Reviewer's report

Title: Kinetics of cancer

Version: 1 Date: 11 July 2005

Reviewer: William George G Thilly

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General
This paper intends to provide means to analyze tumor incidence or mortality data in mice of differing genotypes so that "research can move to the next stage in which the mechanistic consequences of particular genetic pathways are related to the dynamics of carcinogenesis".

Unfortunately, the authors appear to depend on Armitage and Doll (1954) based on the thinking of Nordling who imagined multiple mutations in cell populations of constant cell number. Curiously so do most cancer researchers. But in Armitage and Doll (1957) A two-stage theory of carcinogenesis in relation to the age distribution of cancer. Br. J.Canc. 9:161-169 we first see cognizance of the pathological condition of preneoplasia, a slow growing colony that in humans may take 30-60 years to produce a rapidly growing lethal tumor.

In addition to Moolgavkar (1981) Moolgavkar's group has published more recent analyses as have Stein's group (e.g., Stein WD. Analysis of cancer incidence data on the basis of multistage and clonal growth models. Adv Cancer Res. 1991;56:161-213) and our own group (e.g., Herrero-Jimenez P et al. Population risk and physiological rate parameters for colon cancer. The union of an explicit model for carcinogenesis with the public health records of the United States. Mutat Res. 2000 Jan 17;447(1):73-116).

We have also considered mouse lifetime tumor mortality kinetics in animals not subjected to carcinogenic regimens but have found them to be qualitatively different from human data to the point that their relevance to human carcinogenesis may be reasonably doubted. For instance if one simply groups the set of X mice in an experiment such that there are five or more deaths in time intervals of equal length commencing with the first observed cancer death, one can define the cancer mortality rate in each such interval as # cancer deaths/# of surviving mice at the beginning of each interval.

These data invariably show that after an early period of zero cancer deaths the cancer death rate (for a particular form of cancer) reaches a stable maximum that continues through the lifespan of the mouse strain used or until there are too few surviving mice to calculate this fraction. in short mouse cancer death rates MCDR ~ 0 for t<D and MCDR~ K for t>D where K is the maximum observed death rate for each form of cancer and mouse strain and D is the mouse age at which the plot Integral MCDR vs. age (t) intercepts with the x-axis. The simple "delay + constant cancer death rate" observation obtained for multiple rodent strains used in the National Toxicology Program control (untreated) groups. TUsing the reasoning of Armitage and Doll(1957) these data analyzed in this way suggests a single oncomutational event is necessary and sufficient for rodent carcinogenesis and the maximum rate, K, would depend on the number of oncomutations per mouse x time.

This approach is believed to be original with the reviewer but is shared freely with the authors and BioMed Central readers should this paper be published.

The discussion of mismatch repair phenotype and cancer death rates suffers from another
widespread but, to my knowledge, untested hypothesis that the phenotypic change related to MMR\(^{-}\)-
genotypes is expressed through higher mutation rates and not through some other related
phenotype. Insofar as MMR mutants can be selected in bacterial or human cell cultures by
resistance to killing by some methylating agents, I do not think it prudent to assume that the mutator
phenotype created in humans from MMR gene heterozygotes is in fact the cause of the peculiar
colonic tumors of Lynch syndrome (HNPCC).
The authors hold out the possibility that the preferred form of analysis may provide mechanistic
information but in fact they correlate microsatellite instability measurements with their derived "rate"
parameter. If there were evidence relating microsatellite change rates with any known murine
oncomutation this might prove interesting but I am unaware of such evidence nor is any cited.

In brief, I do not believe the authors have achieved their laudable goal and have not added to the
value of mathematical models to analyze age-specific cancer rates in humans or experimental
animals.

Major Compulsory Revisions (that the author must respond to before a decision on publication can
be reached)

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the
author can be trusted to correct)

Discretionary Revisions (which the author can choose to ignore)

What next?: Reject because scientifically unsound

Level of interest: An article of insufficient interest to warrant publication in a scientific/medical
journal

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:

I have received notification of allowance for a patent that uses age-specific allelic decline to identify
unknown genes in the human genome that carry inherited alleles placing an individual at genetic risk
for a particular form of cancer. These claims are based on analyses of age-specific cancer mortality
rates not unrelated to the effort attempted by the authors, e.g. Tomita-Mitchell et al. (1998)
Otherwise, I declare I have no other competing interests.