Estimating Cancer Risks at Very Low Doses

Has radiobiology helped?

Can radiobiology help?

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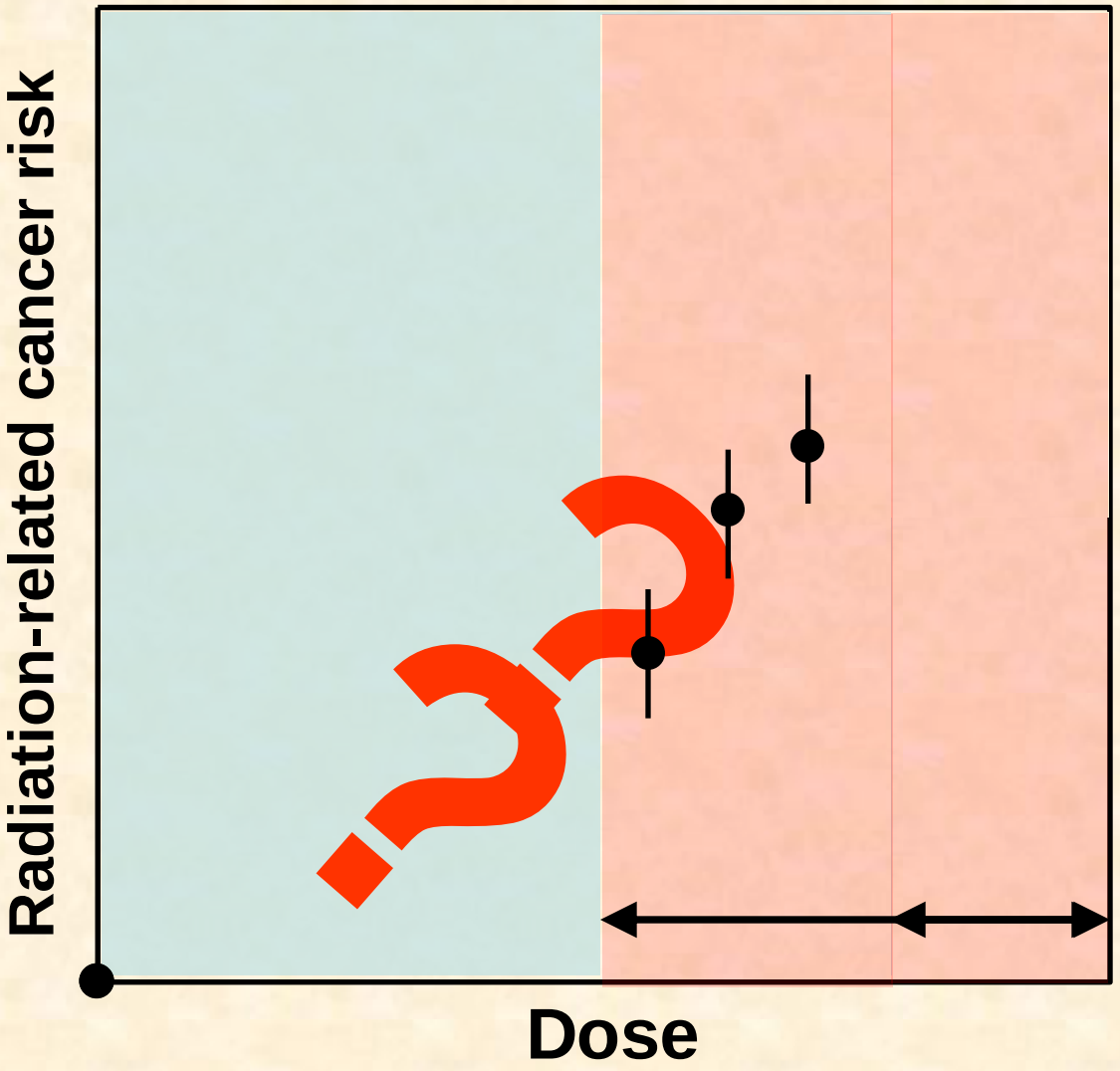
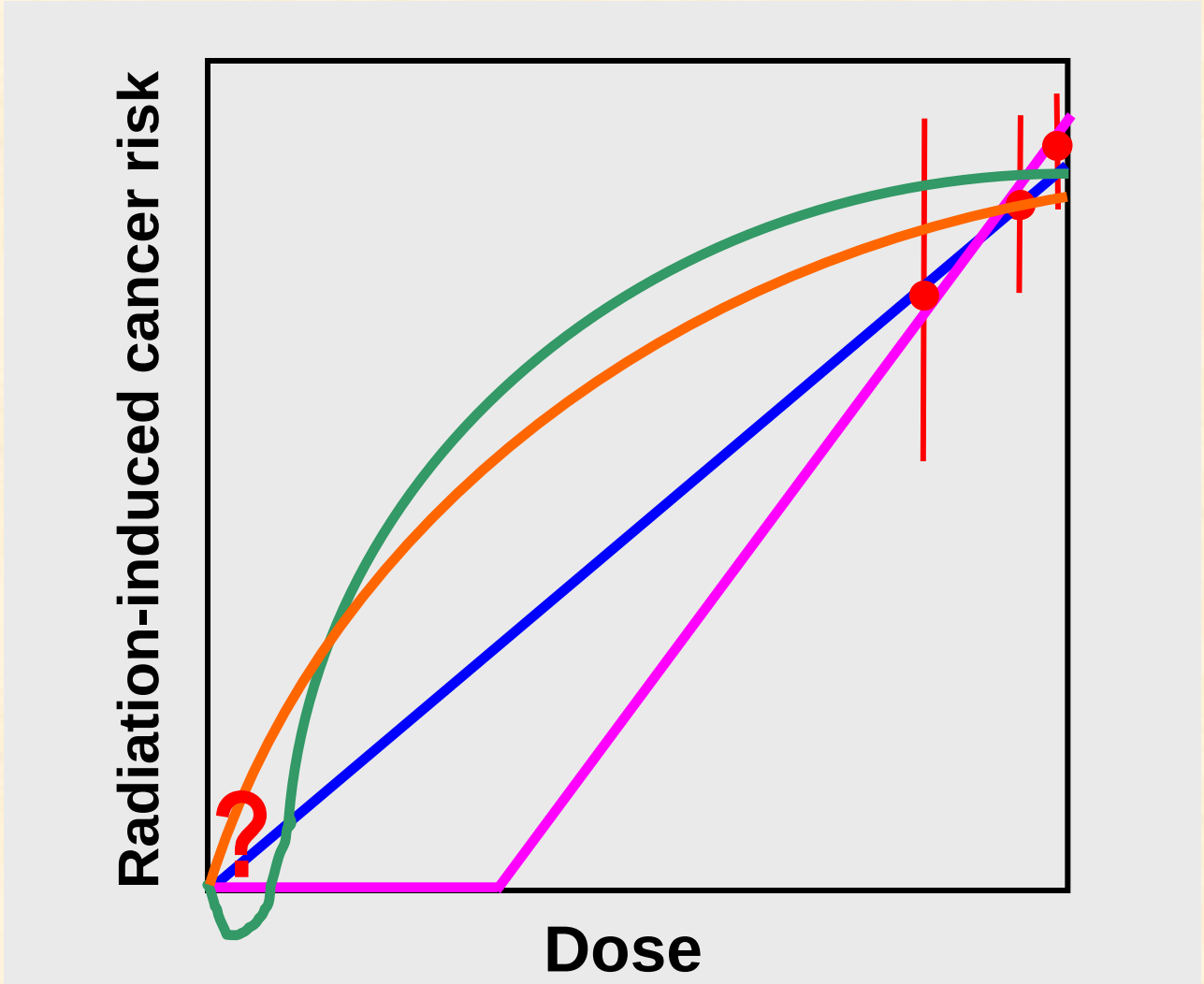
What is the issue here?



Searching for the most appropriate methodology to extrapolate measured cancer risks to very low doses



BEIR-VII arguments

Experimental results

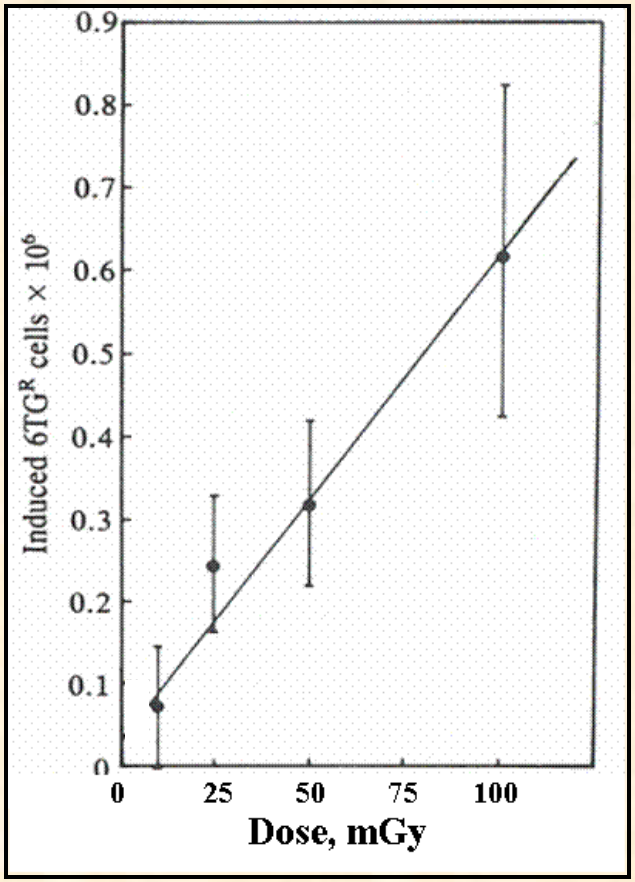
Epidemiological, cytogenetic and mutagenesis results are all consistent with linearity, at low doses where statistically significant measurements are possible

Biophysical argument

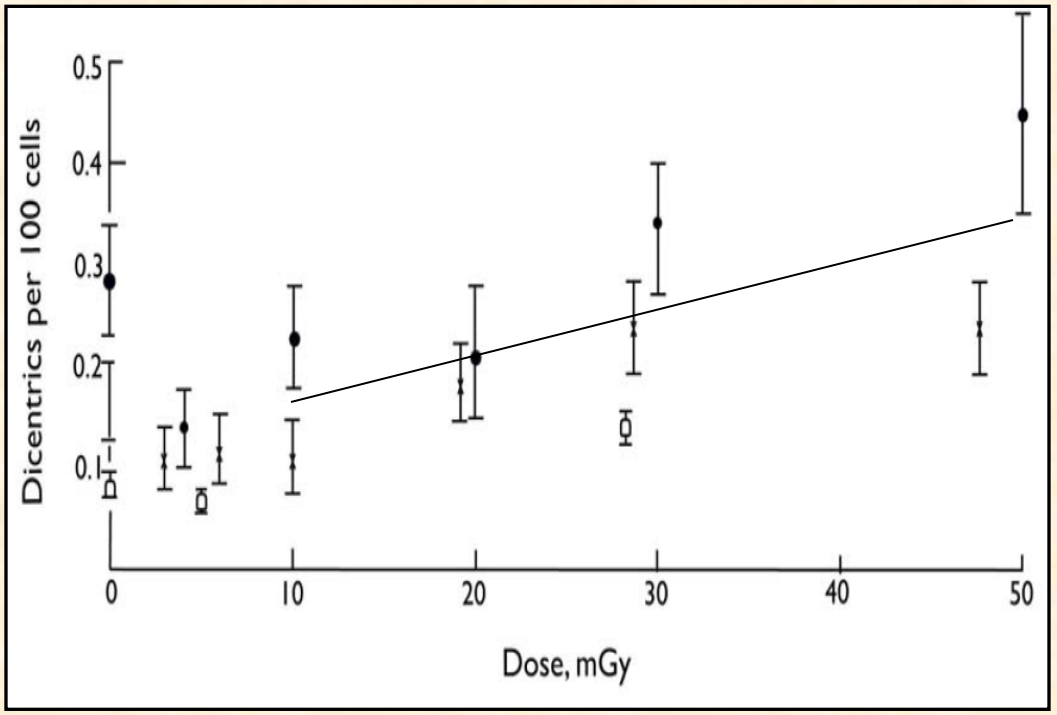
At very low doses, as the dose goes down, the type of damage stays the same (a hit from a single photon), but the *number* of damaged cells decreases linearly

BEIR-VII Arguments

Experimental Data - Biological



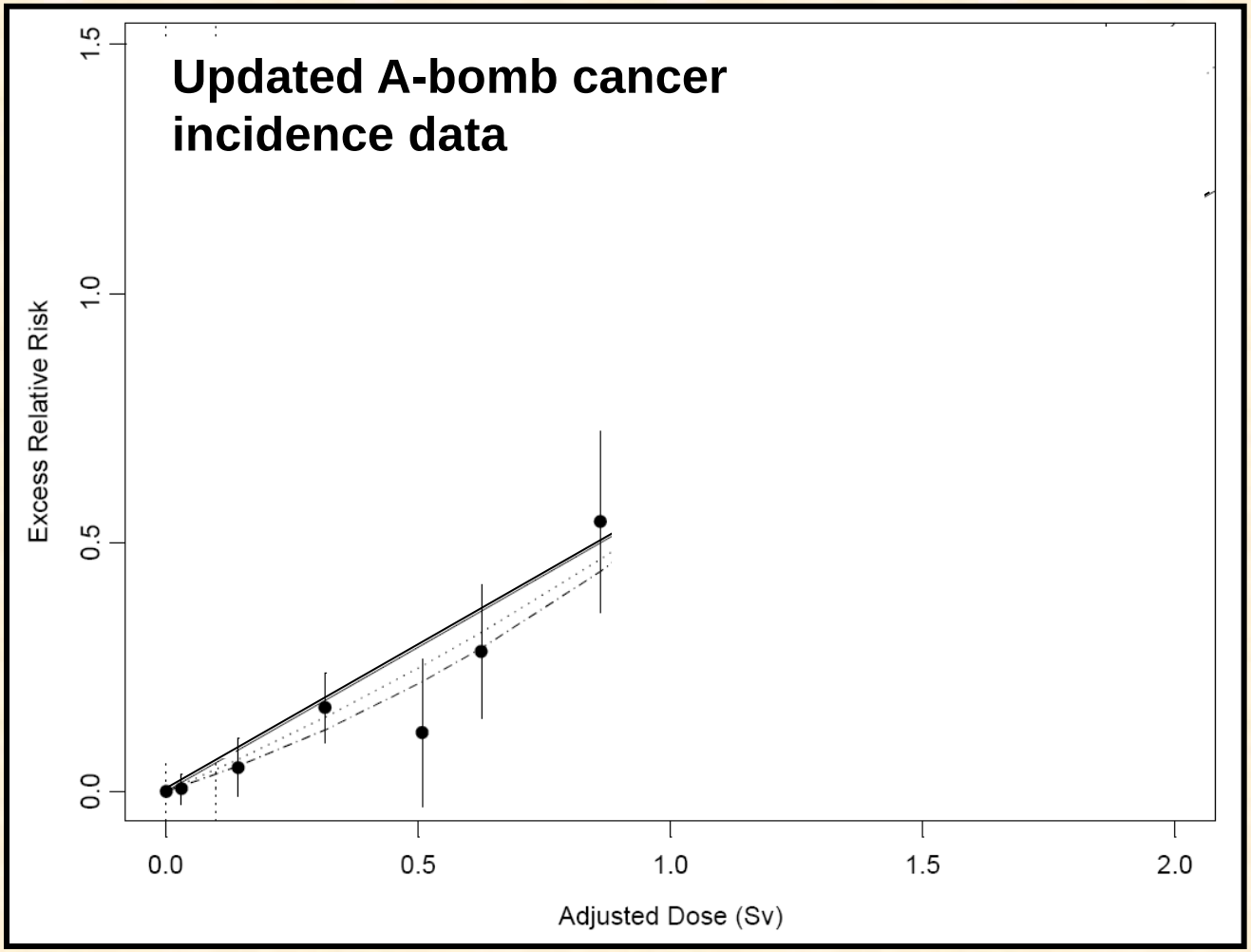
Mutation Induction



Dicentric Aberration Induction

BEIR-VII Arguments

Experimental Data - Epidemiological



BEIR-VII arguments

Experimental results

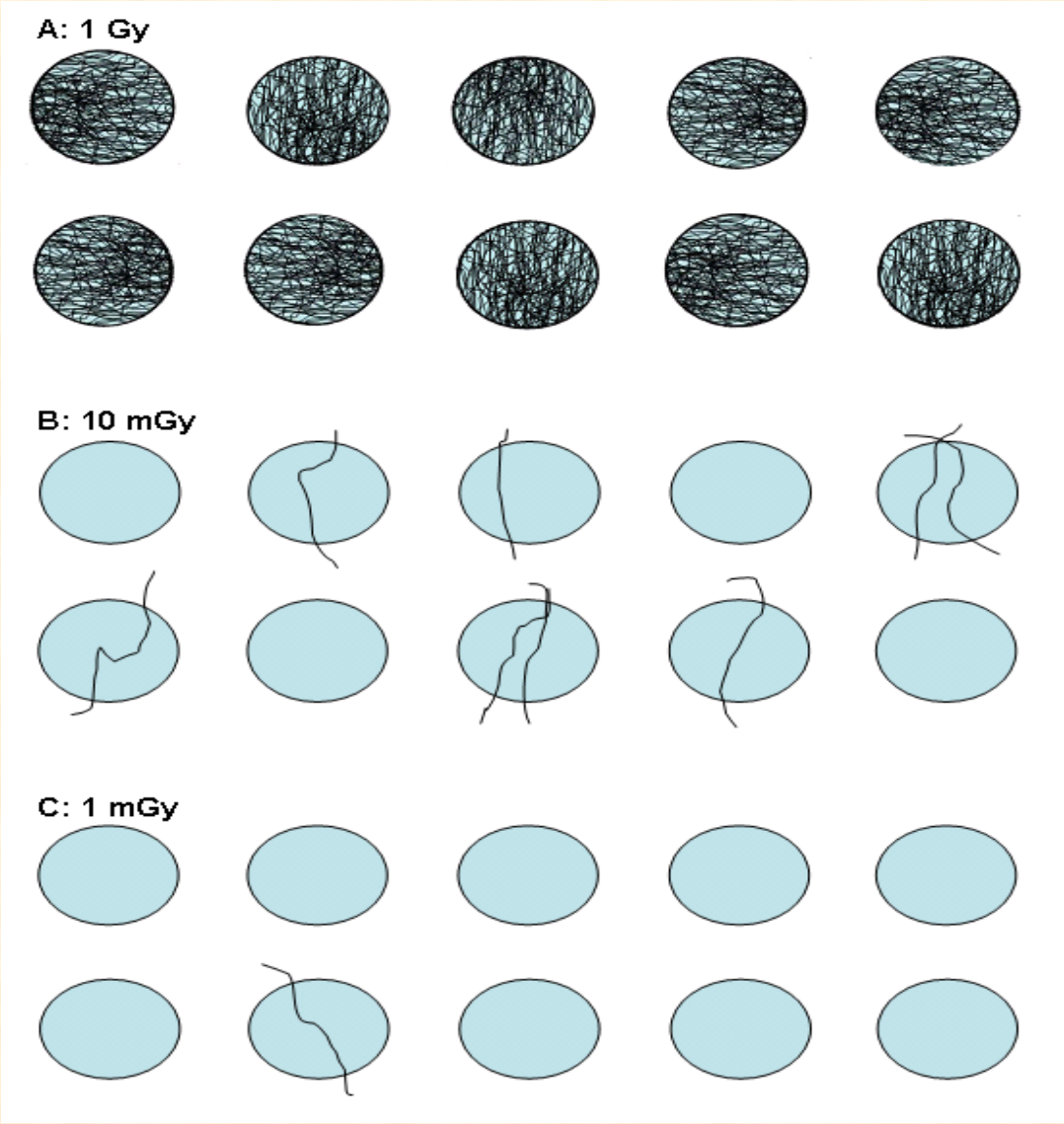
Epidemiological, cytogenetic and mutagenesis results are all consistent with linearity, at low doses where statistically significant measurements are possible.

weak

Biophysical argument

At very low doses, as the dose goes down, the type of damage stays the same (a hit from a single photon), but the *number* of damaged cells decreases linearly.

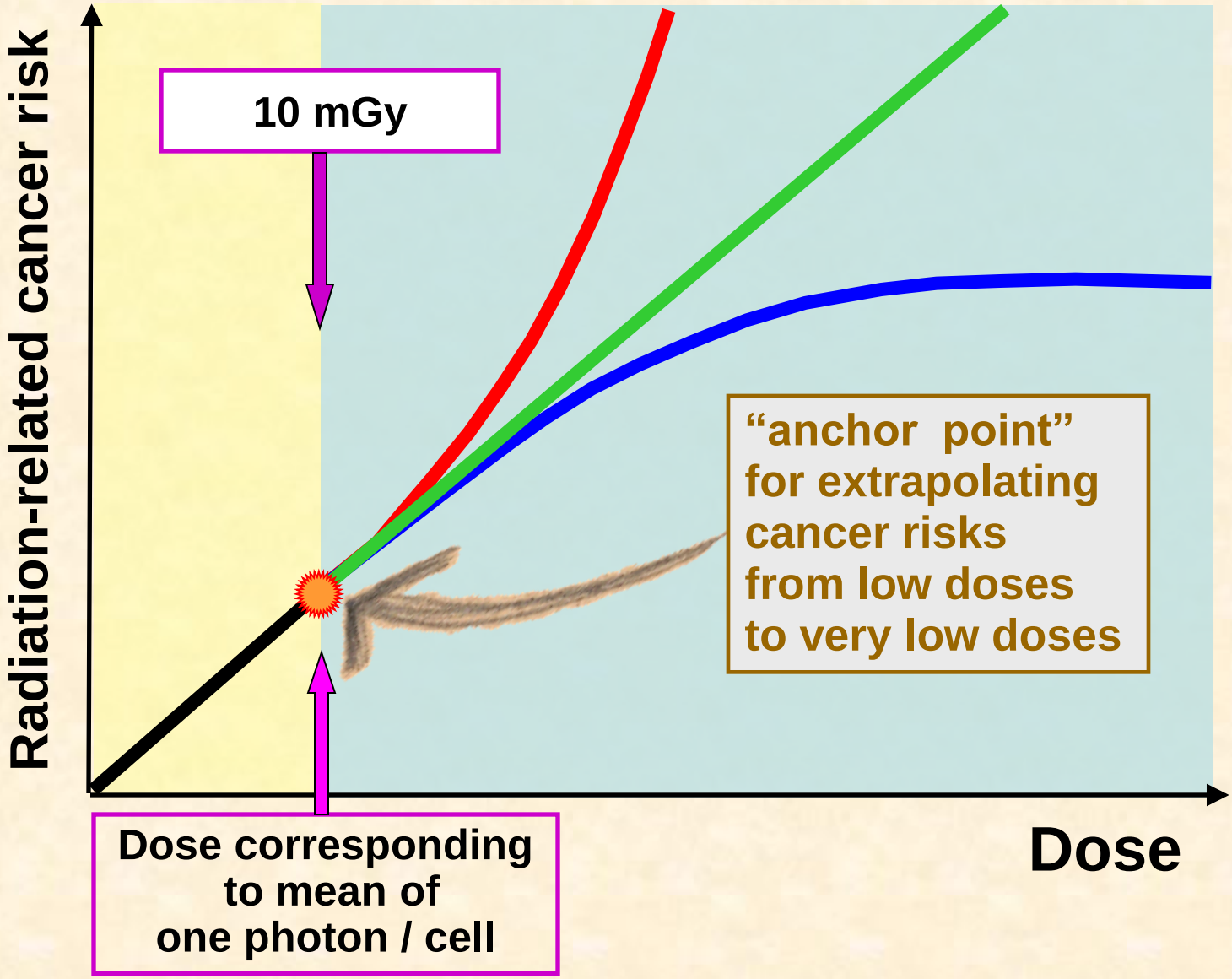
The heart of the biophysical argument: x-ray track structure at 1 Gy, 10 mGy and 1 mGy



The Biophysical Argument

1. It is assumed that low doses around 10 mGy are associated with an increase in human cancer risk
2. At this dose, most irradiated cell nuclei will be traversed by one or at most a few physically-distant electron tracks
3. At low doses, decreasing the dose by (say) a factor of 10 will decrease the number of damaged cells by a factor of 10, all hit by essentially a single photon
4. Given that the energy deposition is the same, one would not expect qualitatively different biological processes to be active at (say) 1 mGy that were not active at 10 mGy
5. Based on this argument, the risk of most radiation-induced endpoints would decrease linearly, without threshold, from ~10 mGy down to arbitrarily low doses

The Biophysical Argument



Toward estimating risks in the sub mGy range:

The Big needs

1. **Epidemiological evaluation of cancer risks specifically in the 10 mGy (1 rad) region**
   - **Epidemiological studies specifically designed to maximize the likelihood of detecting effects at 1 rad, if they are there…**

The significance of inter-cellular communication for radiation-induced cancer

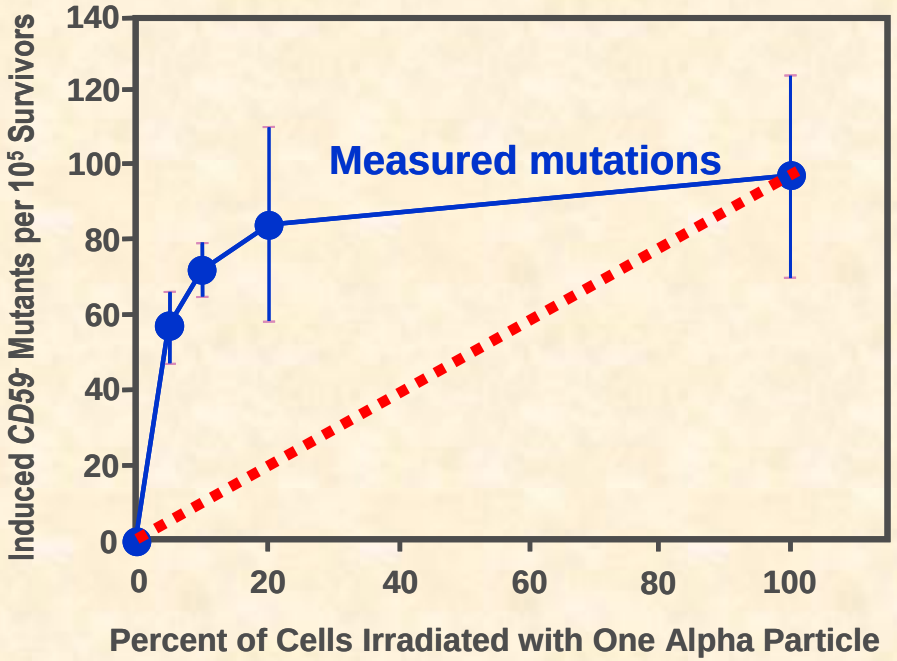
- **The biophysical argument refers to the development of monoclonal tumors by autonomous (independently developing) cells**

- **Are radiation-carcinogenic processes counteracted / amplified by mechanisms at the inter-cellular, tissue or organism level?**

Cells in tissue certainly talk to each other, but what are the implications for low-dose risks?

- **The most quantified radiation-related inter-cellular response is the bystander effect**

- **Where bystander responses have been quantitated, they have shown saturation**



- **In such cases, extrapolating linearly from low to very low doses could underestimate the risk**

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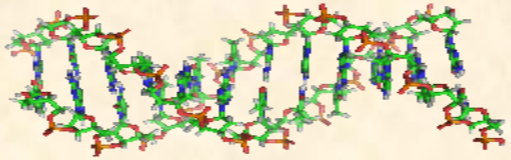
2. **Understanding the significance of multi-cellular effects in radiation carcinogenesis**
   - Are bystander effects relevant for radiation carcinogenesis?

Who gets radiation-induced cancer?

- **Irradiated populations typically show small increase in cancer risks**
  - **Are these cancers random stochastic events… the roll of the dice?**

  - **Or are they largely confined to radiosensitive sub-groups?**



Genetic predisposition for the development of radiation-associated meningioma: an epidemiological study

Pazit Flint-Richter, Siegal Sadetzki

Lancet Oncol 2007;8:403-410

Summary

Background Ionising radiation is an established risk factor for meningioma, yet less than 1% of irradiated individuals develop this tumour. Familial aggregation of meningioma is rare. We aimed to assess whether genetic factors can modify the risk for meningioma formation after the initiating effect of radiation, by comparison of the frequency of meningiomas in families that included irradiated and unirradiated siblings.

Methods This study was based on a larger epidemiological, genetic case-control study, and included 525 families that were divided according to irradiation and disease status of each of the family's index participant: 160 had radiation-associated meningioma (RAM); 145 were irradiated and did not develop meningioma; 85 had meningioma with no previous history of irradiation; and 135 were unirradiated and did not develop meningioma. Data were collected by questionnaires.

Findings We found additional first-degree relatives with meningioma in 17 families (11%) in the RAM group, whereas only between one and two such families (1%) were found in the other groups ($p<0\cdot0001$). All meningiomas seen in the families of the RAM group were in irradiated participants. Also, 22 families (10%) in the RAM group had members with cancers in irradiated sites (including head, neck, and chest) compared with 9 (5%) of irradiated controls ($p=0\cdot04$).

Interpretation This dataset of families, which included irradiated and unirradiated, and also affected and unaffected family members, created a natural experiment. Our results support the idea that genetic susceptibility increases the risk of developing meningioma after exposure to radiation. Further studies are needed to identify the specific genes involved in this familial sensitivity to ionising radiation. DNA repair and cell-cycle control genes, such as the ataxia-telangiectasia gene, could be plausible candidates for investigation.

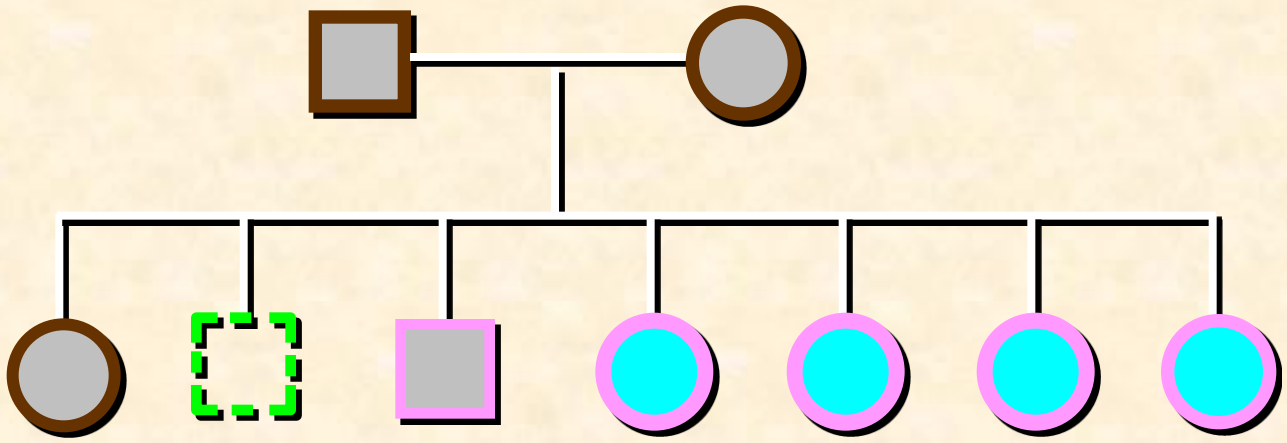
Familial Study of Children Irradiated for Tinea Capitis

525 families

Some irradiated, some meningiomas 160 families	**Some irradiated, no meningiomas 145 families**
None irradiated, some meningiomas 85 families	**None irradiated, no meningiomas 135 families**

Flint-Richter and Sadetski, Lancet Oncology 2007

Family #1
(Origin: Morocco)



Irradiated
Unirradiated
Status unknown
Meningioma
No meningioma

Flint-Richter and Sadetski, Lancet Oncology 2007

Inter-Individual Radiosensitivity: Radiation Carcinogenesis

- **Almost all the radiation-associated cancers occurred in a very few families**
- **Genetic susceptibility appears to markedly increase the risk of radiation-associated meningioma (but not the risk of meningioma in general)**

- **If this were generally true in radiation carcinogenesis, radiation safety limits would be too strict for most people, and not strict enough for a few people ....**

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The Big needs

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2. **Understanding the significance of multi-cellular effects in radiation carcinogenesis**
   - Are bystander effects relevant for radiation carcinogenesis?

3. **Understanding the significance of inter-individual radiosensitivity in radiation carcinogenesis**
   - Studies with outbred mice?
   - Large scale screening of radiosensitivity?

Estimating Cancer Risks at Very Low Doses

Has radiobiology helped? ***The table is set, but it's currently more qualitative than quantitative***

Can radiobiology help? ***Yes, we are now on the road to quantitation***