Analele Universităţii de Vest din Timişoara
Vol. LI, 2007
Seria Fizică

THE IMPACT OF NON-TARGETED CELLULAR EFFECTS INDUCED BY LOW EXPOSURES OF IONIZING RADIATION ON LUNG CANCER RISK

Lucia-Adina Truta-Popa[1], Werner Hofmann[2], Constantin Cosma[1]

[1] *Faculty of Environmental Sciences, Babes-Bolyai University, 400192 Cluj-Napoca, Romania*
[2] *Division of Physics and Biophysics, Department of Materials Engineering and Physics, University of Salzburg, 5020 Salzburg, Austria*

Abstract
The objective of this study was to investigate the effect of non-targeted cellular mechanisms on the shape of the lung cancer risk function at low, chronic exposure, relative to the targeted effects induced by alpha particles. The biological endpoint studied in this paper was oncogenic transformation, assumed to be a fundamental step in the induction of carcinogenesis.
An initiation-promotion model was proposed for the assessment of lung cancer risk due to the targeted cellular effects. In general, non-targeted effects such as genomic instability and bystander effects amplify the biological effectiveness of a given radiation dose by actually increasing the number of cells affected, in comparison to the number of cells directly irradiated. On the other hand, mechanisms such as induction of apoptosis and adaptive response usually decrease the risk values and thus could be regarded as defense mechanisms against oncogenesis.
The non-targeted effects modifying the initial response at the cellular level that will be more thoroughly studied in this paper are genomic instability and induction of apoptosis by surrounding cells.
Keywords: lung cancer, low doses, radon, genomic instability, induction of apoptosis.

1. Introduction

Before the newly observed non-targeted cellular effects were considered, mathematical models that assumed cells have sensitive targets that could be "hit" and therefore damaged by radiation, were used to quantify radiation effects, although the mechanisms implied in damaging the targets were not fully known [1]. This study presents such an initiation-promotion (IP) model, which considers the number of hits in the assessment of lung cancer risk induced by radon when quantifying the damage directly induced by the deposition of energy in the irradiated cell, but also incorporates non-targeted effects, such as genomic instability and induction of apoptosis. Almost all human tumors show non-targeted effects, i.e. genomic instability, [2] manifested as a diverse set of biological endpoints including cellular transformation [3]. The impact of the indirect radiation induced mechanisms on oncogenic transformation was selected, because there are more quantitative experimental *in vitro* data available for this biological endpoint [4], [5], [6]. The objective of the present study was to explore the role of non-targeted cellular radiation effects on the shape of the dose-

effect curve in the low dose region, i.e. to investigate whether these mechanisms will increase or decrease lung cancer risk at radon exposure levels characteristic of indoor exposures.

2. 1. The Initiation-Promotion Model

In the present initiation-promotion (IP) model, which represents a simplified version of the state-vector-model (SVM) of radiation carcinogenesis [7, 8], lung cancer risk R(D) is expressed as the product of the initiation function I(D) and the promotion function P(D). Initiation and promotion functions were derived from experimentally observed *in vitro* oncogenic transformation TF (D_n) and survival data for C3H 10T1/2 mouse cells exposed to charged particles of varying LET [5, 6] and rat tracheal epithelial (RTE) cells irradiated with ^{241}Am alpha particles [4].

The lung cancer risk R(D) induced by exposure to radon is given by:

$$R(D) = C \cdot \sum_{i=1}^{n} TF(D_n) \cdot \{\lambda_1 + \lambda_2 \cdot p \cdot [1 - \exp(-\gamma \cdot D_n)]\} \cdot P_n$$

where λ_1 is the normal mitotic rate of lung cells, equivalent to a cycle time of 30 days, which may increase to λ_2, the rate of division under conditions of extensive tissue damage and cellular replacement, corresponding to a cycle time of approximately one day, p denotes the probability that a progenitor cell will divide as a direct result of the inactivation of an epithelial target cell [9], P_n is the probability that a cell receives n hits, and C is a scaling factor. More details about this model were described elsewhere [9].

For the comparison of model predictions with epidemiological data in the low exposure region, the Czech miner data reported by Tomasek et al. [10] were used, applying a dose-exposure conversion factor of 5 mGy/WLM [9]. In order to facilitate this comparison, all risk functions were normalized to a relative risk (RR) of 4.44 at 135 WLM (0.675 Gy) for the Czech miner data (note: the primary goal of this study was to examine the shape of the dose-effect curve at low exposures and not the absolute number of lung cancer cases). The calculations indicate excellent agreement between the epidemiologically observed relative risk and the theoretically predicted risk, consistent with the linear- no threshold hypothesis.

3. Results and Discussions

Genomic Instability

There is sufficient *in vitro* evidence that both low and high LET radiations may induce genomic instability in individual cells that is transmitted to their descendants, producing cellular damage in the progeny of irradiated cells even after many generations [3].

Thus, for protracted exposures, each cellular generation is affected by both direct exposure to ionizing radiation and radiation-induced genetic alterations induced in preceding generations.

If genomic instability is incorporated into the IP-model, predicted risks (whether or not this effect depends on radiation dose) are higher than estimated for direct radiation-induced damage at all exposure levels. However, if normalized to a RR of 4.4 at 135 WLM (0.675 Gy), then the two scenarios produce different results. In case of independence of dose, the shape of the dose-effect curve is not affected at all, while the dose dependency reduces the risk in the low dose region relative to the higher doses (Figure 1).

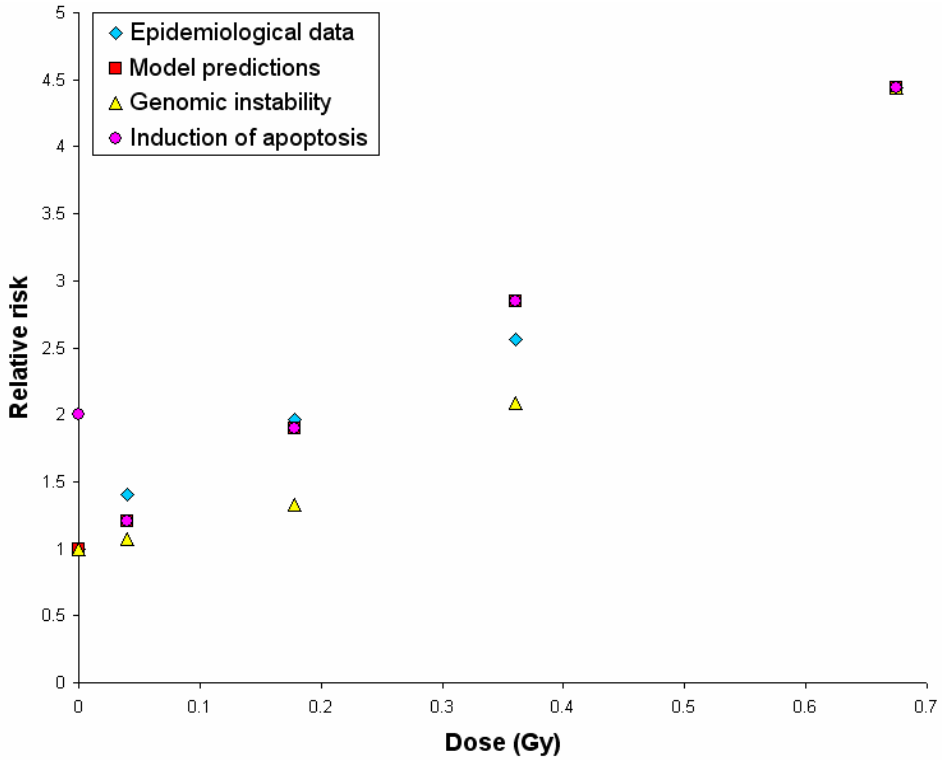

FIG. 1: The effect of genomic instability and induction of apoptosis on lung cancer risk

Induction of Apoptosis by Surrounding Cells

Transformed cells produce superoxide anions in the surrounding microenvironment that participate in intercellular signaling. These signals can be eliminated by their non-transformed neighbors through intercellular induction of apoptosis [11]. This potential step against oncogenesis results from a complex system of interactions of reactive oxygen and nitrogen species, which do not require direct cell contact [12]. Available data suggest that initiating events in the apoptotic cascade were induced in unexposed cells by a signal produced by irradiated cells in the same population [13]. The experimental results reported by Portess et al. [14] were chosen to explore the effect of induced apoptosis on oncogenic transformation. In this study, transformed cells were forced into apoptosis by surrounding non-transformed cells, stimulated by exposures to low doses of ionizing radiation, notably

alpha particles [14]. The number of apoptotic cells in non-irradiated transformed cells increased with dose in the low dose range, approaching a plateau value of about 20% at around 100 mGy. While this effect decreases the carcinogenic risk at doses above 100 mGy by 20%, this also implies that induced apoptosis is less effective at lower doses; this slightly increases the risk at the lowest doses relative to higher doses (Figure 1).

4. Conclusions

Although the goal of the present study to investigate the effect of two non-targeted mechanisms on the shape of the lung cancer risk function at chronic, low level exposures was achieved, some limitations of the model have to be recognized. For example, the results of the present study suggest that the effect of genomic instability and induction of apoptosis on the shape of the dose-response relationship may be different than on the absolute values of lung cancer cases. Indeed, genomic instability causes a substantial reduction of the risk at low doses, while induction of apoptosis slightly increases the risk. Moreover, the indirect effects described in this study indicate that the relevant target for the detrimental effects of radiation may be much greater than single cells, e.g. a collection of cells or small tissue volumes.

References

1. M. A. Khadim, S. R. Moore, E. H. Goodwin, Mutation Research, 568 (2004) 21-32
2. J. B. Little, J. Radiol. Prot., 23 (2003) 173-181
3. W. Morgan, J. Day, M. Kaplan, E. McGhee, C. L. Limoli, Rad. Res., 146 (1996) 247-258
4. C. Kugel, I. Bailly, F. Tourdes, J. L. Poncy, J. Radiat. Res. 43 (2002) 27-34
5. R. C. Miller, S. A. Marino, D. J. Brenner, S. G. Martin, M. Richards, G. Randers-Pehrson, E. J. Hall., Rad. Res., 142 (1995) 54-60
6. D. Bettega, P. Calzolari, G. Chiorda, L. Tallone-Lombardi, Radiat. Res., 131 (1992) 66-71
7. D. J. Crawford-Brown, W. Hofmann, Int. J. Radiat. Biol., 57 (1990) 407-423
8. W.Hofmann, D.Crawford, H.Fakir, G.Monchaux, Radiat. Prot. Dosim., 122 (2006)345-348
9. W. Hofmann, L. A. Truță-Popa, H. Fakir, Proc. of the IRPA Conference, Paris, (2006)
10. L. Tomasek, A. Rogel, M. Tirmarche, N. Mitton, Radiat. Res. (in press) (2007)
11. G. Bauer, Anticancer Res., 20 (2000) 4115-4139
12. M. Schimmel, G. Bauer, Int. J. Oncol., 19 (2001) 299-304
13. F. M. Lyng, C. B. Seymour, C. Mothersill, Br. J. Cancer, 83 (2000) 1223-1230
14. D. I. Portess, G. Bauer, M. A. Hill, P. O'Neill, Cancer Res., 67 (2007) 1246-1253