Mechanistic models of carcinogenesis: An application to lung-cancer risk in the Mayak nuclear workers

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Overview:
- We analyze lung cancer mortality following Plutonium exposure in the Mayak workers cohort (Sec. 1).
- Goal: Develop multi-stage models (Sec. 2) to obtain a mechanistic understanding of lung carcinogenesis and the contribution of radiation.
- The results suggest that 3-stage models offer an improved description, compared to the widely used 2-stage model (Sec. 3). Both point to a radiation-enhanced proliferation rate as a mechanism.
- This may give a mechanistic interpretation of certain features of the radiation risk (Sec. 4), such as a nonlinear dose response or the combined effect of radiation and smoking.

1. Data set
The Mayak-workers cohort totals ~25k employees of the Mayak Plutonium-production facility in Ozyorsk (Russia), with follow-up period 1948-2008 (Gilbert, Rad. Res. 2012). These have been exposed to rather large Plutonium doses (internal, protracted exposure). We focus on lung cancer, for which there are many cases (895) owing to inhalation.
We restrict the main analyses to the subcohort defined by:
- Males
- Information on smoking (yes/no)
- Alcohol
- Annual Plutonium dose rates (measured or negligible)
- Mortality (8604 persons; 386 cases)

2. Mechanistic vs. descriptive models
2.1 Descriptive model (“modeling the final hazard”)
As a benchmark, a standard descriptive model is employed. Here the mortality rate (hazard) is parametrized in terms of baseline and excess risk:
- \( h_0(t) = h_0(t) \times [1 + \text{ERR}(t)] \)
- \( \text{ERR}(t) \): Baseline excess mortality rate on age, cell number (smoking)...

2.2 Mechanistic models (“modeling the multi-stage process”)
In our mechanistic approach, carcinogenesis is modeled as a stochastic process in terms of numbers of cells, \( X_j \), at different (pre-)malignant stages \( j=1...k \). There are two key concepts:
- Mutations (Poisson process): Transitions to a more advanced stage at probability proportional to available cell number \( X_j \) and mutation rate \( \mu_j \)
- Proliferation (birth/death process): Premalignant cells can multiply, proportional to clonal growth rate \( \mu_j \), and cell number \( X_j \)

External agents (radiation, smoking) may increase these rates, which is determined by the fit. We test families of models with 2 and 3 stages, but also a two-pathway model (Sec. 5).

3. Best-fitting models: Mechanisms
The best models suggest that Pu radiation enhances the net clonal-growth rate: \( \gamma_j(t) = \gamma_j + \delta(t) \gamma_j \).
Typically, the growth rate saturates for dose rates \( d \approx 0.05 \text{Gy/a} \).
Interpretation: Bystander signaling or cell-killing-induced repopulation through premalignant cells [Meckbach (1981); Gelehrter (2000)]; 3-stage models (3SC), in particular with a radiation effect at an early stage, lead to an improved fit w.r.t. the 2-stage model.

4. Radiation risk: exposure scenarios
4.1 Age dependence
As an illustration, we plot the hazard of the 2-stage model (TSCE):
- For smokers / non-smokers
- For exposure at \( d = 0.01 \text{Gy/a} \) from age 25 to 60 (thick lines) and baseline (thin)

Smoking/Pu interaction: For a wide age range after exposure, the risk is almost multiplicative (additive on log scale). This is because an additional growth rate \( \delta(t) \) leads to exponentially more pre-malignant cells, \( \approx e^{\delta(t) d} \).

Age dependence: During exposure, the excess hazard increases almost exponentially (proliferation). This reflects in the initial increase of the ERR per dose before falling off, similar to the 3SC models (Fig.1). An early-stage effect leads to a delayed risk response.

4.2 Dose-response relationship
In contrast to the linear dose response assumed in the descriptive model, ERR \( \approx 0.5Y^3 \), the multi-stage models show a highly nonlinear dose response:
- Exponential increase (due to proliferation)
- Saturation at high dose/age and ages
- Critical dose for 3-stage models (reflects competition between growth in stages 1&2)

5. Role for genomic instability?
In contrast to e.g. colon cancer, where genomic instability is known to affect the risk [Nowak (2001); Lerman (2004)], the situation is less clear for the lungs. We have tested models with two pathways (Fig.): a "normal" path plus a "destabilized" one with higher mutation rates.

No two-path model gives an improvement beyond the 2-stage model. Whether this relates to the lack of power of the data or to the irrelevance of a second path in lung cancer remains an open question.