. Incidence of myeloid leukemia in RF male mice exposed to whole-body x-irradiation. (From Upton AC: Cancer Res 21:717–729, 1961)





Intestinal tumors in 6-8 weeks old female or male C57BL/6J-Apc1638N/+ mice exposed to 5 Gy γ-rays

Courtesy of Al Fornace Jr.

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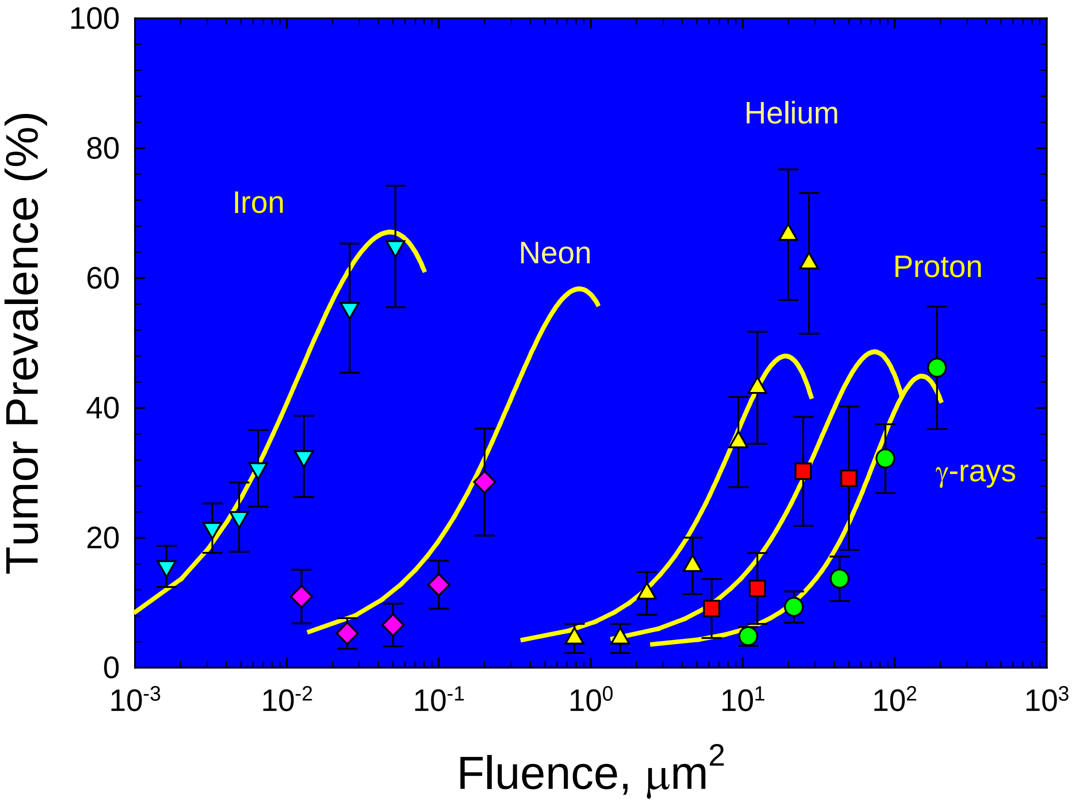
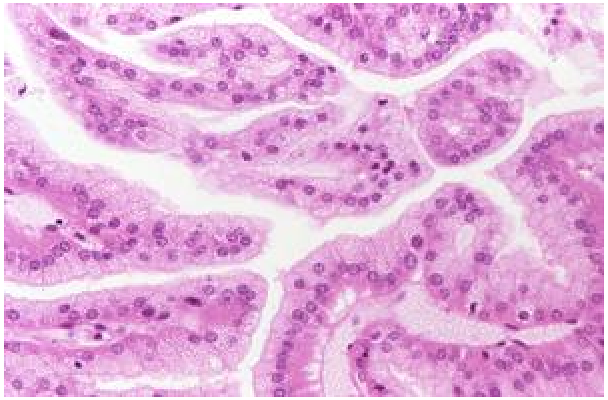
Harderian gland tumors in B6CF1 mice

Alpen *et al. Radiat. Res*. (1993)



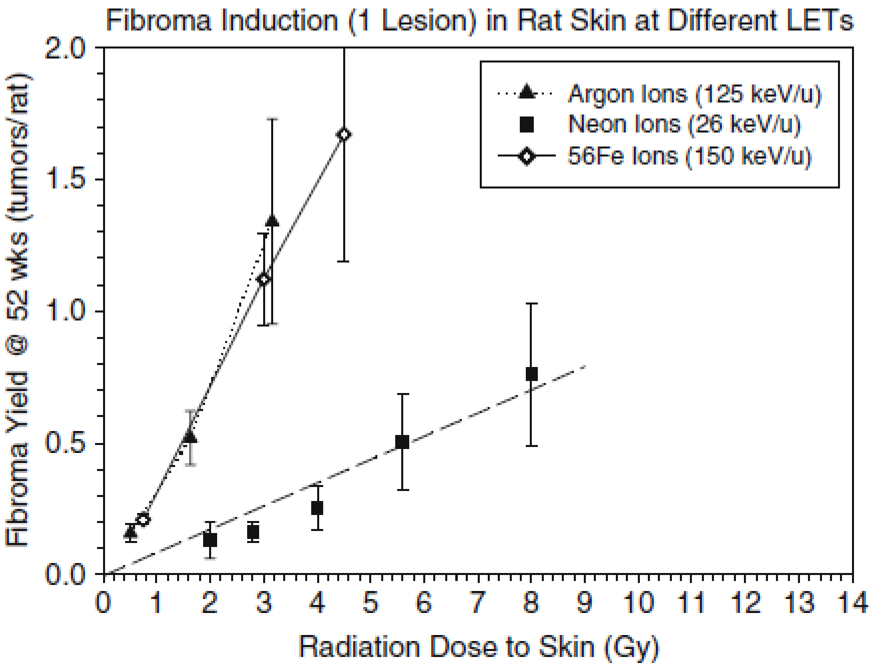


Harderian gland adenoma

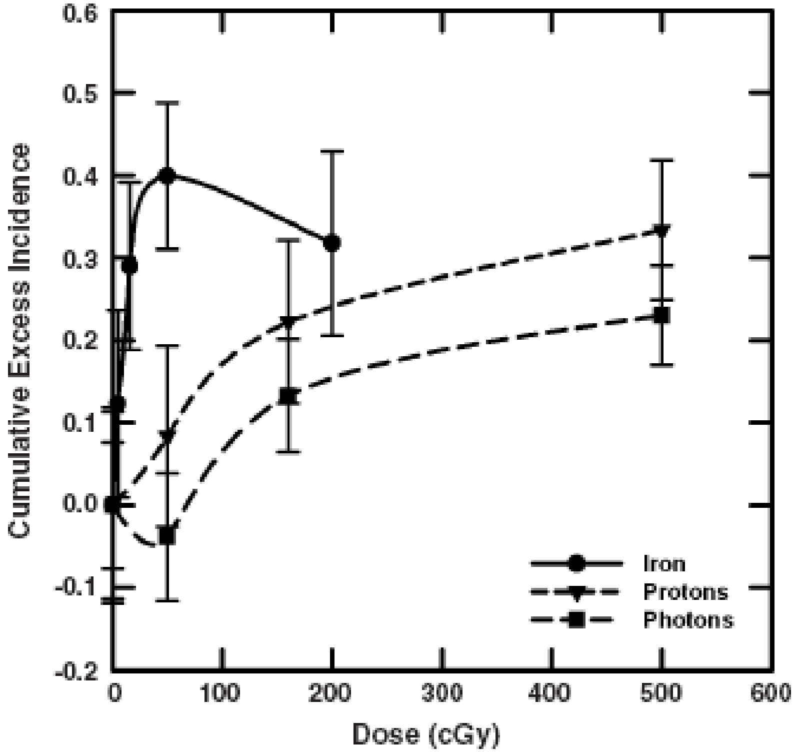
Experiments at LBNL

Tumorigenesis promotion by hormones from isogeneis grafts of the pituitaries

Solid cancers in rats



Skin cancers, Burns et al. 2007



Mammary cancer, Dicello et al., 2004

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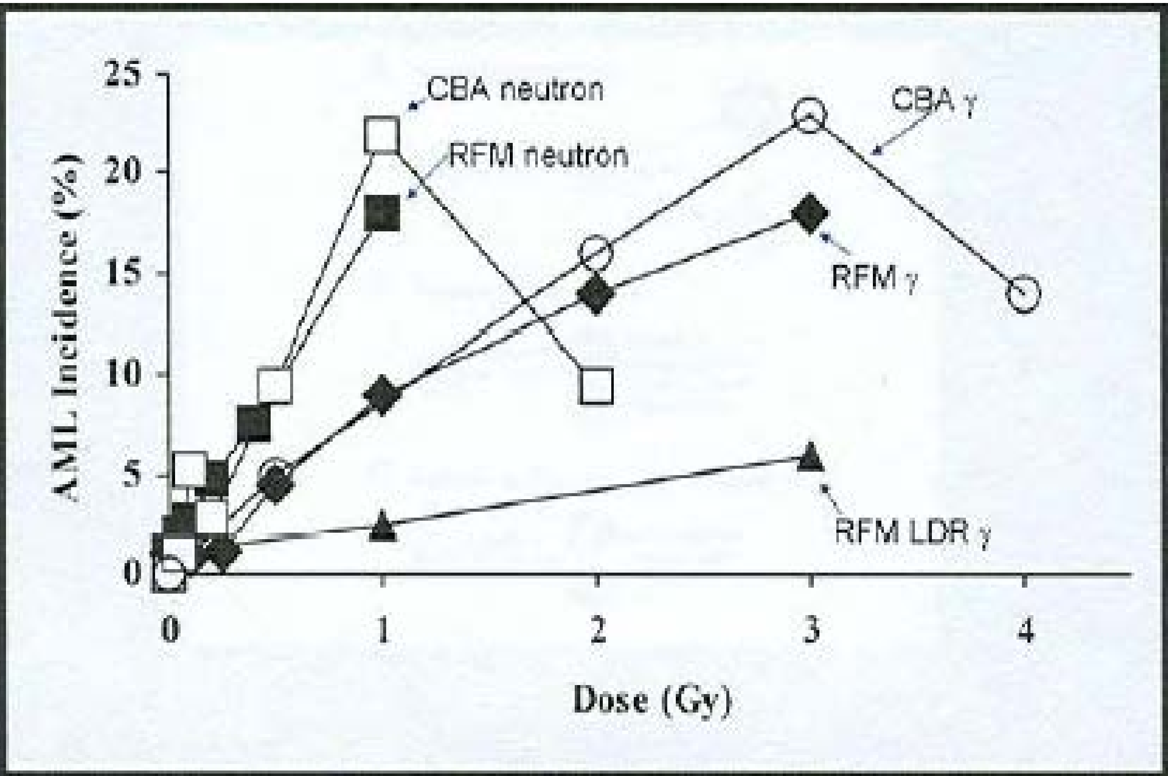
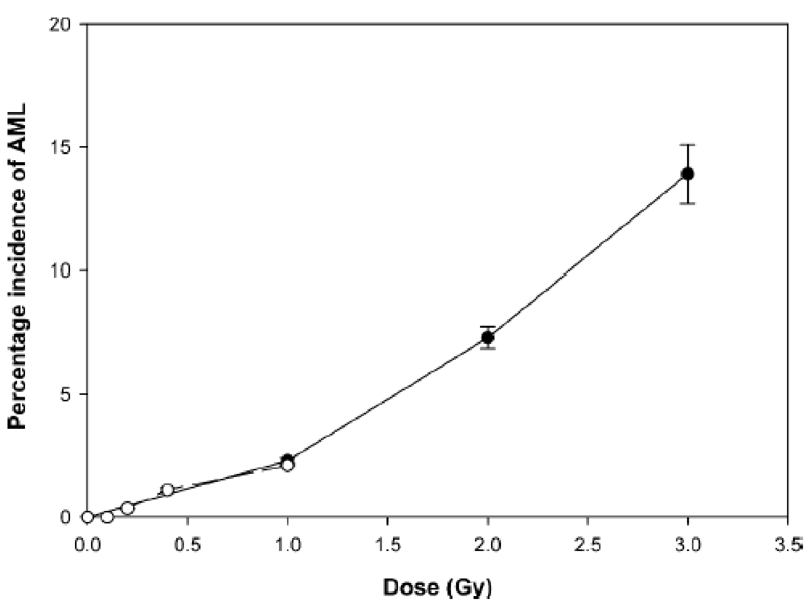
Neutron-induced acute myeloid luekemia in mice

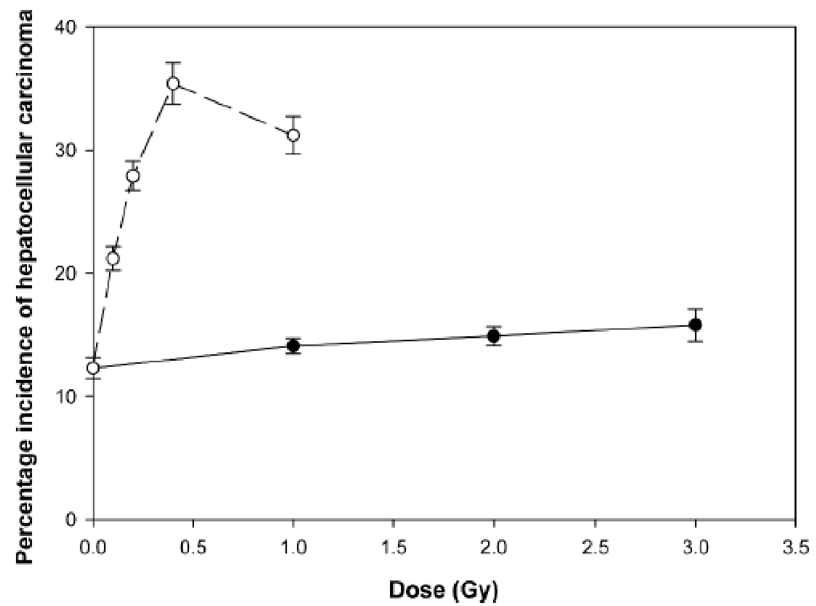


Ullrich RL, Preston RJ. 1987. *Radiat. Res.* 109:165
Mole RH, Papworth DG, Corp MJ. 1983. *Br. J. Cancer* 47:285
Upton AC, Randolph ML, Conklin JW, Melville GS, Conte FP, Sproul JA. 1970. *Radiat. Res.* 41:467

Dose rates: 4.2 rad/min to 552 rad/min

Radiation leukemogenesis in CBA mice



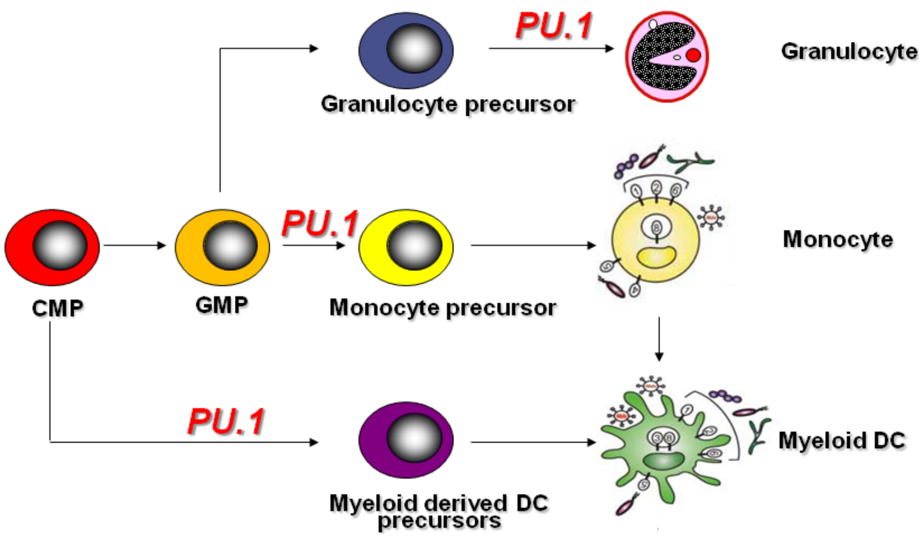


Incidence of Acute Myeloid Leukemia and Hepatocellular Carcinoma in Mice Irradiated with 1 GeV/nucleon ^{56}Fe Ions

Michael M. Weil,[a,1] Joel S. Bedford,[a] Helle Bielefeldt-Ohmann,[b] F. Andrew Ray,[b] Paula C. Genik,[a] Eugene J. Ehrhart,[b] Christina M. Fallgren,[a] Fitsum Hailu,[a] Christine L. R. Battaglia,[a] Brad Charles,[b] Matthew A. Callan[a] and Robert L. Ullrich[a]

AML in mouse

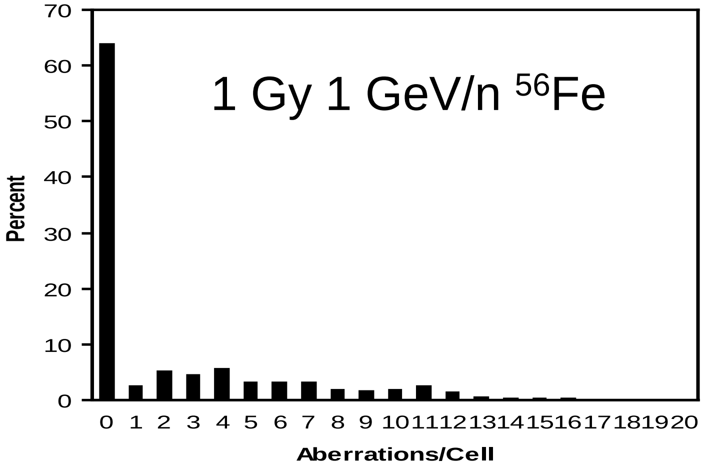
- More than 90% of mouse AML present LOH in chromosome 2 (Silver *et al., Genes Chromosomes Cancer* 1999)
- The deletion involves the PU.1 transcription factor (Suraweera *et al., Oncogene* 2005)
- In more than 70% of radiation-induced murine AML the LOH is hemizygous loss accompanied by point mutations in the region encoding the ETS DNA-binding domain, leading to base substitutions at the R235 residue of the protein.
- PU.1 mutations in human AML is rare, but deletions in specific chromosomes are often found
- *Flt3*-ITD mutations, common in human AML, can be found also in some murine AML, and is mutually exclusive with PU.1 loss (Finnon *et al., Leukemia* 2012)

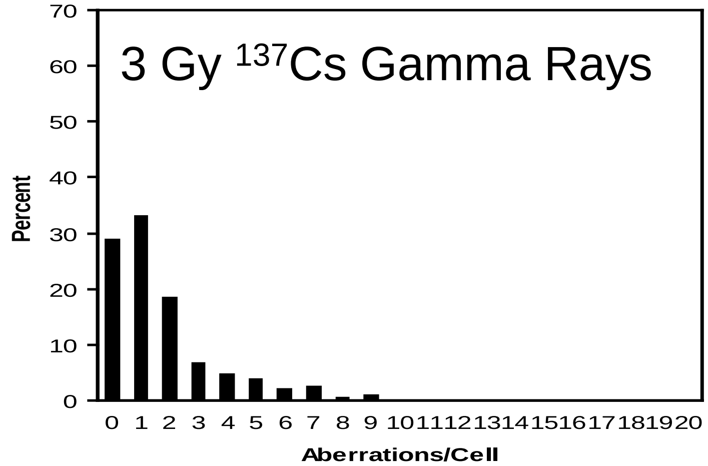


CMP=common myeolid progenitor
GMP=granulocyte/monocyte precursor
DC=dendritic cell

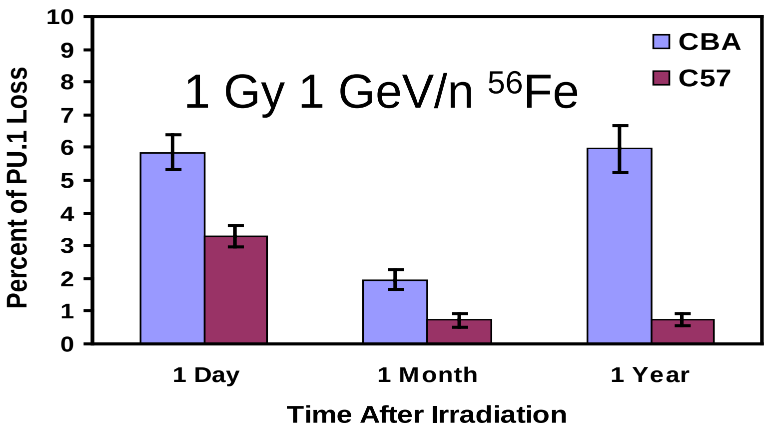
Chromosomal Aberrations in Mouse Bone Marrow Cells

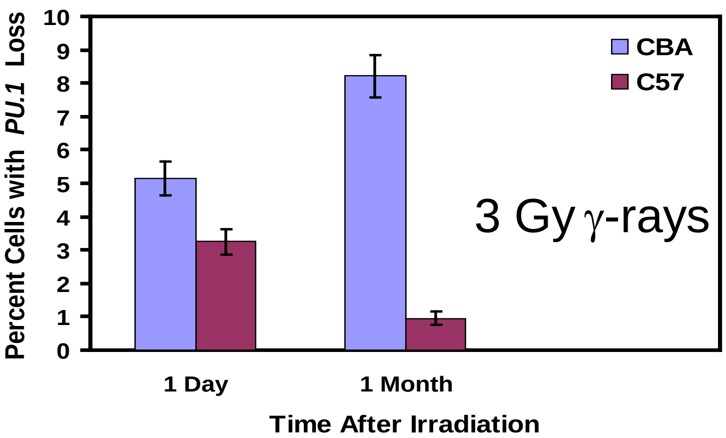
Total aberrations, 1 day post-irradiation





Deletions in chromosome 2 (including transcription factor PU.1)





Colorado State University

Radiation Leukemogenesis NSCOR

NASA

Courtesy of M. Weil

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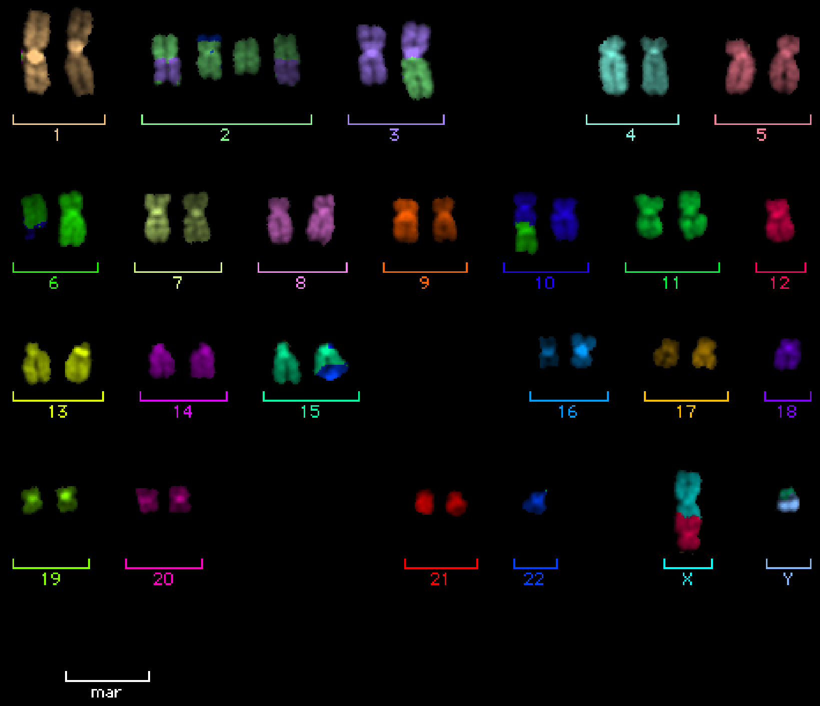
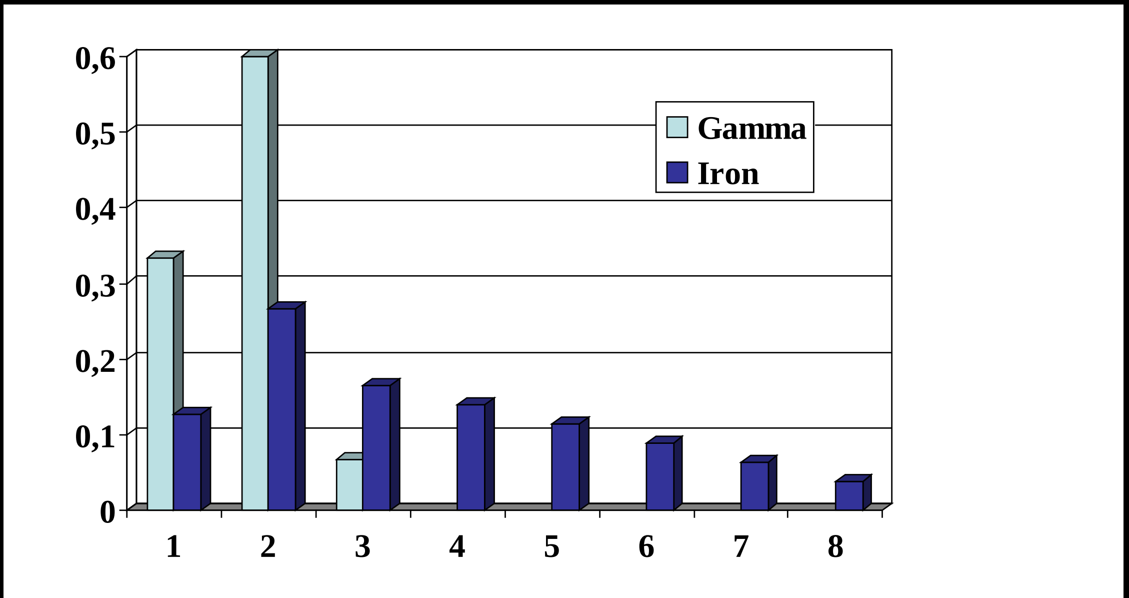
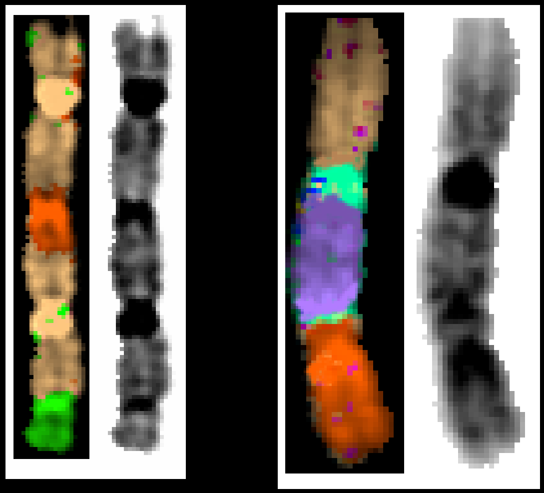
Chromosomal aberrations induced by 1 GeV/n Fe-ions (147 keV/μm) in human blood lymphocytes visualized at the 1° post-irradiation cycle

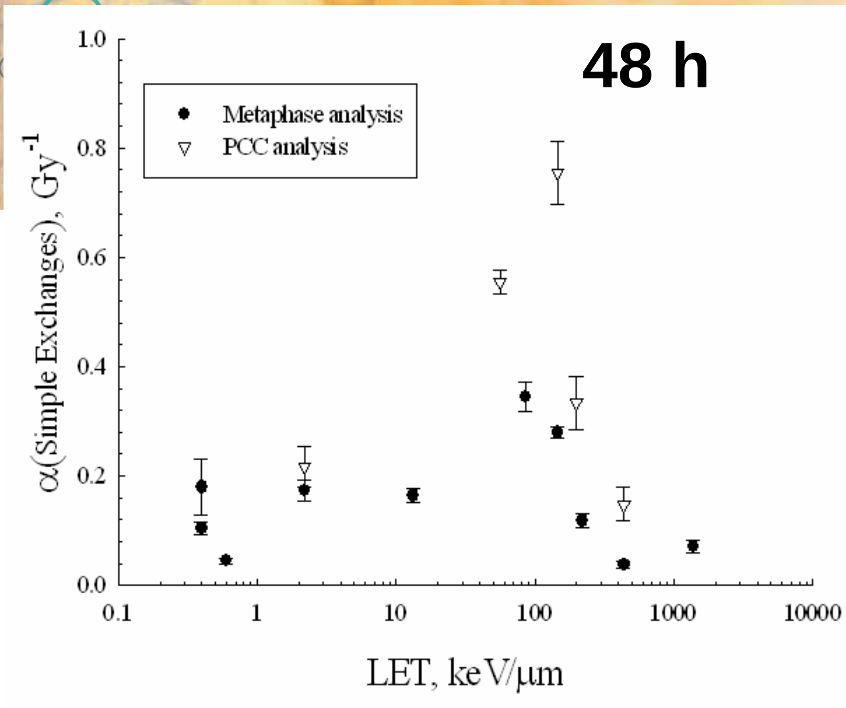


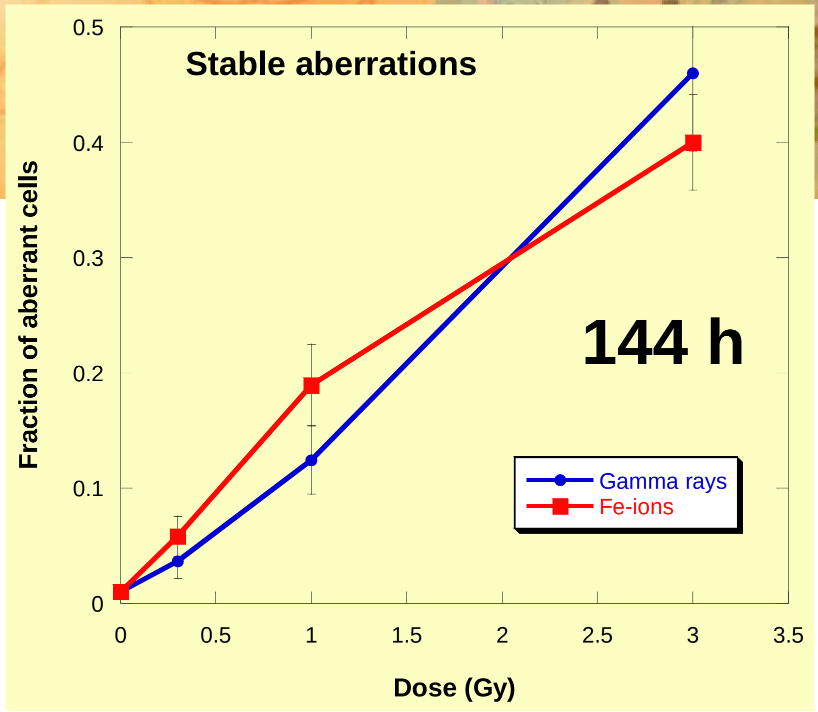
Frequency distribution of aberrant chromosomes/cell (Dose = 0.3 Gy)

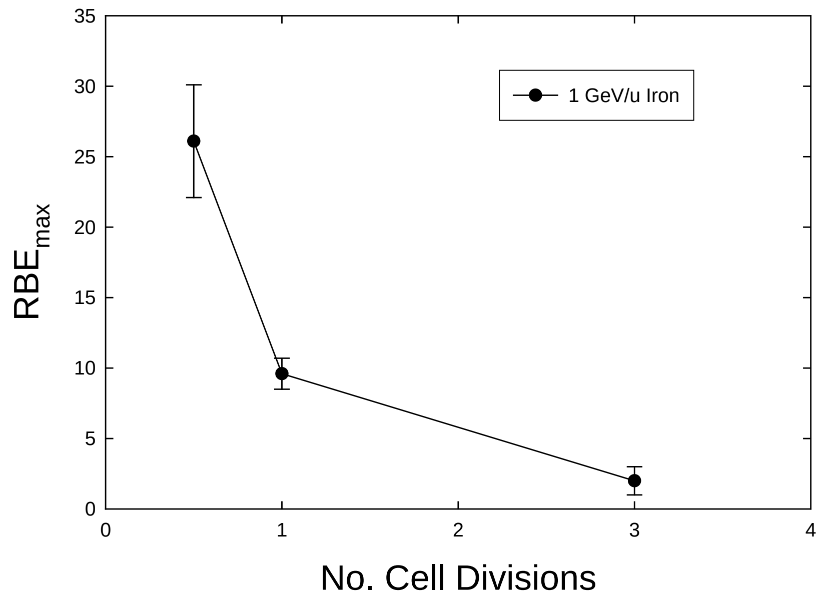




Durante *et al.*, *Radiat. Res.* 2002

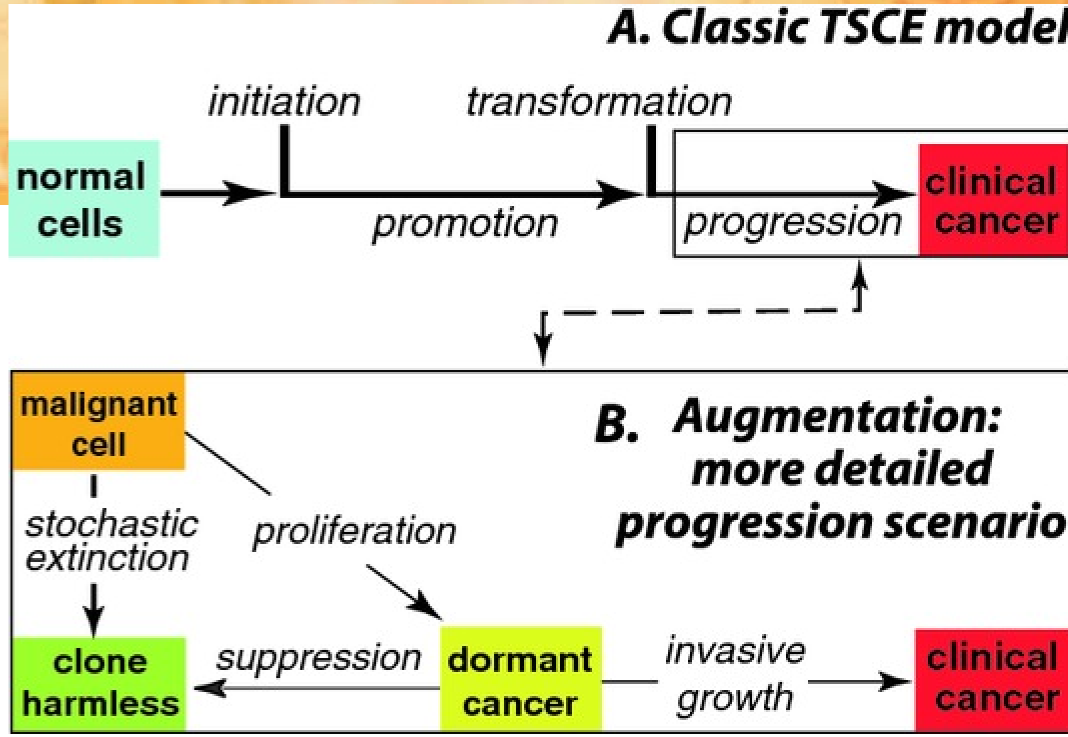






Most heavy-ion induced rearrangements are lethal

Durante & Cucinotta, *Nature Rev. Cancer* 2008



Fakir, Hofmann & Sachs, *Radiat. Environ. Biophys*. 2010

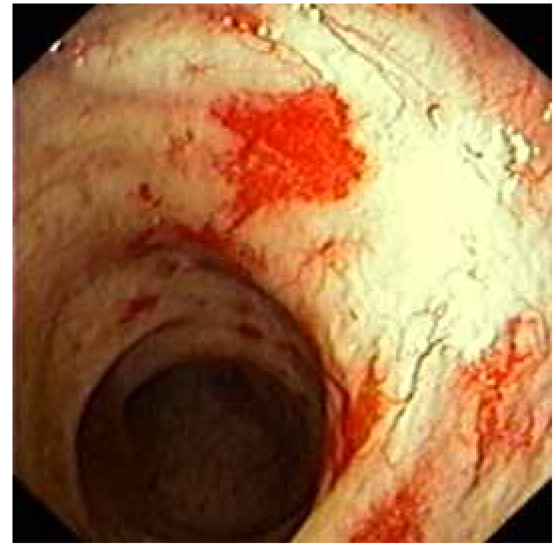
Hypothesis

When radiation is an *initiating* agent (e.g. in liquid cancers) – chromosome aberrations are important – dose-reponse curve sublinear – RBE of heavy ions is low

When radiation is a *promoting* agent (e.g. hepatocellular carcinoma or solid cancers in general?) – inflamamtion is important – dose-response curve can be supralinear with plateau – RBE of heavy ions is high

Radiation-induced inflammation

Detection of elevated IL-6 and IL-8 is associated to lung cancer 2 years or more after the test (Pine et al., *J. Natl. Cancer Inst*. 2011)



Proctitis in the rectum caused by radiotherapy of the prostate

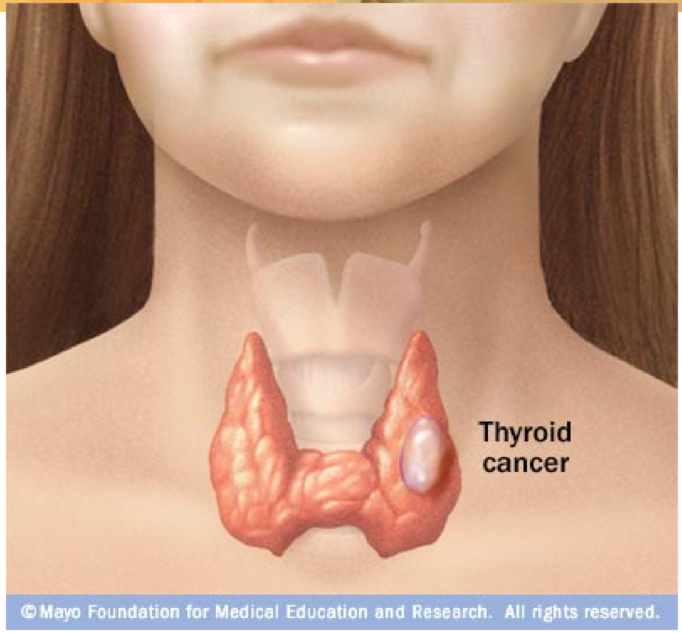
Thyroid cancer and Chernobyl

The main health effect of the 1986 Chernobyl nuclear power plant accident was a sharp increase in papillary thyroid carcinoma (about 6,000 childhood thyroid cancers)

Approximately 87% of the Chernobyl PTC carry rearrangements in the RET thyrosine kinase (Fusco *et al.*, *Nature* 1987)

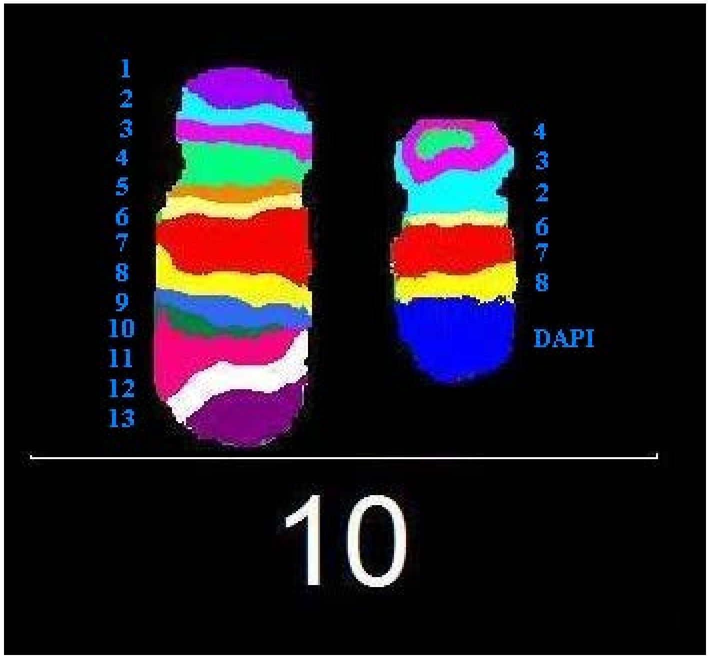
RET/PTC1 is a paracentric inversion that juxtaposes the RET tyrosine kinase domain to the promoter and the first exon of the highly expressed gene H4 (Greco *et al.*, *Cell* 1990)

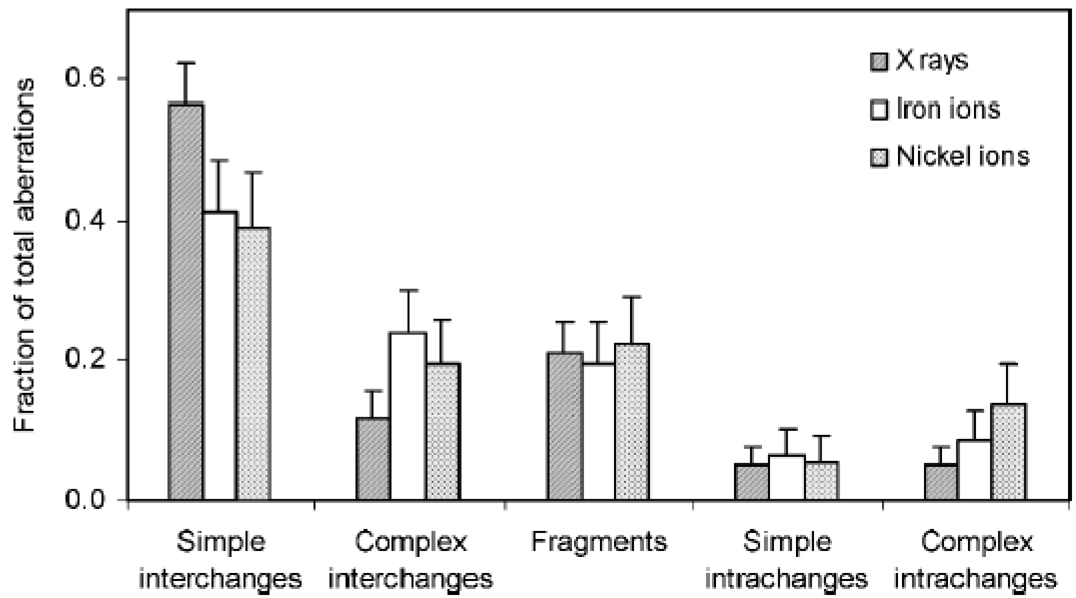
RET and H4 are in close proximity in human thyroid interphase cells, but not in hematopoietic human cells or rodent thyroid cells (Nikiforova *et al.*, *Science* 2000)



Argentina's President Cristina Fernandez shows her scar after surgery for a PTC in January 2012

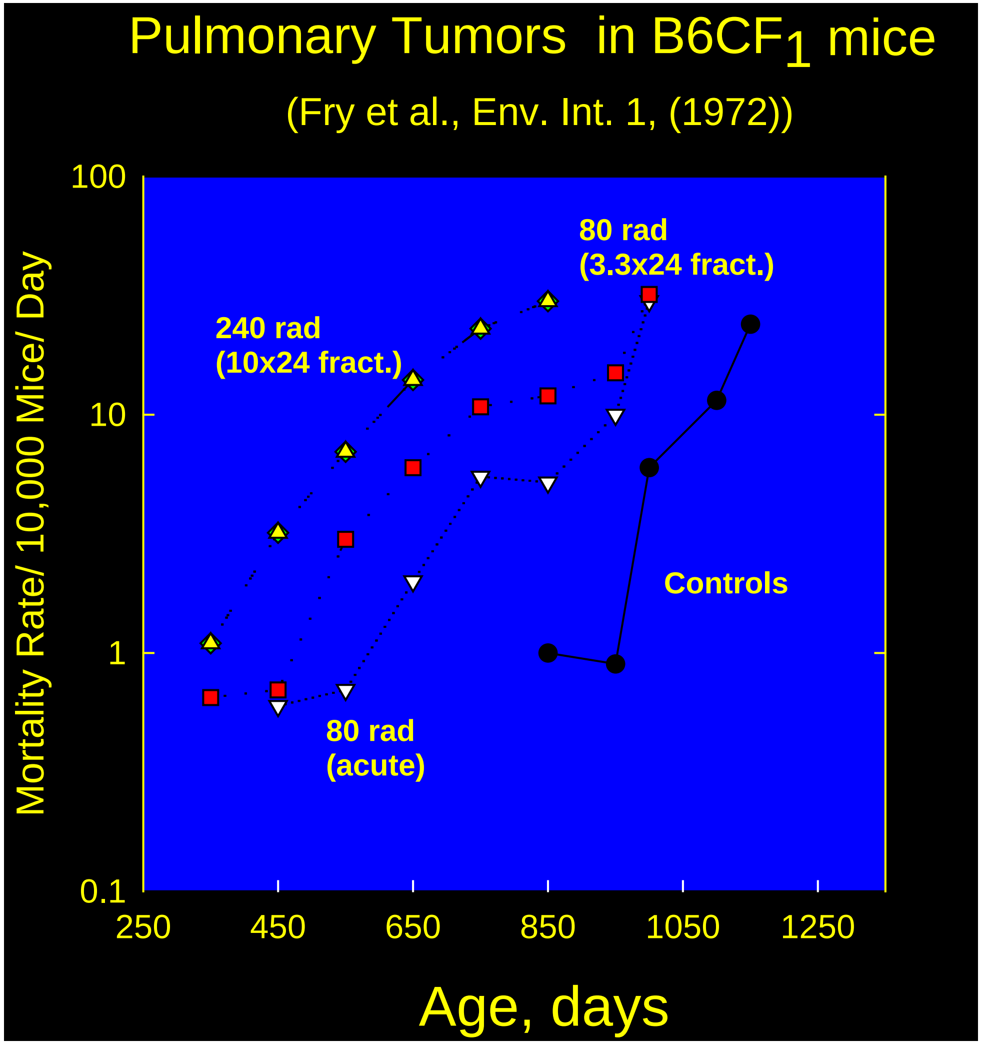
Molecular estimate of RBE of thyroid cancer



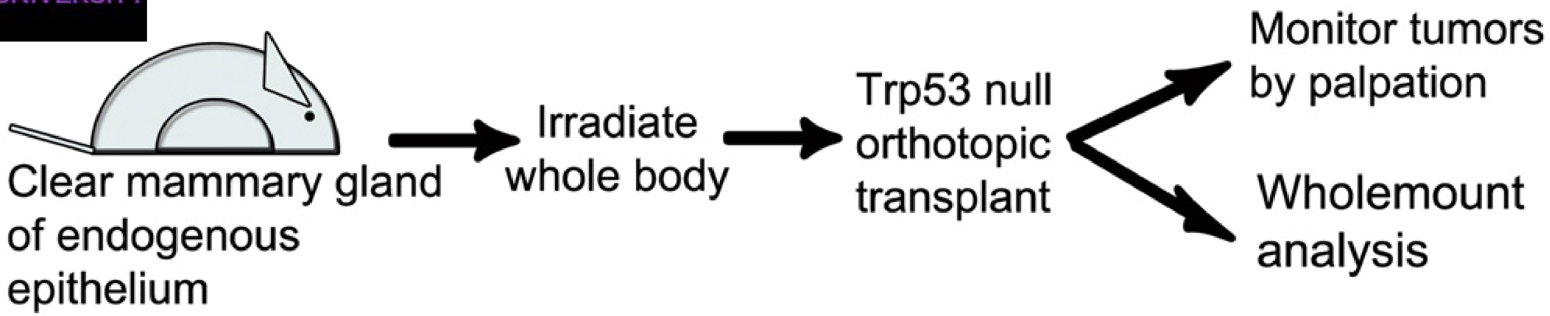


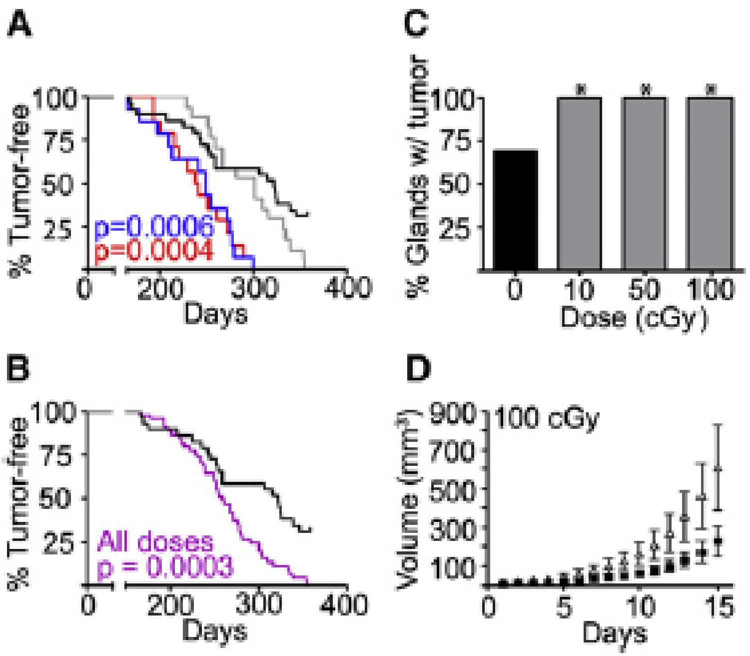
Measurements of intra-arm intrachanges in human thyroid cell chromosome 10 points to a RBE~1 of heavy ions (Pignalosa *et al.*, *Radiat. Res*. 2010)

„how much“ or „when“?



Transplantation of oncogenic Trp53-null epithelium into an irradiated host





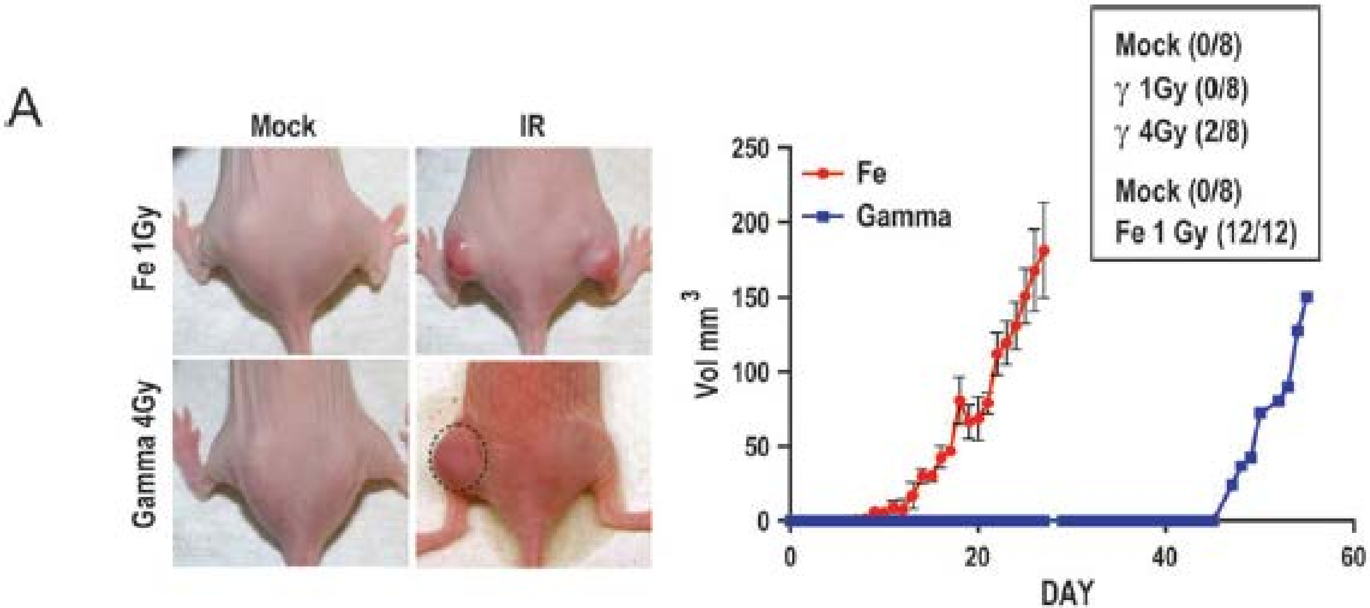
Reduced latency of mammary tumors in animals irradiated with 10-100 cGy X-rays

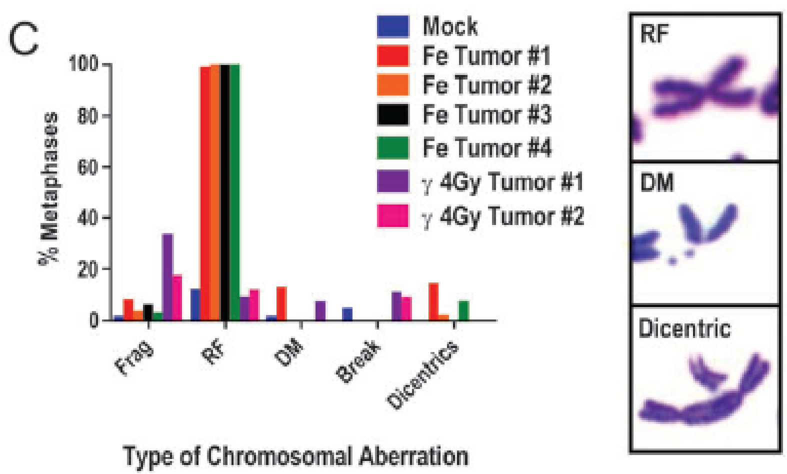
Preliminary heavy ion results show that tumor latency was decreased when the host was irradiated with 30 cGy Fe and 80 cGy Si particles but not by 10 or 30 cGy Si or 80 cGy Fe

Barcellos-Hoff *et al.*, *Cancer Cell* 2011

Irradiated Ink4a/Arf-/- murine astrocytes are tumorigenic in nude mice

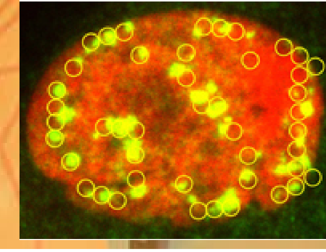
Latency is higher in tumors produced by cells exposed to γ-rays than Fe-ions

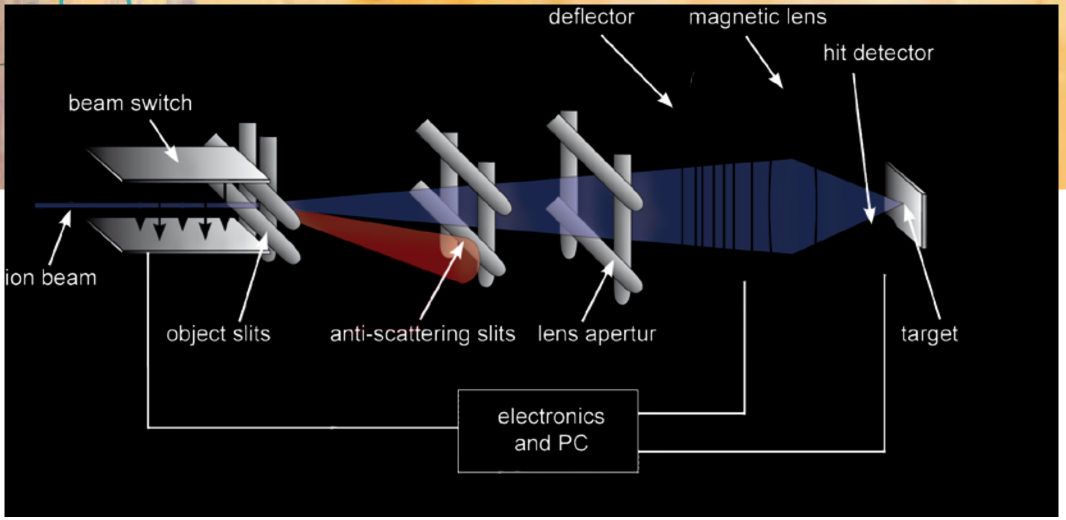




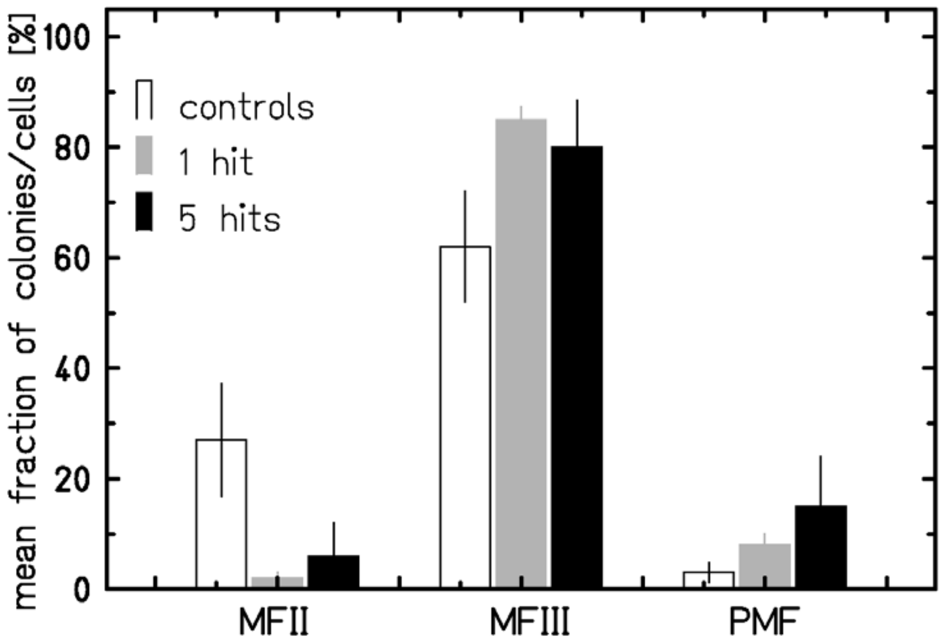
UT SOUTHWESTERN MEDICAL CENTER

Burma *et al.*, *Carcinogenesis* 2010

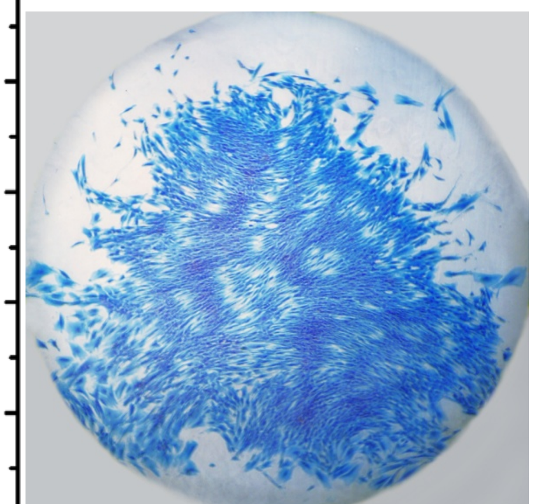




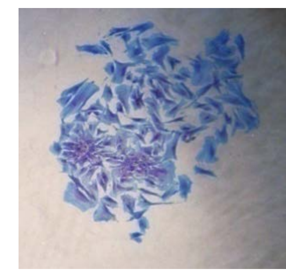
Senescence of normal human fibroblasts after single heavy-ion nuclear traversals

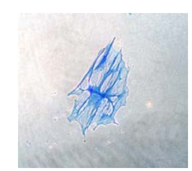


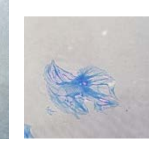
MFII (colonies)



MFIII (colonies)

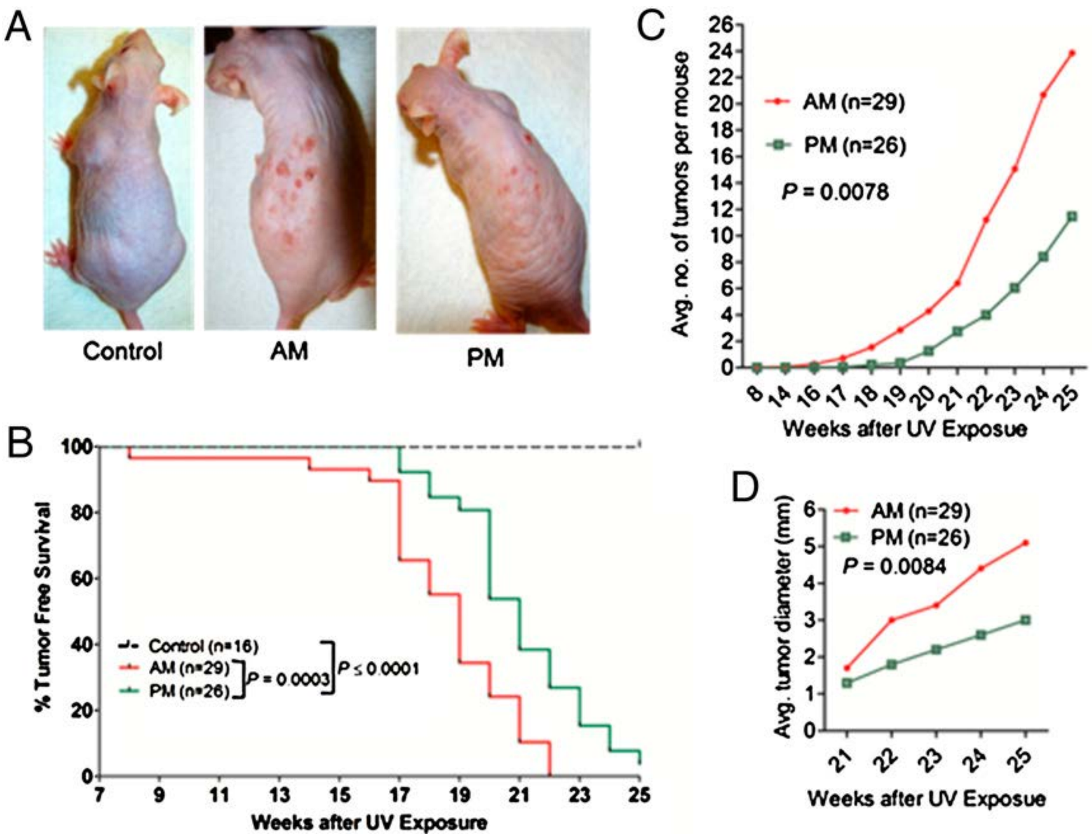


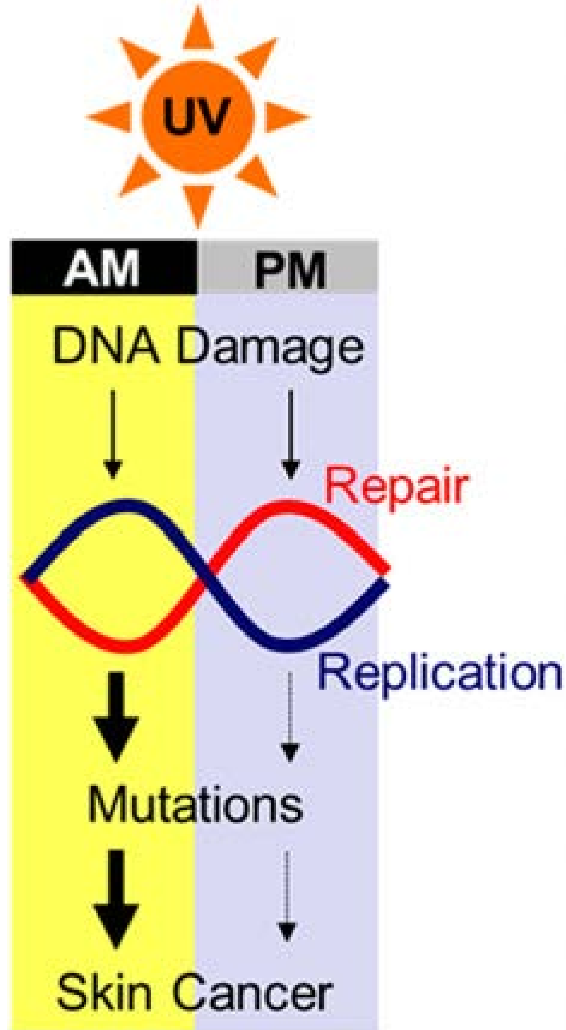




Fournier *et al.*, *Sci. Rep.* 2012

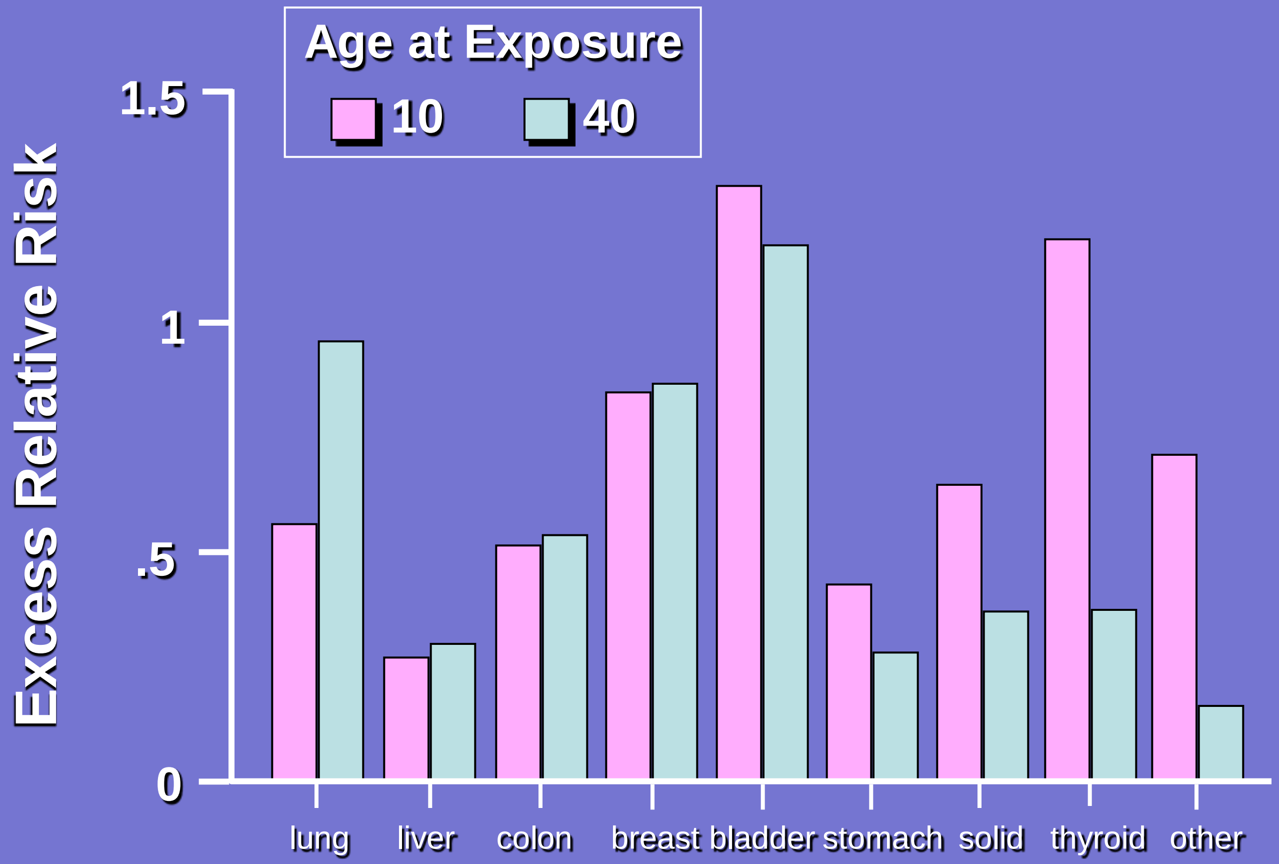
Chronoradiobiology: another time dimension?





Sancar *et al., Proc. Natl. Acad. Sci. USA* 2011

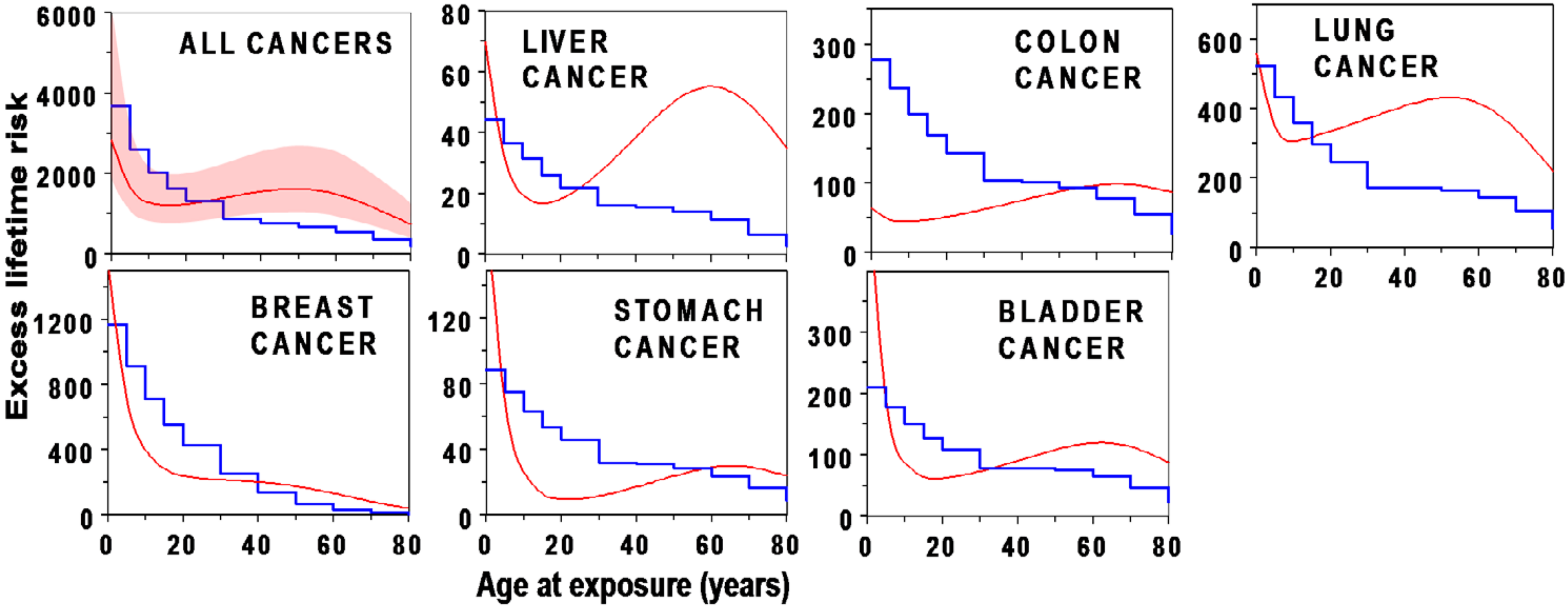
Age at exposure: A-bomb survivors‘ data



Gender averaged ERR’s at age 70 for exposure at age 10 or 40
LSS Report 14, 2012.

The role of promotion in radiation-induced carcinogenesis

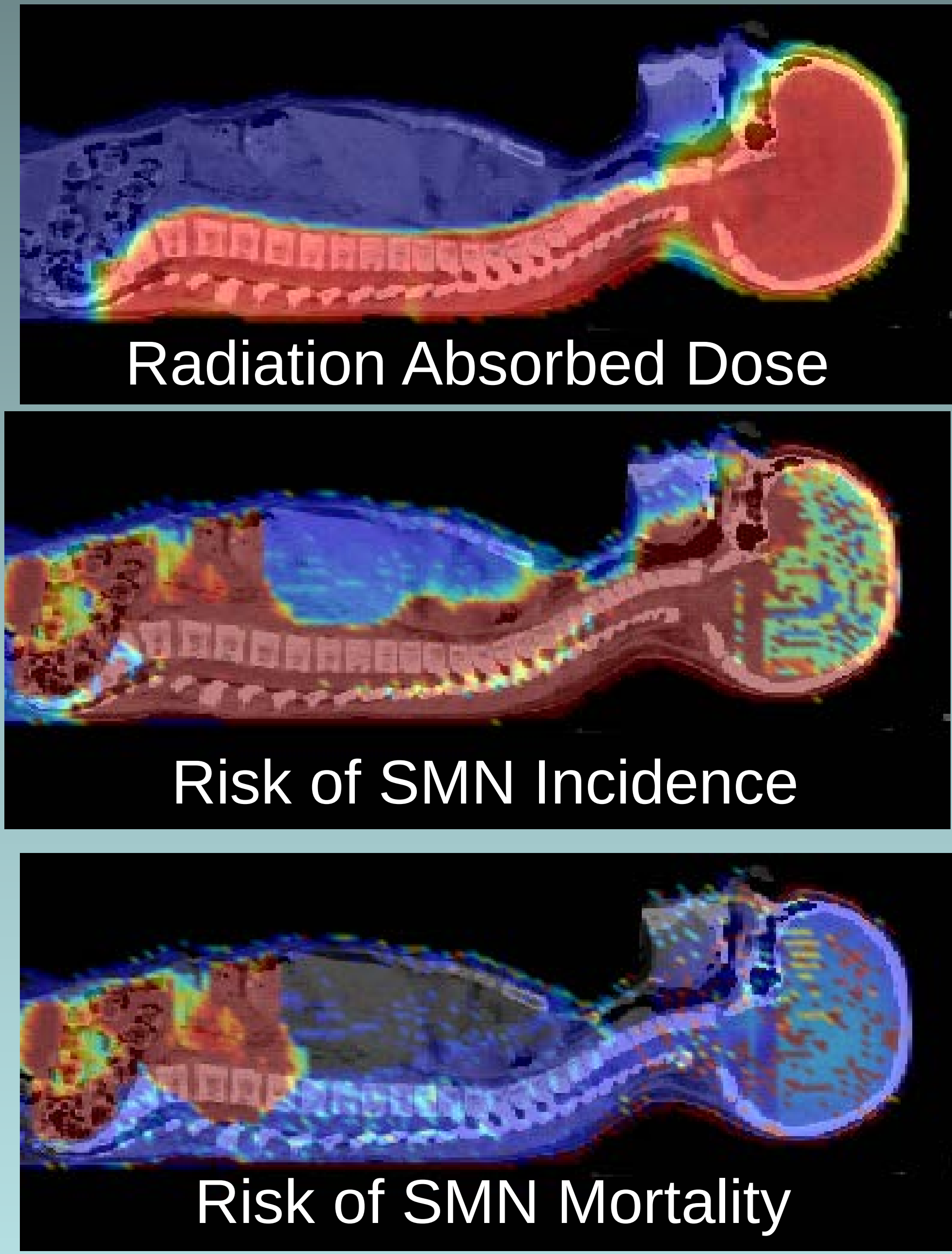
Excess lifetime risks per 0.1 Gy per 10^5 persons



Blue = BEIR VII (2006), including initiation only

Red = Analysis (Shuryak et al. J. Natl. Cancer Inst. 2010) of same A-bomb data, but allowing radiation-induced promotion of pre-existing pre-malignant cells (dormant tumors)

Secondary Malignant Neoplasms (SMN) in particle therapy



Comparison of relative radiation dose distribution with the corresponding relative risk distribution for radiogenic second cancer incidence and mortality. This 9-year old girl received craniospinal irradiation for medulloblastoma using passively scattered proton beams. The color scale illustrates the difference for absorbed dose, incidence and mortality cancer risk in different organs.

Newhauser and Durante, Nature Rev. Cancer 2011

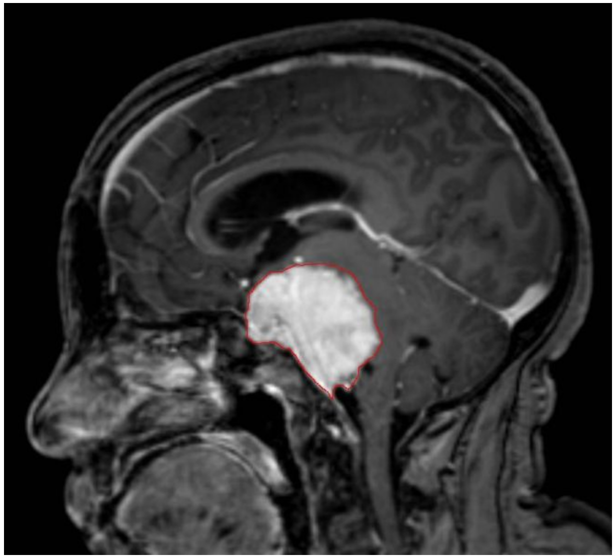
FAIR

Radiation carcinogenesis: for all or for a few?

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)
- Ronckers *et al Can. Ep. Biomarkers Prev*. 2008

Tinea capitis in Israel and meningioma



Meningioma is the most common benign brain tumor

After WWII, thousands of children were irradiated (1-6 Gy X-rays) in Israel for an epidemic of tinea capitis (ringworm of the scalp)

Overall, 1% of the irradiated children developed meningioma

However, the increased risk is basically caused by a subgroup of 17 families out of 160 (11%) with meningioma cases, where the risk was of 4 in 5

Only 1% of the control families had multiple cases of menigioma in the same family

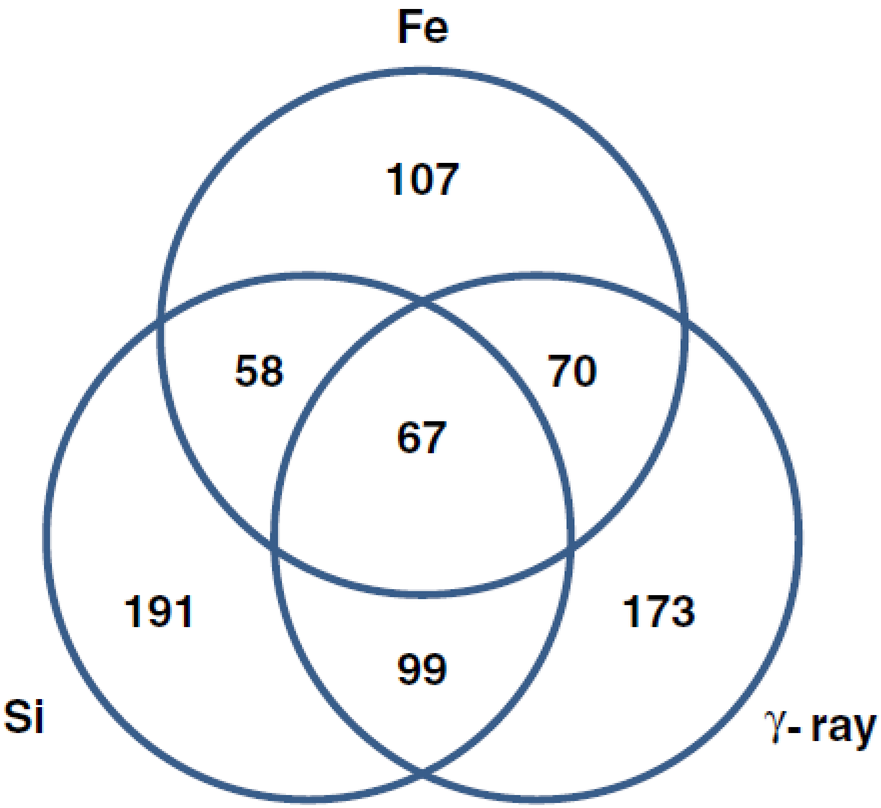
SNPs analysis suggests co-inheritance of multiple risk alleles rather than a single gene

Is then radiation carcinogenesis only visible for a subgroup of sensitive individuals?

Flint-Richter & Sadetzky, *Lancet Oncol*. 2007, *Br. J. Cancer* 2011

Radiogenomics in particle therapy

- To develop a genetic risk profile for individualization of radiation dose prescriptions
- Genetic variations include single nucleotid polymorphism (SNP), copy number variations (CNV), epigenetic changes
- Candidate-gene approach: DNA repair (BRCA1/2), cytokine production (TGFb), scavenging of free radicals (SOD2) etc.
- So far no association found between SNP and radiotoxicity (Barnett *et al., Lancet Oncol*. 2012)
- Large differences in gene expression have been observed in vitro after γ-rays or charged particles



Differentially expressed genes in human bronchial epithelial cells exposed to γ-rays or heavy ions (Ding *et al., BMC Genomics* 2013)

Conclusions

Epidemiology proves that densely ionizing radiation is a carcinogenic agent, but only few data for densely ionizing radiation (see next seminar)

In vitro systems: quantitative information on the RBE-LET relationship, similar to cell killing or mutations: but are they representative of the complex in vivo situation?

Animal data suggest that the RBE depends on the tumor and on the mechanism (initiation or promotion)

Age- and dose-dependence also depends on mechanims: inflammation for high-dose/age (high RBE?), initiation for low dose/age (low RBE?)

The different radiation quality may impact the latency rather than the risk

Genetic predisposition may lead to a major brakthrough in our estimates of quality factors

Thank you very much

- **M. Durante (Director)**
- **G. Kraft (Helmholtz Professor)**
- **G. Taucher-Scholz (DNA repair)**
- **S. Ritter (Stem cells)**
- **C. Fournier (Late effects)**
- **C. Hartel (Clinical radiobiology)**
- **M. Scholz (Biophysical modelling)**
- **M. Krämer (Treatment planning)**
- **C. Graeff (Medical Physics)**
- **C. La Tessa (Radiation physics)**

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