

An examination of radiation hormesis mechanisms using a multi-stage carcinogenesis model

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Introduction

Tumour-reducing, bio-positive effects of low doses of ionising radiation have been discussed in a controversial manner for many decades. Feinendegen, Pollycove and colleagues have proposed several concepts that may give rise to hormesis effects. One key aspect of their hormesis concept is based on the idea that the radiologically induction of cellular defence mechanisms, such as DNA repair and radical scavenging, may reduce the harmful effects of endogenous DNA damage. We have used a multi-stage cancer model to conduct a series of sensitivity studies. The results of these sensitivity studies have been used to help identify critical model inputs and to help define the shapes of the cumulative lung cancer incidence curves that may arise when dose and dose rate dependent cellular defence mechanisms are incorporated into a multi-stage cancer model.

Methods

The model comprises the main stages of carcinogenesis: initiation, clonal expansion of initiated cells, malignant transformation and a lag time, t_0 , of tumour formation. Rate constant k describes the induction of genomic instability in State 0 and State 1

$$k = \Omega \sum_i \varphi_i (\Sigma_i^{endo} + \Sigma_i^{rad} \dot{D})$$

Σ_i^{endo} expected number of i th type (simple or complex) lesion created by endogenous processes ($\text{cell}^{-1} \text{ year}^{-1}$)

Σ_i^{rad} expected number of i th type lesion created by radiation ($\text{mGy}^{-1} \text{ cell}^{-1}$)

\dot{D} dose rate (mGy yr^{-1})

φ_i probability the i th type of lesion is misrepaired

Ω probability that a mutation formed at a random location in the DNA

induces genomic instability by modifying the expression or function of a critical gene.

Rate constant k_{mt} was assumed to be independent of dose and dose rate.

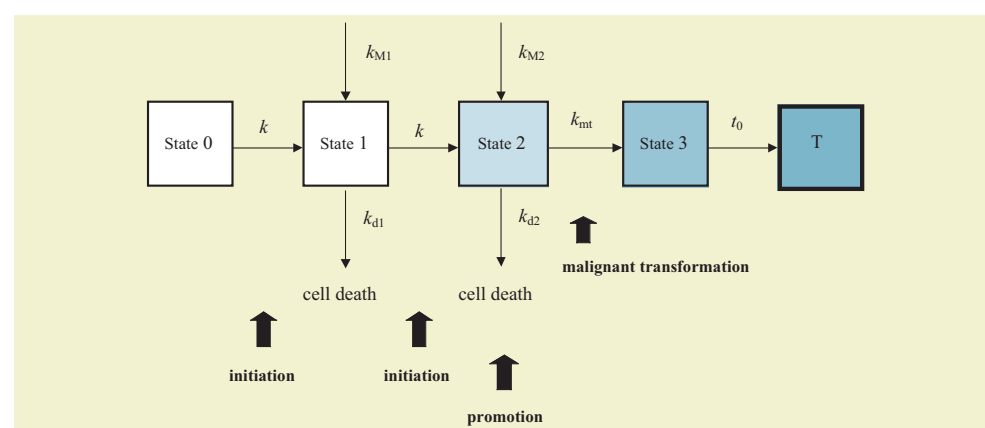


Figure 1. Cells in State 0 are normal somatic (stem) cells. State 0 cells require three critical mutational events to transition to a fully malignant state (State 3). Once transformed (initiated), cells cannot return to a normal (undamaged) state.

To incorporate adaptive protection into the model, k is rewritten as

$$k = \frac{\Omega}{D(D)} \sum_i \varphi_i (\Sigma_i^{endo} / F(D) + \Sigma_i^{rad} \dot{D}) \quad \text{with}$$

$$F(\dot{D}) = A_f \left\{ 1 + B_f \exp \left[-C_f \left(\dot{D} - \dot{D}_f \right)^2 \right] \right\}$$

$$G(\dot{D}) = A_g \left\{ 1 + B_g \exp \left[-C_g \left(\dot{D} - \dot{D}_g \right)^2 \right] \right\}$$

$G_i(\dot{D})$ and $F_i(\dot{D})$ account for changes in the φ_i as a function of dose rate and for changes in the radical scavenging capacity of a cell, respectively. $\dot{D}_f = \dot{D}_g = 2.67 \text{ mGy yr}^{-1}$, the background dose rate in the U.S. $A_p, B_p, C_p, A_g, B_g,$ and C_g are adjustable parameters. Their values were gained by producing functions as given in Figure 2.

To obtain estimates for Ω , other model inputs were set *a priori* to the best estimate values gained from the literature. Then, Ω was adjusted so that the cumulative lung cancer incidence rate for the 75 mGy and 1 Gy were consistent with the values reported by the ICRP.

Acknowledgements

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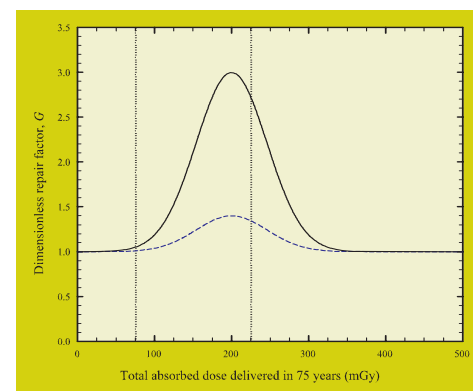


Figure 2. Representative examples of the dimensionless DNA repair function, $G(D)$. The vertical dotted lines indicate the typical dose range expected from naturally occurring radiation sources, i.e., background radiation. The lower dose bound is set at 75 mGy (1 mGy yr^{-1}), and the upper dose bound is set at 225 mGy (3 mGy yr^{-1}).

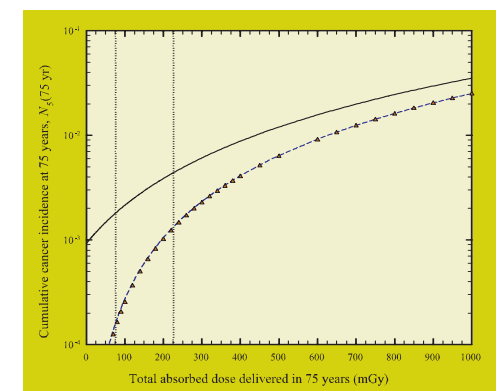


Figure 3. Contribution to cumulative lung cancer incidence of DNA damage formed by endogenous processes and ionizing radiation. Radiation hormesis effects are not included in this set of calculations ($A_f = A_g = 1$ and $B_f = B_g = 0$). Solid line: DNA damage formed by ionizing radiation and endogenous processes. Dashed line: endogenous processes create simple damages but not complex damages ($\Sigma_{cl}^{endo} = 0$). Triangle: $\Sigma_{cl}^{endo} = \Sigma_{sl}^{endo} = 0$.

Results

Figure 3 shows the model-predicted cumulative lung-cancer incidence level with and without the endogenous DNA damage terms (i.e., $\Sigma_{cl}^{endo} = 0$ and $\Sigma_{sl}^{endo} = 0$). Figure 4 illustrates the effects that radiation-induced adaptations in DNA damage repair (left panel) and radical scavenging (right panel) may have on the cumulative incidence of lung cancer. For all of the studies shown in Figure 4, F and G reach a maximum at 200 mGy (i.e., the dose that corresponds to $\dot{D}_f = \dot{D}_g = 2.67 \text{ mGy yr}^{-1}$). Figure 5 shows the combined effects of cellular adaptations in radical scavenging and DNA repair processes.

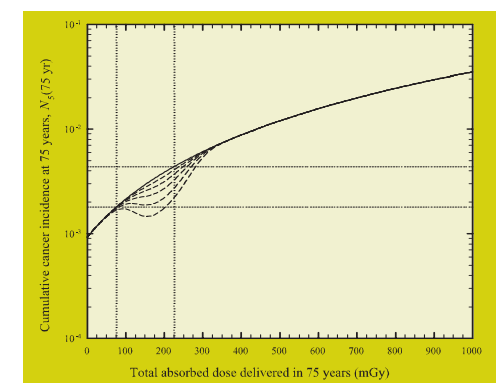
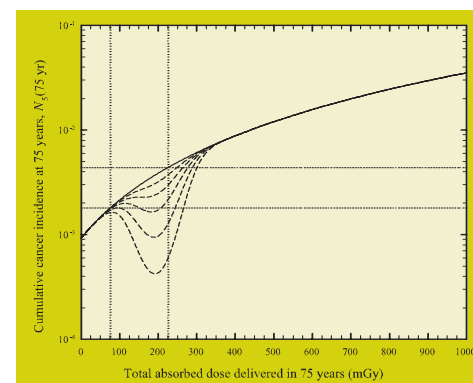


Figure 4. Effects of cellular adaptations in DNA repair and enzymatic radical scavenging. Solid line: no radiation hormesis effects. Dashed lines show the effects of selecting parameters that give peak values for F and G in the range from 1.1 to 5 (refer to Figure 2). Left panel: effects of cellular adaptations in DNA repair ($F = 1$ and $1.1 \leq G \leq 5$). Right panel: effects of cellular adaptations in enzymatic radical scavenging ($1.1 \leq F \leq 5$ and $G = 1$).

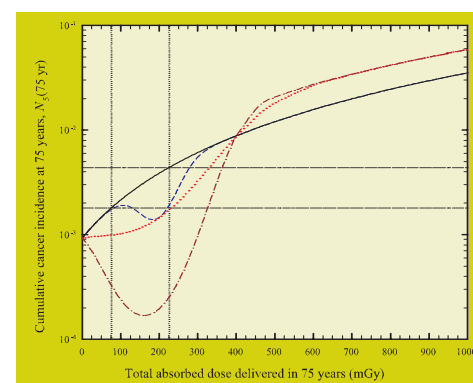


Figure 5. Solid line: no radiation hormesis effects. Dashed line: effects of radical scavenging and DNA repair (F and G in the range from 1 to 1.4). Dotted line: combined effects of radical scavenging and DNA repair (F and G in the range from 0.8 to 1.4). Dash-Dotted line: combined effects of radical scavenging and DNA repair (F and G in the range from 0.8 to 3).

Conclusions

- For dose levels comparable to background radiation, endogenous DNA damage may account for 70 - 90% of the predicted cancers. For a lifetime dose of 1 Gy, endogenous processes may account for as much as 30% of the predicted cancers.
- These predictions are sensitive to the rate at which double strand breaks and other multiply damaged sites are created by endogenous processes (Σ_{cl}^{endo} parameter). Predictions are insensitive to Σ_{sl}^{endo} .
- Additional research is required to determine if and to what extent endogenous processes can create complex DNA damages.
- In the current model, U-shaped curves are only produced when both the accuracy of DNA repair and the capacity for radical scavenging are enhanced 3 fold.

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