Fractal Geometry and Nonlinear Analysis in Medicine and Biology

Research Article ISSN: 2058-9506

Age-specific incidence of malignancy in relation to the epigenetic model of cancer progression

Patrick A Riley

Totteridge Institute for Advanced Studies, The Grange, Grange Avenue, London N20 8AB, UK

Abstract

Numerical and analytic calculations of the per cell probability of undergoing malignant transformation utilising realistic estimates of mutation frequencies are shown to be consistent with the proposal that the initiating event of carcinogenesis is the result of mutations causing defective vertical transmission of epigenetic gene silencing and that carcinogenic progression embodies multiple genetic derangements resulting from this, suggesting that the Epigenetic Theory of Cancer Progression provides a satisfactory explanation for the observed hypermutability of malignant tumours.

Introduction

Among the major factors that determine the incidence of cancer are the size of the cell population at risk, the number of genes involved in generating the characteristics of malignant transformation, and the relevant mutation rate. Generally the recorded cancer incidence rates in humans accord with an approximately sixth power of age suggesting that six independent mutational events are necessary to bring about malignancy, *i.e.* six genes need to be affected. This poses a problem because estimates of the average mutation rate in humans is in the range 10^{-6} per gene per year which underestimates by several orders of magnitude the probability of a normal cell undergoing transformation to a malignant cell, a difficulty that has been appreciated for a long time [1]. Clearly a solution to the dilemma is to postulate that carcinogenesis involves a raised mutation rate, and hypermutability has been suggested by a number of authors [2-6].

Two-stage carcinogenesis

The basic idea is consistent with the accepted pathological division of carcinogenesis into two phases respectively known as initiation and progression [7], in which the initiating events occur against a background of normal mutation probability and the progression involves an enhanced mutation rate. This Two-Stage Model of carcinogenesis is eminently compatible with the recent proposal that the second (progression) phase is due to epigenetic failure to retain the pattern of gene silencing when a differentiated cell divides [8]. In this scenario, initiation involves the mutation of genes instrumental in accurately duplicating the epigenetic gene silencing patterns. Damage to these genes results in the failure of fidelity of vertical inheritance of gene silencing with the development of progressive clonal aberration.

This proposal is entirely consistent with what is currently known about the gene silencing mechanism which involves DNA methylation and chromosomal structure [9]. As anticipated if the initiation process causes derangement of the gene silencing pattern, DNA methylation defects have been reported in most (if not in all) cancers [10,11]. Moreover, progression is associated with chromosomal instability and abnormal gene expression [12], and these facets are crucial anomalies that comprise cytologically diagnostic features of malignancy. Furthermore, if the abnormal characteristics of cancer cells are the result of the anomalous expression of normal gene products the affected cells will not present novel antigenic markers and hence fail to elicit an immune response. Another advantage of the epigenetic theory of progression is that, since it relies on the vertical transmission of genetic information, this phase will not take place in non-dividing cells, thus accounting for the absence of primary cancers in non-proliferative tissues like the central nervous system.

The model

The basis of the model is that carcinogenesis is viewed as taking place in two stages: (1) Initiation due to mutation of genes involved in the fidelity of vertical transmission of epigenetic pattern; and (2) Progression due to defective epigenetic inheritance by the affected clone with resultant chromatin abnormalities and inappropriate gene expression.

In the second phase it is not clear what genes have to be affected or which factors are necessary and sufficient for the expression of the malignant phenotype (such as invasion and metastasis) but, since defective epigenetic transmission will generate divergent clones exhibiting a variety of properties, it is reasonable to assume that the 'effective' mutation rate will be 2 to 3 orders of magnitude greater than that of the initiating mutations.

Numerical model

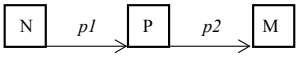
To model this two-stage carcinogenic process we may envisage

Correspondence to: Patrick A Riley, Totteridge Institute for Advanced Studies, The Grange, Grange Avenue, London N20 8AB, UK, **E-mail:** p.riley@ucl.ac.uk

Key words: *Cancer, carcinogenesis, malignancy, mutation, epigenetics, gene silencing, two-stage model, initiation, progression, hypermutability*

Received: September 03, 2015; **Accepted:** October 19, 2015; **Published:** October 23, 2015

successive transfers (*p1* and *p2*) between three compartments: normal (N), initiated pre-malignant (P), and malignant (M) cells:



We can write the expression for the transfer probabilities in terms to take account of the number of genes involved at each stage (*g1* and *g2*), the respective mutation rates (μ_1 and μ_2), and the successive periods of time involved (t_1 and t_2), where the total time is $t = t_1 + t_2$, as follows:

$$p1 = \left[1 - \exp\left(-\mu_1 t_1\right)\right]^{g1}$$
$$p2 = \left[1 - \exp\left(-\mu_2 t_2\right)\right]^{g2}$$

The incidence of malignancy can be inferred from the probability of transfer to the malignant compartment. Solving the successive transfer equations numerically using a computer program utilizing nested loops gives the resulting transfer from normal to malignant (N → M) compartments comparable with the recorded cancer incidence data (assuming a susceptible cell population per person of 10^{15}) if the constants are set at values: $\mu_1 = 10^{-6}$; $\mu_2 = 10^{-3}$; $g1 = 2$; $g2 = 6$ (Figure 1).

Analytic model

An analytic solution can be derived as follows:

On the basis that for small values of the mutation rate (μ):

$$\left[1 - \exp\left(-\mu t\right)\right]^{g} \approx \left(\mu t\right)^{g}$$

The equivalent analytic solution of the two-stage model is obtained by the integral:

$$p_t = \int_0^t \left[\mu_1 \left(t - t_2\right)\right]^{g1} . \left[\mu_2 t_2\right]^{g2} . dt_2$$

which has the general solution:

$$p_t = \mu_1^{g1} . \mu_2^{g2} . t^{(g1+g2+1)} \frac{g1!g2!}{(g1+g2+1)!}$$

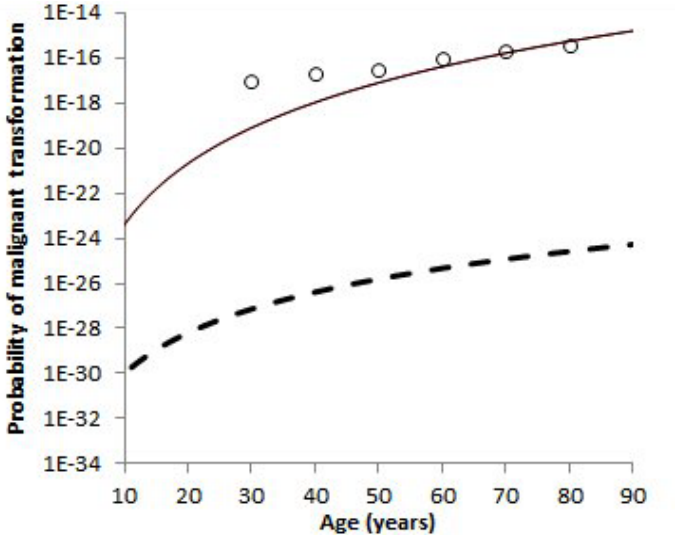


Figure 1. Comparison of single-stage carcinogenesis (interrupted line) and the two-stage model (solid line) with incidence data (○). The ordinate shows the probability of malignant transformation per cell calculated from the clinical data assuming 10^{15} cells at risk per person. The incidence data were obtained from the average age-specific incidence of all cancers, excluding non-melanoma skin cancers, per 100,000 population (UK) 2009-2011, available from the Office for National Statistics (Cancer Statistics: Registrations Series MB1).

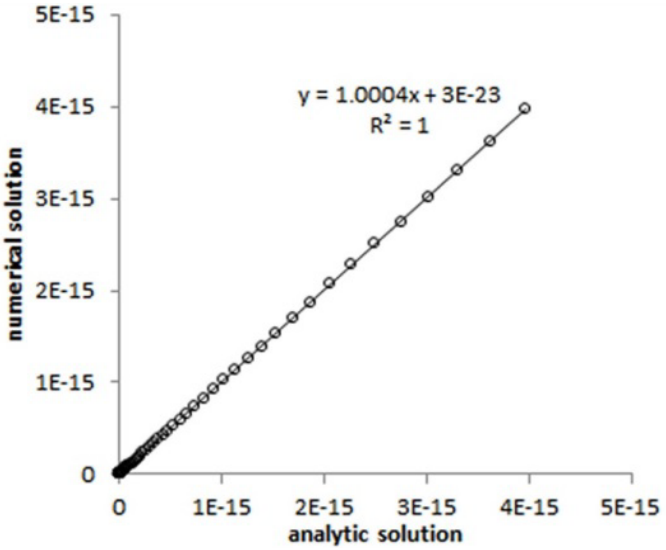


Figure 2. Comparison of results of the numerical and the analytic versions of the two-stage model. The linear trend line data (shown on the graph) show that the results are identical except for a small initial discrepancy.

which gives essentially identical results to those calculated by the numerical model (Figure 2).

Discussion

The Two-stage model is compatible with cancer incidence data although it slightly underestimates the incidence of malignancies in the young age cohort. Part of this is due to the complexity of the disease since different tissues are differentially susceptible and exposed to different relative risk. It is known that childhood cancers and some haematological malignancies manifest special patterns. Also, the model as presented here does not take account of several significant factors such as the normal proliferation rate of the tissue or the effects of clonal expansion. Included among the influences not embraced by the simple treatment advanced here are the effects of variable micro environmental factors such as hormones, nutrient and oxygen supply, etc., the effect of cell death such as the loss of abnormal cells, and the presence of pre-existing mutations in rendering the cells more or less vulnerable to carcinogenesis. Obviously the results of the model will be affected by environmental mutagens which will have the effect of altering the mutation rate influencing initiation, and there are other matters not explicitly covered by the present exposition, in particular the distinction between the age-specific incidence patterns found for different tissues. Examination of incidence data [13] shows that the rates are influenced by such factors as the population size of the cells at risk; for example, the incidence of cancer of the breast in men is much lower than in females which would be accounted for by differences in susceptible cell population size in the region of $N = 10^{11}$ in males compared to 5×10^{12} in females [14]. This is further complicated in women by the reduction in the size of the epithelial cell population at risk of transformation following the withdrawal of hormonal stimulation at the menopause. Also, there is evidence of susceptible individuals in which the intrinsic mutation rate may be higher. This is known to be the case in *xeroderma pigmentosum*, a condition in which skin cells are sensitive to ultraviolet light and the mutation rate in the photosensitive cells is elevated thus raising the incidence of skin cancer in affected individuals [15]. The question of pre-existing

crucial mutations has been mentioned and there is striking evidence of this in the case of retinoblastoma where sporadic incidence requires two mutational events whereas retinoblastoma trait, where one gene is already affected, shows a much higher incidence [16]. Nevertheless, in the human population over 90% of malignancies are carcinomas, and the overall cancer incidence on a world-wide basis [17] follows the general pattern subsumed here.

The calculations presented show that the two-stage model embodying the notion that the enhanced genetic variability of the progression phase is due to defective epigenetic control resulting from the initiating mutations, is consistent with the observed age-specific incidence of human cancer.

Acknowledgements

I am grateful to the late Sir James Lighthill and Professor Joan Walsh for help and encouragement in formulating the general Two-stage model. I thank Professor Giorgio Bianciardi for his kind invitation to submit this paper.

References

1. Hanahan D, Weinberg RA (2000) The hallmarks of cancer. *Cell* 100: 57-70. [Crossref]
2. Loeb LA, Springgate CF, Battula N (1974) Errors in DNA replication as a basis of malignant changes. *Cancer Res* 34: 2311-2321. [Crossref]
3. Riley PA (1982) Is the establishment of a clone exhibiting defective DNA repair the initial stage of carcinogenesis? *Med Hypotheses* 9: 163-168. [Crossref]
4. Riley PA (1990) Is the initial event in carcinogenesis an enhancement of the mutation rate? *Free Radic Res Commun* 11: 59-63. [Crossref]
5. Loeb LA (1997) Transient expression of a mutator phenotype in cancer cells. *Science* 277: 1449-1450. [Crossref]
6. Loeb KR, Loeb LA (2000) Significance of multiple mutations in cancer. *Carcinogenesis* 21: 379-385. [Crossref]
7. Berenblum L (1974) Carcinogenesis as a Biological Problem. New York: Elsevier Press.
8. Riley PA (2014) Failure of fidelity of vertical transmission of epigenetic patterning as the basis of cancer. *Melanoma Res* 24: 424-427. [Crossref]
9. Law JA, Jacobsen SE (2010) Establishing, maintaining and modifying DNA methylation patterns in plants and animals. *Nat Rev Genet* 11: 204-220. [Crossref]
10. Baylin SB, Jones PA (2011) A decade of exploring the cancer epigenome - biological and translational implications. *Nat Rev Cancer* 11: 726-734. [Crossref]
11. Fukushige S, Horii A (2013) DNA methylation in cancer: a gene silencing mechanism and the clinical potential of its biomarkers. *Tohoku J Exp Med* 229: 173-185. [Crossref]
12. Nowell PC (1976) The clonal evolution of tumor cell populations. *Science* 194: 23-28. [Crossref]
13. Doll R, Peto R (1981) The Causes of Cancer. Oxford: Oxford University Press.
14. Riley PA (1989) Biochemical features of malignant cell populations. In: Kotyk A (Ed.), Highlights of Modern Biochemistry 2: 1445-1457.
15. Li L (2007) Nucleotide Excision Repair. In: DNA Repair, Genetic Instability and Cancer. World Scientific Publishing 75-86.
16. Du W, Pogoriler J (2006) Retinoblastoma family genes. *Oncogene* 25: 5190-5200. [Crossref]
17. Parkin DM, Muir CS, Whelan SL, Gao YT, Ferlay J, et al. (1992) Cancer Incidence in Five Continents. Vol. 6. Lyon: IARC Scientific Publications.