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TECHNIQUE OF ANALYSING THE EFFECT OF RELATIVE RISK FACTORS IN THE DEVELOPMENT OF A TUMOR UNDER THE HYPOTHESIS OF IMMORTALISATION OF NORMAL STEM CELLS

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***Abstract*:** The objective of this investigation is to find out the extent to which the parameters controlling the growth of a tumor at two stages are effective in reducing the hazard rate under the assumption of immortalisation of Normal stem cells. It has been shown that the reduction in primary proliferations (Normal to Normal and Initiated cells my mutation) will be more effective in reducing the Relative Risk of cancer than that of secondary proliferation (Initiated to Initiated and Tumor cells).

***Index Terms*: Hazard rate, Initiated cells, Normal stem cells, Relative risk.**

I. INTRODUCTION

Mackillop et al. (1983) and Buick and Pollak (1984) have supported the idea of assuming the immortalization of Normal stem cells for obtaining the hazard rate of growth of tumor. It has been assumed that a cancer tumor develops from a single Normal stem cell in two stages as given by Moolgavkar and Knudson (1981).

Jha (2021) showed 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. Assuming that α_1 and α_2 are primary proliferation (Normal to Normal and Initiated cells by mutation) and secondary proliferation (Initiated to Initiated and Tumor cells by mutation) parameters respectively. $b_1(t)$ and $b_2(t)$ are birth rates of Normal and Initiated cells respectively and $d_1(t)$ is the death rate of Normal stem cells. Here $d_2(t)$ (death rate of Initiated cells) is zero because of assumption of immortalization of Normal stem cells. The motivation is to find out to what extent the parameters controlling the growth of the tumor at two stages are effective in reducing hazard rate or postponing the date of appearance of tumor.

II. METHODOLOGY

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). Following Jha (2021), the assumptions for developing the model are as follows:

(i) The organ is well developed by time t_o (the initial time), so n(o) = n_o (say) is very large ($n_o \cong 10^6$ to 10^9).

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

(iii) $b_i(t) = b_i,\ d_1(t) = d_1$ and $d_2(t) = 0;\ i = 1, 2.$

(iv) The Tumor cell causes malignant tumor with probability one, and the time period for the development of a clinically detectable tumor from a Tumor cell is short relative to the time for the transformation process of Normal stem cells into Tumor cells.

(v) We denote by

$$P_1(t) = P[n(t) = i_1,\ i(t) = i_2,\ x(t) = i_3 \mid n(0) = n_o, i(0) = x(0) = 0]$$

$$P_2(t) = P[i(t) = j_1,\ x(t) = j_2 \mid i(0) = 1,\ x(0) = 0]$$

and the corresponding p.g.f. are

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

and $\phi(t) = \sum_{j_1} \sum_{j_2} x_2^{\ j_1}\, x_3^{\ j2} P_2(t),$

where, x_1, x_2 and x_3 are dummy variables.

Models for Primary and Secondary stage of carcinogenesis when $d_2(t) = 0$:

In developing two-stage stochastic models of carcinogenesis under immortalization of Normal stem cells, the Ricatti equation as described by Tan (1991) for solving $\phi(t)$ is given by

$$\frac{d}{dt}\phi(t) = b_2\phi^2(t) + [\alpha_2 x_3 - (b_2 + \alpha_2)]\phi(t) \qquad (1)$$

Putting $(b_2 + \alpha_2) - \alpha_2\, x_3 = k$ in equation (1), we obtain (2)

$$\frac{d}{dt}\phi(t) = b_2\phi^2(t) - k\phi(t)$$

$$\Rightarrow \quad \frac{d}{dt}\phi(t) + k\phi(t) = b_2\phi^2(t)$$

$$\Rightarrow \quad \frac{1}{\phi^2(t)}\frac{d}{dt}\phi(t) + k[\phi(t)]^{-1} = b_2 \qquad (3)$$

Putting $\frac{1}{\phi(t)} = Z$ in (3), we obtain;

$$-\frac{dZ}{dt} + kZ = b_2$$

$$\Rightarrow \quad \frac{dZ}{dt} - kZ = -b_2$$

$$\Rightarrow \quad \frac{d}{dt}(Ze^{-kt}) = -b_2 e^{-kt} \tag{4}$$

Integrating (4), we obtain;

$$Ze^{-kt} = \frac{b_2 e^{-kt}}{k} + C \tag{5}$$

where, C is the constant of integration.

Initially, i.e. at t = 0,

$$Z = \frac{1}{\phi(0)} = \frac{1}{x_2} \tag{6}$$

Substituting (6) in (5), we obtain

$$C = \frac{1}{x_2} - \frac{b_2}{k}$$

Substituting the value of C in (5), we obtain;

$$Ze^{-kt} = \frac{b_2}{k} e^{-kt} + \frac{1}{x_2} - \frac{b_2}{k}$$

$$\Rightarrow \quad Z = \frac{b_2}{k} + \frac{e^{kt}}{x_2} - \frac{b_2}{k} e^{kt}$$

$$\Rightarrow \quad \phi(t) = [\frac{b_2}{k} + \frac{e^{kt}}{x_2} - \frac{b_2}{k} e^{kt}]^{-1} \tag{7}$$

Differentiating (7) w.r.t. t, we obtain;

$$\phi^1(t) = -[\frac{b_2}{k} + \frac{e^{kt}}{x_2} - \frac{b_2}{k} e^{kt}]^{-2} \ [\frac{ke^{kt}}{x_2} - b_2 e^{kt}] \tag{8}$$

The hazard rate of growth of tumor vide Tan (1999)

$$\hat{\lambda}(t) = -\frac{\psi^1(1,0;t)}{\psi(1,0;t)} \tag{9}$$

where, $\psi(t) = e^{n_0[\phi(t)-1][e^{\alpha_1 t}-1]}$ (10)

Differentiating $\psi(t)$, we obtain;

$$\psi^1(t) = e^{n_0[\phi(t)-1][e^{\alpha_1 t}-1]} n_o[\phi^1(t)\{e^{\alpha_1 t}-1\} + \{\phi(t)-1\}\alpha_1 e^{\alpha_1 t}] \quad (11)$$

$\psi(1,0;t)$ and $\psi^1(1,0;t)$ are obtained by putting $(x_2 = 1$ and $x_3 = 0)$ in equations (10) and (11) respectively. Under the immortalization of Normal stem cells (i.e. when $d_2 = 0$), $\phi(t) \cong \phi(1,0;t)$ and $\phi^1(t) \cong \phi^1(1,0;t)$ are given by equations (7) and (8) respectively.

Therefore, we have;

$$\hat{\lambda}(t) = -n_0[\phi^1(1,0;t)\{e^{\alpha_1 t}-1\} + \{\phi(1,0;t)-1\}\ \alpha_1\ e^{\alpha_1 t}] \quad (12)$$

where,

$$\phi(1,0;t) = [\frac{b_2}{b_2+\alpha_2} + e^{(b_2+\alpha_2)t} - \frac{b_2}{b_2+\alpha_2} e^{(b_2+\alpha_2)t}]^{-1} \quad (13)$$

and

$$\phi^1(1,0;t) = -[\frac{b_2}{b_2+\alpha_2} + e^{(b_2+\alpha_2)t} - \frac{b_2}{b_2+\alpha_2} e^{(b_2+\alpha_2 t)}]\ \alpha_2 e^{(b_2+\alpha_2)t} \quad (14)$$

are obtained by putting $x_2 = 1$ and $x_3 = 0$ in (7) and (8) and using (2).

We consider some special cases for verification of the result:

We should have

$\hat{\lambda}(t) = 0$ for $\alpha_1 = 0$

$\hat{\lambda}(t) = 0$ and $t = 0$

$\hat{\lambda}(t) = 0$ for $\alpha_2 = 0$

Case I: When, $\alpha_1 = 0$

(12) gives, $\hat{\lambda}(t) = -n_0[\phi^1(1,o;t) \times 0 + \{\phi(1,o;t)-1\} \times 0]$ (15)

$= 0$

Case II: When t = 0

$\phi(1, 0; t) = 1$ and $e^{\alpha_1 t} - 1 = 0$

$\Rightarrow \quad \hat{\lambda}(t) = 0$ (16)

Case III: When $\alpha_2 = 0 \Rightarrow \phi(1,0,t) = 1$ and $\phi^1(1,0,t) = 0$

$\Rightarrow \quad \hat{\lambda}(t) = 0$ (17)

Therefore, the result (12) is verified for all the three special cases.

III. NUMERICAL ILLUSTRATION

Let us discuss a particular case with $b_2 = 0.05$. Suppose $\alpha_1 = \alpha_2 = 0.000001$ is one situation naming it as standard situation. Now, we have two experimental situations for comparing the Relative Risks under 10% increase of α_1 and α_2 respectively for different t. Denote, the hazard rate of growth of tumor in the standard situation (i.e. $b_2 = 0.05,\ d_2 = 0.00,\ \alpha_1 = 0.000001 = \alpha_2$)) at time *t* by $\lambda_{10}(t)$. Further suppose $\lambda_{20}(t)$ and $\lambda_{30}(t)$ denote the hazard rates under 10% increase of α_1 and α_2 over standard situation respectively. The variations in hazard rates over t in the above three situations are exhibited in the table 1.

Table 1: Hazard rates over t with 10% increase in α_1 and α_2 respectively

Time (t)	$b_2 = 0.05$		
	$\hat{\lambda}_{10}(t)$	$\hat{\lambda}_{20}(t)$	$\hat{\lambda}_{30}(t)$
1	$n_0(2.15126\times10^{-12})$	$n_0(2.36638\times10^{-12})$	$n_0(2.3564\times10^{-12})$
2	$n_0(4.310324\times10^{-12})$	$n_0(4.741355\times10^{-12})$	$n_0(4.801375\times10^{-12})$
3	$n_0(6.7855\times10^{-12})$	$n_0(7.464042\times10^{-12})$	$n_0(7.43413\times10^{-12})$
4	$n_0(9.385598\times10^{-12})$	$n_0(10.324132\times10^{-12})$	$n_0(10.27416\times10^{-12})$
5	$n_0(12.120109\times10^{-12})$	$n_0(13.332084\times10^{-12})$	$n_0(13.362122\times10^{-12})$
10	$n_0(29.487\times10^{-12})$	$n_0(32.435657\times10^{-12})$	$n_0(32.435743\times10^{-12})$

Suppose, $\hat{RR}_{10}(t) = \dfrac{\hat{\lambda}_{20}(t)}{\hat{\lambda}_{10}(t)}$ denotes the estimates of Relative Risk at time t because of increasing α_1 by 10% and

$\hat{RR}_{20}(t) = \dfrac{\hat{\lambda}_{30}(t)}{\hat{\lambda}_{10}(t)}$ denotes the estimates of Relative Risk at time t because of increasing α_2 by 10%.

The behaviour of Relative Risks over time in above two cases is exhibited in Table 2.

Table 2: Relative Risk under 10% increase of α_1 and α_2 respectively for different t

t	$\hat{RR}_{10}(t)$	$\hat{RR}_{20}(t)$
1	1.099997	1.095358
2	1.100002	1.113924
3	1.099998	1.095591
4	1.099997	1.098673
5	1.099997	1.102475
10	1.099999	1.100002

IV. CONCLUSION

The findings of the table 2 clearly show that in the case of immortalisation of Normal stem cells, controlling the primary stage proliferation from Normal to Normal and Initiated cells by mutation or controlling the secondary stage proliferation from Initiated to Initiated and Tumor cells by mutation is equally effective in controlling the growth of tumor over time. It may be seen that there is no effect of time on the Relative Risk in the case of immortalisation of Normal stem cells (i.e. $d_2 = 0$). Although the result shows that under the hypothesis of immortality of Normal stem cells relative changes in α_1 and α_2 produce equal Relative Risk; but the reduction of α_1 will be more effective in reducing the Relative Risk than that of α_2 because by reducing α_1 the proportion of Initiated cells are reduced which is instrumental to reducing Tumor cells ultimately.

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