Cancer Modeling

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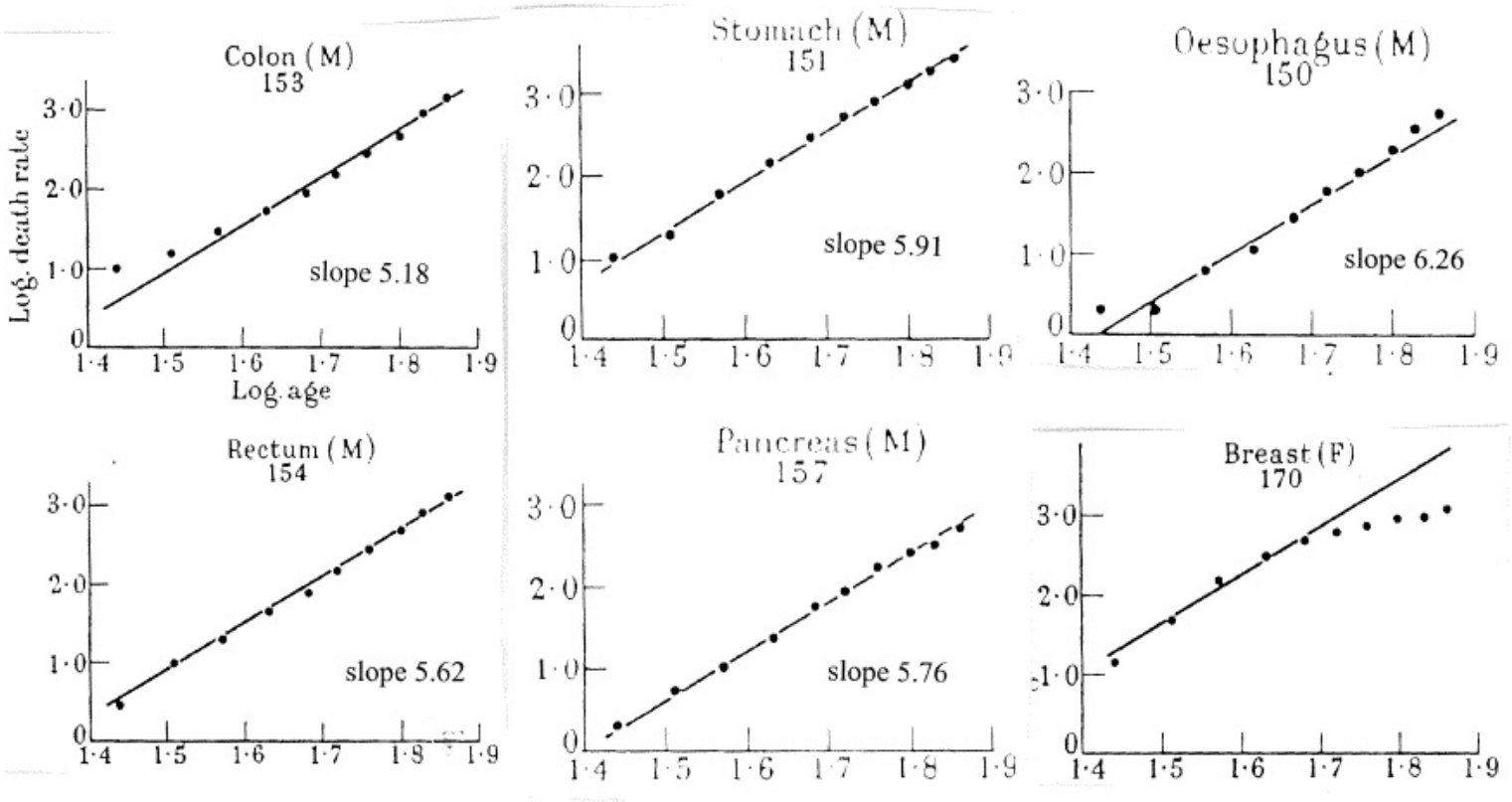
Armitage and Doll (1954)

noticed that log-log plots of cancer incidence data are linear for a large number of cancer types.



Multi-stage theory of carcinogenesis

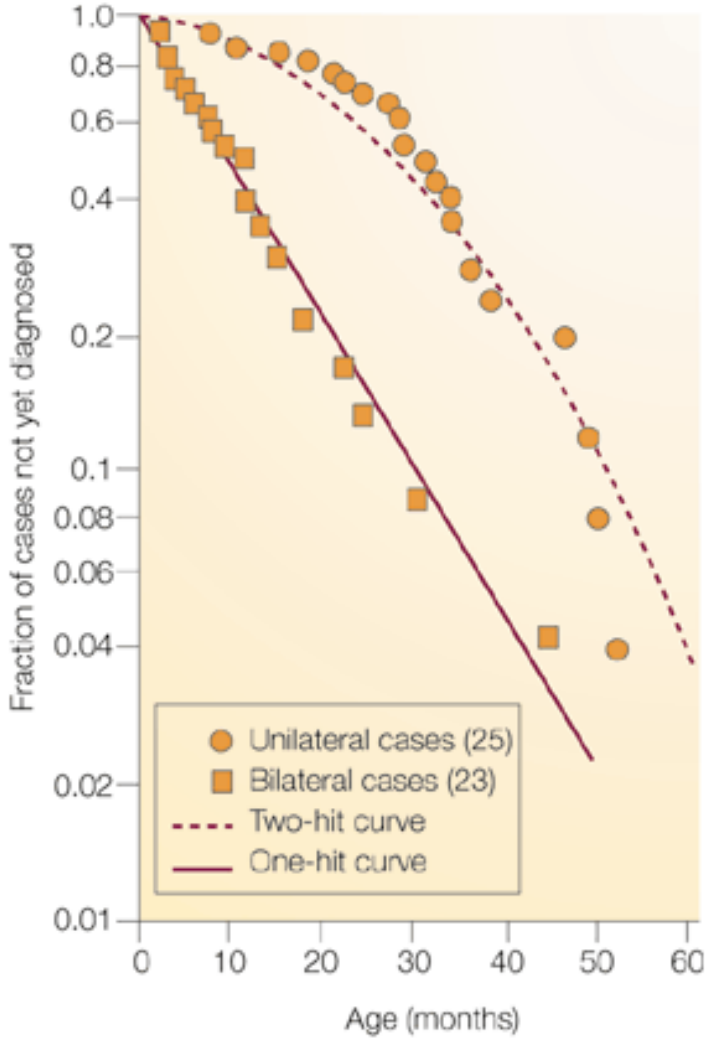
From the fact that colorectal cancer incidence has a slope of 5.18 in men, the authors concluded that colon cancer is a six stage process. The math was very simple:

Suppose X_i are independent and have an exponential distribution with rates u_i. The sum $X_1 + \cdots + X_k$ has a density function that is asymptotically

$$u_1 \cdots u_k \frac{t^{k-1}}{(k-1)!} \qquad \text{as } t \to 0$$

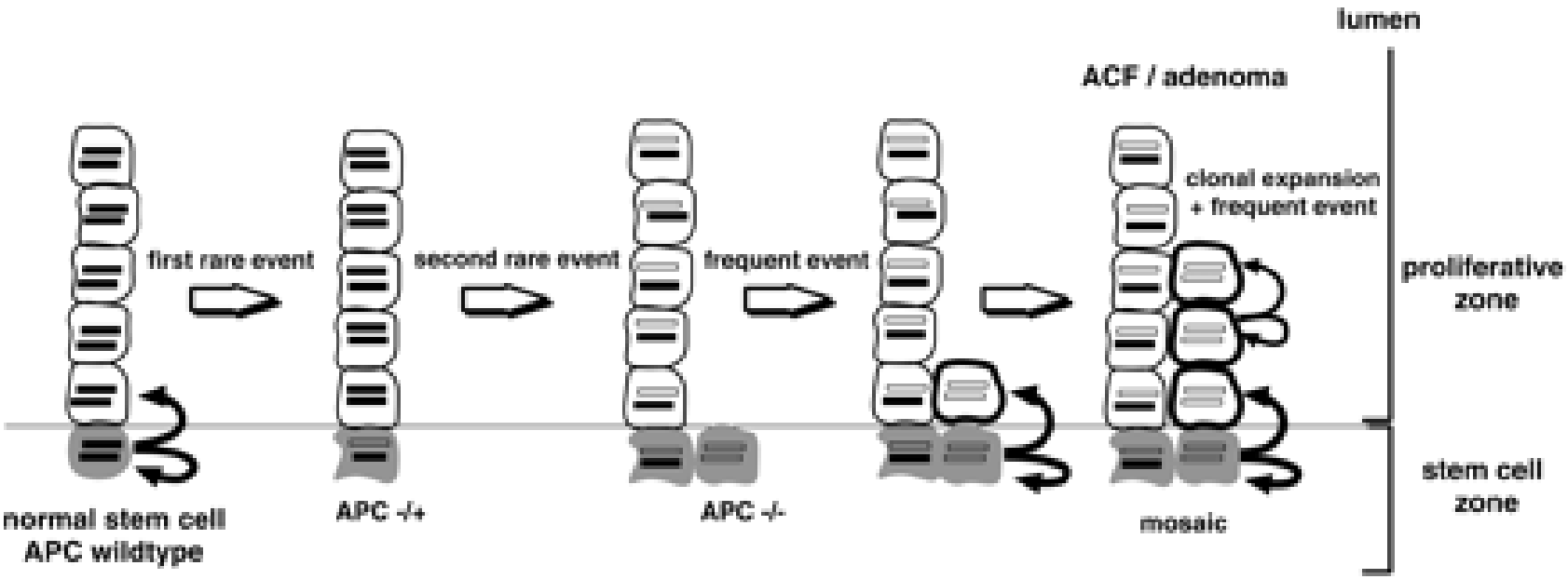
Incidence of Retinoblastoma

Knudson's two hit hypothesis $\longrightarrow$ tumor-suppressor genes



Progression to Colon Cancer

Luebeck and Moolgavakar (2002) PNAS fit a four stage model to incidence of colon cancer by age.



What are the stages ?

- In sporadic cases of colon cancer the first two stages inactivation of the tumor suppressor gene *APC* adenomatous polyposis coli.
- KRAS is an **oncogene** (one mutation turns it on). It acts as a molecular on/off switch, once it is turned on it recruits and activates proteins necessary for the propagation of growth factor
- The final stage is thought to involve the inactivation of *TP*53 the gene which makes *p*53. Mutant p53 can no longer bind DNA in an effective way, and as a consequence the p21 protein whose production it stimulates is not made available to act as the 'stop signal' for cell division.

Things are not so simple

- In 20% of colon cancers, *APC* is not mutated but instead the oncogene β-catenin (in the same pathway) is. This and other examples suggest that features of the disease are due to disrupting certain molecular pathways not necessarily specific mutations.
- One of the main aims of large scale sequencing of cancer tumors is to find mutations that are potential drug targets. However many statistically significant mutations are "passengers" that occurred on the same chromosome with a causative mutation.

Within Tumor Heterogeneity

Even more problematic than heterogeneity between patients is the large amount of intra-tumor diversity:

- Different subpopulations within a tumor may have varying types of response to any given treatment, making total tumor reduction and prevention of resistance difficult.
- Heterogeneity levels are associated with aggresiveness of disease (e.g., in Barrett's esophagus and prostate cancer).
- Studies have also shown mutational heterogeneity between primary tumors and metastases in breast cancer, explaining lack of response to EFGR antibody therapy in patients that appeared to have no mutation in KRAS.