Analysis of Relative Risk Factors During Primary and Secondary Stages of Carcinogenesis Causing Growth of a Tumor

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Abstract - The objective of this investigation is to find out the relative risks during the primary and the secondary stages of carcinogenesis while affecting the time of growth of a tumor. This result highlights the effectiveness of treatment during the early stage of cancer than that of the same in the advanced stage by reducing hazard rate or postponing the date of appearance of tumor.

Key Words: Feller-Arley birth and death process, Hazard rate, Relative Risk, Ricatti equation, Two stage carcinogenesis.

Introduction

Moolgavkar and Kundson (1981), evolved two stage model of carcinogenesis. They have given the genesis of Tumor cells initially from Normal stem cells; which under the process of primary proliferation give rise to Normal stem cells as well as Initiated (or Intermediate) cells by mutation. Again, the Initiated cells under the secondary proliferation process give rise to Initiated cells and Tumor cell by mutation. They have further assumed that a Tumor cell will cause malignant tumor with probability one.

Moolgavkar, Dewanji and Venzon (1988) have extended this two stage model into non-homogenous cases. Tan and Singh (1987) have applied the Moolgavkar Knudson two-stage model to assess effects of metabolism of carcinogens on tumor development.

Assuming that the primary proliferation from Normal to Normal and Initiated cells by mutation take place with probability $\alpha_1$ and the secondary proliferation from Initiated cell to Initiated and Tumor cells by mutation occur with probability $\alpha_2$, while the birth and death rates of Normal and Initiated cells are time dependent, the objective of the present paper is to investigate the effect of reduction of $\alpha_1$ and $\alpha_2$ as well as other related time dependent parameters (say $b_1(t)$, $d_1(t)$ being the birth and death rates of Normal stem cells and $b_2(t)$, $d_2(t)$ being corresponding rates for Initiated cells) on the hazard rate or the time of occurrence of a tumor. The motivation of this analysis is to find out to what extent the parameters controlling the growth of the tumor at the primary ($\alpha_1, b_1(t), d_1(t)$) stage is more effective than those in secondary ($\alpha_2, b_2(t), d_2(t)$) stage in reducing hazard rate or postponing the date of appearance of tumor.

Notations and Assumptions

Suppose, $n(t), i(t)$ and $x(t)$ denote the number of Normal stem cells, Initiated cells and Tumor cells at time $t$ respectively. On the line of Tan and Brown (1987), the assumptions for developing the model are:

(i) The organ is well developed by time $t_0$ (the initial time), so $n(0) = n_0$ is very large ($n_0 \approx 10^6$ to $10^9$)

(ii) The birth-death processes and the mutation processes are independent of each other.

(iii) $a_i(t) = a_i, b_i(t) = b_i$ and $d_i(t) = d_i; i = 1,2$ are independent of $t$.

(iv) We denote by

$$P_1(t) = P_1(i_1, i_2, i_3; t) = P[i(t) = i_1, i(t) = i_2, x(t) = i_3]$$

$$P_2(t) = P_2(j_1, j_2; t) = P[i(t) = j_1, x(t) = j_2]$$

$$\psi(t) = \sum_{i_1} \sum_{i_2} \sum_{i_3} x_1^{i_1} x_2^{i_2} x_3^{i_3} P_1(t)$$

and $\varphi(t) = \sum_{j_1} \sum_{j_2} x_1^{j_1} x_2^{j_2} P_2(t)$; where $x_1, x_2$ and $x_3$ are dummy variables.

Models for primary and secondary stages of Carcinogenesis

Under the above conditions Tan (1991) has shown that $\varphi(t)$ satisfies the time dependent non-linear Ricatti equation given by

$$\frac{d}{dt} \varphi(t) = b_2 \varphi^2(t) + [\alpha_2 x_3 - (b_2 + d_2 + \alpha_2)] \varphi(t) + d_2$$

subject to the initial condition $\varphi(0) = x_2$, and $\alpha_2 > 0$ and $b_2 > d_2 > 0$

To solve (1), let $a$ and $b$ with $b$ a real numbers for all $x_3$ such that

$$2b_2b = (b_2 + d_2 + \alpha_2 - \alpha_2 x_3) + g(x_3)$$

$$2b_2a = (b_2 + d_2 + \alpha_2 - \alpha_2 x_3) - g(x_3)$$

and $g(x_3) = [(b_2 + d_2 + \alpha_2 - \alpha_2 x_3)^2 - 4b_2d_2]^{1/2}$

Adding (2) and (3); we obtain

$$2b_2(a + b) = 2(b_2 + d_2 + \alpha_2 - \alpha_2 x_3)$$

$$\alpha_2 x_3 = (b_2 + d_2 + \alpha_2) - b_2(a + b)$$

Multiplying (2) and (3); we obtain

$$2b_2(a + b) = 2(b_2 + d_2 + \alpha_2 - \alpha_2 x_3)$$

$$\alpha_2 x_3 = (b_2 + d_2 + \alpha_2) - b_2(a + b)$$
\[ d_2 = b_2 ab \quad \text{(Using (4))} \]  
\[ \text{Substituting (5) and (6) in (1); we get} \]  
\[ \frac{d}{dt} \varphi(t) = b_2[\varphi(t) - a][\varphi(t) - b] \]  
\[ \frac{d}{dt} \varphi(t) = b_2[\varphi(t) - b + b - a][\varphi(t) - b] \]  
\[ \text{Dividing both sides by } (\varphi(t) - b)^2, \text{ we get} \]  
\[ \frac{1}{(\varphi(t) - b)^2} \frac{d}{dt} \varphi(t) = b_2 + b_2(b - a)(\varphi(t) - b)^{-1} \]  
\[ \text{Put } [\varphi(t) - b]^{-1} = m(t) \text{ in (8); we obtain} \]  
\[ \frac{d}{dt} m(t) + b_2(1 - m(t)) = -b_2 \]  
\[ \Rightarrow \]  
\[ e^{b_2(b-a)t} \frac{d}{dt} m(t) + b_2(b-a)m(t) e^{b_2(b-a)t} = -b_2 b_2 e^{b_2(b-a)t} \]  
\[ \Rightarrow \]  
\[ \frac{d}{dt} m(t) e^{b_2(b-a)t} = -b_2 b_2 e^{b_2(b-a)t} \]  
\[ \Rightarrow \]  
\[ m(t) e^{b_2(b-a)t} = -b_2 \int e^{b_2(b-a)t} dt + C; \]  
where C is constant of integration.  
\[ \text{Initially at } t = 0 \]  
\[ m(0) = [(\varphi(0) - b)^{-1} = (x_2 - b)^{-1} \]  
\[ \Rightarrow \]  
\[ C = (x_2 - b)^{-1} + (b - a)^{-1} \]  
\[ \therefore \]  
\[ m(t) e^{b_2(b-a)t} = (b - a)^{-1} \left( 1 - e^{b_2(b-a)t} (x_2 - b)^{-1} \right) \]  
\[ = \left( [(b - a)(x_2 - b)^{-1} \right) - \left( (x_2 - a) + (b - x_2) e^{b_2(b-a)t} \right) \]  
\[ \Rightarrow \]  
\[ m(t) = \frac{[(b - a)(x_2 - b)^{-1} - (x_2 - a)}{(x_2 - b)^{-1} - (x_2 - a)} \]  
\[ \Rightarrow \]  
\[ \varphi(t) - b]^{-1} = \frac{[(x_2 - a)}{(b - x_2) e^{b_2(b-a)t}} \]  
\[ \Rightarrow \]  
\[ \varphi(t) = b + (b - a)[x_2 - b] e^{b_2(b-a)t} + (b - x_2) e^{b_2(b-a)t} \]  
\[ \Rightarrow \]  
\[ \varphi(t) = b + (x_2 - a) + (b - x_2) e^{b_2(b-a)t} \]  
\[ \Rightarrow \]  
\[ \varphi(t) = \frac{[b(x_2 - a) + (b - x_2) e^{b_2(b-a)t}]}{(x_2 - a)} \]  
\[ \Rightarrow \]  
\[ \varphi(t) = \frac{(b_2 + d_2 + a_2 - x_2 x_3)}{4b_2 d_2} = A \]  
\[ \text{in (2) and (3); we obtain} \]  
\[ a = A-B \]  
\[ b = A+B \]  
\[ \text{Substituting (10) and (11) in (9); we obtain} \]  
\[ \varphi(t) = [(A + B)(x_2 - A + B) + (A - B)(A + B - x_2) e^{2b_2Bt}] \]  
\[ \text{Substituting (10) and (11) in (9); we obtain} \]  
\[ \varphi(t) = [(A + B)(x_2 - A + B) + (A - B)(A + B - x_2) e^{2b_2Bt}] \]  
\[ \text{Under the assumption that Normal stem cells follow a homogenous Feller-Arley birth and death process (a density dependent birth and death process with birth and death parameters } b_j(t) = jb(t); \text{ and } d_j(t) = jd(t); \text{ j being the size of the population at time } t; \text{ with parameters } (b_1, d_1, \alpha_1); \text{ } \psi(t) \text{ satisfies the differential equation} \]  
\[ \frac{d}{dt} \psi(t) = b_1 \psi^2(t) + [\alpha_1 \psi(t) - (b_1 + d_1 + \alpha_1)] \psi(t) + d_1 \]  
\[ \text{Subject to } \psi(0) = x_1 \]  
Also it is shown by Tan (1991) under the assumption that \( n(t) \alpha_1(t) \) is finite for all \( t \geq t_0(=0) \) and that the number of mutations that occur during \( (t, t+\Delta t) \) from Normal stem cells follow a Poisson distribution with parameter \( n(t)\alpha_1(t)\Delta t + 0(\Delta t) \) independently, then  
\[ \psi(t_0, t) = \psi(t) = e^{n(t)\alpha_1(t)\Delta t + 0(\Delta t)} \]  
\[ \text{Put } n(x) = n_0 e^{a_1 x_1} \]  
\[ \psi(t) = e^{n_0 \int \alpha_1 e^{a_1 x_1} \varphi(x) - 1] dx} \]  
\[ \psi(t) = e^{n_0 \int \alpha_1 e^{a_1 x_1} \varphi(x) - 1] dx} \]  
\[ \text{Putting } x_2 = A + B = C \]  
\[ A + B - x_2 = D, A + B = E, A - B = F, 2b_2B = G, \]  
\[ \text{in equation (15) with } x_2 = 1 \text{ and } x_0 = 0, \text{ we obtain} \]  
\[ \psi(t) = \psi(1; t) \]  
\[ = e^{n_0 \int \left( \frac{E_{C+D}G^{t-1} - E_{C+D}G^t F_{C+D}G\alpha_1 t - C+D^2 G^{t-1}}{C+D^2 G^t} \right)} \]  
\[ \text{Differentiating (15) with respect to } t \text{ and putting } x_2 = 1 \text{ and } x_3 = 0; \text{ we obtain} \]  
\[ \psi(1; t) = e^{n_0 \left( \frac{E_{C+D}G^{t-1} - E_{C+D}G^t F_{C+D}G\alpha_1 t - C+D^2 G^{t-1}}{C+D^2 G^t} \right) X} \]  
\[ \text{Suppose } \lambda(t) \text{ denotes the hazard rate of growth of tumor given } n_0 \text{Normal stem cells at } t_o(=0) \text{ then} \]  
\[ \lambda(t) = \frac{\psi(1; t)}{\psi(0; t)} \]
\[= -n_o \left[ \frac{C e^{a_1 t} (E-1) [C x_1 + D e^{G t} (a_1 - G)]}{(C + D e^{G t})^2} \right] \]

For \(x_2 = 1, x_3 = 0;\)
\(E - 1 = D, F - 1 = C, H - G = \alpha_1, E - F = 2B\)

Substituting (21) in (20); we obtain
\[\lambda(t) = -n_o \left[ \frac{C D e^{a_1 t} [C x_1 + D e^{G t} (a_1 - G)]}{(C + D e^{G t})^2} \right] \]
\[+ C D e^{(G+a_2) t} [C (a_1 + G)] + D e^{G t} a_1 \]
\[+ 2 B C D G e^{G t} \] + \(C + D e^{G t})^2 \]

Let \(T\) be the time to tumor starting with \(n_o\) Normal stem cells at time \(t_0\) (suppose \(t_0 = 0\)). The probability distribution of \(T\) is given by
\[h_T(t) = \lambda(t) e^{-\int_0^t \lambda(t) dt}, t \geq 0 \]
\[= 0, \text{ otherwise} \]

Some special cases for verification of the result
we should have
\[\hat{\lambda}(t) = 0 \text{ for } \alpha_1 = 0 \]
\[\hat{\lambda}(t) = 0 \text{ for } t = 0 \]
and \(\lambda(t) = 0 \text{ for } b_2 = 0, a_2 = 0, \alpha_2 = 0\)

Case I: When \(\alpha_1 = 0\)
\[\hat{\lambda}(t) = \frac{n_o \left[ C D e^{a_1 t} (C x_1 + D e^{G t} (a_1 - G)) \right]}{(C + D e^{G t})^2} \]
Since, \(D + C - 2B = A + B - 1 + A + B - 2B = 0\)
Therefore \(\alpha_1 = 0 \Rightarrow \lambda(t) = 0\)

Which should be the case as the hazard rate should tend to zero when \(\alpha_1 = 0\)

Case II: When \(t = 0\)
\[\hat{\lambda}(t) = \hat{\lambda}(0) = 0 \text{ verifies the result for } t = 0 \]

Case III: When \(b_2 = 0\)
\[\Rightarrow a_2 = 0, \alpha_2 = 0 \]
\[\Rightarrow A = 1, B = 1, C = 1, D = 1, \text{ and } G = 0 \]
\[\Rightarrow e^{Gt} = 1 \]
\[\Rightarrow e^{(G+a_1)t} = e^{a_1 t} \]
\[\therefore \hat{\lambda}(t) = \frac{n_o \left[ e^{a_1 t} (a_1 + \alpha_1) - e^{a_1 t} (a_1 + \alpha_2) + 0 \right]}{(C + D e^{G t})^2} \]
\[= 0 \]

Numerical Illustration
Assuming \(b_2 > d_2\) and \(\alpha_1\) and \(\alpha_2\) being very small \((\alpha_1, \alpha_2 \approx 10^{-4} \text{ to } 10^{-8})\) which is true in most of the cases and further for satisfying the assumption that \(n_0 \alpha_1\) is finite, \(n_0\) should be very large \((n_0 \approx 10^6 \text{ to } 10^9)\).

Let us discuss a particular situation with \(b_2 = .05\) and \(d_2 = .01\). Suppose \(\alpha_1 = \alpha_2 = .000001\) is one situation naming it as standard situation. Now, we have two experimental situations for comparing the Relative Risks under 10% increase of \(\alpha_1\) and \(\alpha_2\) respectively for different \(t\).

Denoting the hazard rate of growth of tumor in the standard situation (i.e. \(\alpha_1 = \alpha_2 = .000001, b_2 = .05, d_2 = .01\)) at time \(t\) by \(\lambda_s(t)\). Further suppose \(\lambda_1(t)\) and \(\lambda_2(t)\) denote the hazard rates under 10% increase of \(\alpha_1\) and \(\alpha_2\) over standard situation respectively. The variations in hazard rates over \(t\) in the above three situations are exhibited in table I.

### Table I: Hazards rates over \(t\) with 10% increase in \(\alpha_1\) and \(\alpha_2\) respectively

| time \(t\) | \(b_2\) = 0.05, \(d_2\) = 0.01 |
|------------|-------------------------------|
| \(\lambda_1(t)\) | \(\lambda_2(t)\) | \(\lambda_s(t)\) |
| \((\alpha_1 = 0.000001)\) | \((\alpha_2 = 0.000001)\) | \((\alpha_1 = 0.000001, \alpha_2 = 0.000001)\) |
| 1 | \(n_0(1.2967 \times 10^{-12})\) | \(n_0(1.9061 \times 10^{-12})\) | \(n_0(2.4841 \times 10^{-12})\) |
| 2 | \(n_0(3.7715 \times 10^{-12})\) | \(n_0(4.396 \times 10^{-12})\) | \(n_0(4.5933 \times 10^{-12})\) |
| 3 | \(n_0(5.7807 \times 10^{-12})\) | \(n_0(6.4057 \times 10^{-12})\) | \(n_0(6.615 \times 10^{-12})\) |
| 4 | \(n_0(7.962 \times 10^{-12})\) | \(n_0(8.4211 \times 10^{-12})\) | \(n_0(8.73508 \times 10^{-12})\) |
| 5 | \(n_0(11.1389 \times 10^{-12})\) | \(n_0(12.03 \times 10^{-12})\) | \(n_0(12.233 \times 10^{-12})\) |
| 10 | \(n_0(26.84 \times 10^{-12})\) | \(n_0(28.028 \times 10^{-12})\) | \(n_0(28.9028 \times 10^{-12})\) |

Suppose \(\hat{\lambda}_1(t) = \frac{\lambda_1(t)}{\lambda_s(t)}\) denotes the estimates of Relative Risk at time \(t\) because of increasing \(\alpha_1\) by 10%.

and \(\hat{\lambda}_2(t) = \frac{\lambda_2(t)}{\lambda_s(t)}\) denotes the estimates of Relative Risk at time \(t\) because of increasing \(\alpha_2\) by 10%.

The behaviour of relative risks over time in above two cases is exhibited in table II.

### Table II: Relative Risks under 10% increase in \(\alpha_1\) and \(\alpha_2\) respectively for different \(t\)

| \(t\) | \(b_2 = .05, d_2 = .01\) |
|------|-----------------|
| 1 | \(RR_1(t)\) | \(RR_2(t)\) |
| 1.469962 | 1.915709 |
## Conclusion

The findings of the table I and table II clearly show that controlling the primary stage proliferation from Normal to Normal and Initiated cells by mutation is more effective in controlling the growth of tumor than controlling the secondary stage proliferation from Initiated to Initiated and Tumor cells by mutation. It may be seen that with increase of $t$ both $RR_1(t)$ and $RR_2(t)$ tend to unity which is quite plausible; because malignant tumor is 100% fatal by assumption, although the relative difference between $RR_2(t)$ and $RR_1(t)$ is maintained (i.e. $RR_2(t) > RR_1(t)$ for all finite $t$).

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