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Mathematical description and prognosis of synergistic interaction of radon and tobacco smoking

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Background: Radon and its short-lived decay products are considered as the important sources of public exposure to natural radioactivity. The synergistic interaction between tobacco smoking and radon is known to be an actual problem. This study has provided a mathematical description and prognosis of the carcinogenic effects after combined action of radon with smoking. ***Materials and Methods:*** A simple mathematical model was adjusted for the optimization and prognosis of the synergistic interaction of radon with smoking. The model postulates that the occurrence of synergism is to be expected as a result of additional carcinogenic damage arising from the interaction of sublesions induced by the two agents under consideration. ***Results:*** The predictions of the model were verified by comparison with experimental data published by other researchers. The model appears to be appropriate and the predictions valid. ***Conclusion:*** The suggested mathematical model predicts the greatest level of synergistic effect and condition under which this level is reached. The synergistic effect appeared to decline with any deviation from the optimal value of the ratio of carcinogenic effective damages produced by each agent alone. **Iran. J. Radiat. Res., 2007; 4 (4): 169-174**

Keywords: *Radon, smoking, synergistic interaction, mathematical model, carcinogenesis.*

INTRODUCTION

A certain level of background exposure to ionizing radiation and natural or man-made chemicals is always presented in the environment. Thus, all assessments of toxicity, carcinogenicity or mutagenicity of chemical, physical and biological agents should be performed as studies on their combined effects. For example, people are exposed to a indoor radon concentration combined at most time with other agents including tobacco smoking. It is well known from epidemiological and toxicological studies that the kind of interaction which occurs between tobacco smoking and radon may be synergistic, i.e. can lead to the effects, the sum of which is greater than that expected from the addition of the effects from separate exposures to the individual agents [1-3]. This problem is especially important for high natural background areas [4]. A new concept of the synergistic interaction and a simple mathematical model based on this conception has been developed earlier to predict and optimize the synergy when hyperthermia was simultaneously applied together with any of the following modalities: ionizing radiation, ultrasound, ultraviolet light, microwaves and some chemical agents [5-7]. The model suggests that the synergism is expected from some additional effective lesions arising from the interaction of sublesions induced by both agents. These sublesions are considered ineffective after each agent is taken alone. The model predicts the dependence of the synergistic interaction on the ratio of effective lesions produced by each agent applied the greatest value of the synergy as well as the condition under which it can be achieved. However, the model was mainly tested for inactivation of cells differing by their origin. Therefore, it would be of interest to accommodate this model for the description, optimization and prognosis of synergistic effects between tobacco smoking and radon. Thus, this study was designed to implement two purposes: (a) to adjust a

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mathematical model to describe the synergistic interaction between radon and tobacco smoking; (b) to test the validity of the proposed model.

MATERIALS AND METHODS

In the estimation of the synergistic effect as regard to carcinogenic action, the synergistic enhancement ratio (k) can be defined as the ratio of the number of cancer cases registered due to the combined action of two carcinogenic factors (N_{comb}), to the sum of the number of the carcinogenic events resulting from each agent considered separately:

$$\mathbf{k = \frac{N_{comb}}{N_1 + N_2}} \qquad (1)$$

where N_1 and N_2 are the numbers of cancer cases induced by radon and tobacco smoking, respectively. We note that the number of cancer cases is in direct proportion to hypothetical effective damages finally responsible for the carcinogenic events. Then the synergistic enhancement ratio defined by equation (1) reflects the ratio of the corresponding effective damages induced by the combined action of both agents (N_{comb}) to the sum of the effective damages produced by radon (N_1) and tobacco smoking (N_2).

The model does not apply such a value as a dose from an individual agent, since it is designed for the description of the combined effects of agents which can be completely different by their nature and action mechanism. However, this model can deal with different factors, as it operates with non-dimensional ratio of the effective damages produced by the agents under consideration. The model suggests that carcinogenic agents, in addition to the effective damages resulting from the carcinogenic events, produce some precarcinogenic sublesions. Let us assume that p_1 and p_2 are the numbers of sublesions that occur per a single effective damage induced by ionizing radiation and tobacco smoking, respectively. It should be pointed out at this stage, that the applied model does not postulate or define the nature or type of neither effective damage nor sublesions which occur. Thus this can be of any type. What the model does offer is an empirical mean for their quantitative estimation. These precarcinogenic sublesions are considered to be non-effective, when each agent is applied separately. Additional carcinogenic effective damages responsible for the synergy are assumed to arise from the interaction of precarcinogenic sublesions. As the first step of modelling, let us assume that one sublesion resulting from one individual agent reacts with one sublesion produced by another agent, thus producing an additional effective damage. In other words, the additional carcinogenic damage is produced during the combined action of agents, as a result of the interaction of these precarcinogenic sublesions. Thus, in terms of the model presented by equation (1), the synergistic enhancement ratio, k, may be given by:

$$\mathbf{k = \frac{N_1 + N_2 + \min\{p_1 N_1; p_2 N_2\}}{N_1 + N_2} = 1 + \frac{\min\{p_1; p_2 N_2 / N_1\}}{1 + N_2 / N_1}} \qquad (2)$$

Here, the term $\min\{p_1N_1;p_2N_2\}$ is a minimal value from two variable quantities, p_1N_1 and p_2N_2, which determine the numbers of additional effective damages arising due to the interaction between precarcinogenic sublesions produced by radon (p_1N_1) and tobacco smoking (p_2N_2). It can be easily demonstrated that, if the cancer induction under combined action of agents is mainly produced by tobacco smoking, or in other words $p_1N_1<p_2N_2$, then the parameter p_1 may be represented as follows:

$$\mathbf{p_1 = (k-1)(1 + N_2 / N_1)} \qquad (3)$$

In contrast, if the cancer events are mainly induced by the action of ionizing radiation $p_1N_1>p_2N_2$, the parameter p_2 can be determined by the following equation:

$$\mathbf{p_2 = (k-1)(1 + N_1 / N_2)} \qquad (4)$$

It can be demonstrated in a purely

mathematical means that under condition

$$p_1N_1 = p_2N_2 \qquad (5)$$

the synergistic interaction should be characterized by the greatest value and can be calculated as follows:

$$k_{max} = 1 + \frac{p_1p_2}{p_1 + p_2} \qquad (6)$$

Thus, using equations (3) and (4), one can estimate, on the basis of real experiments, the basic model parameters p_1 and p_2. Then the synergistic enhancement ratio for any ratio of N_2/N_1, its greatest value, and the condition under which this is yielded can be derived from equations (2), (6), and (5), respectively.

RESULTS

In order to apply the model to experimental data, it is necessary to define two basic parameters p_1 and p_2. Each of these is calculated for such experimental conditions, when one of the agents induces more precarcinogenic sublesions then another. Two sets of epidemiological data are available for a definition of the interactions between radon and tobacco smoke interaction-miner and residential study data. The first set of data, i.e. miner data, describes a situation in which the subjects were exposed to high radon concentrations, and here the impact of the action of radon on the lung cancer induction rate is greater than that of the smoke inhalation component. Knowledge of such a condition is necessary in order to define the model parameter p_2. In this case, $\min\{p_1N_1;p_2N_2\}=p_2N_2$ and the synergistic enhancement ratio is calculated according to the following equation:

$$k = 1 + \frac{p_2N_2/N_1}{1 + N_2/N_1} = 1 + \frac{p_2}{1 + \frac{1}{N_2/N_1}} \qquad (7)$$

According to this Equation, the value for k is increased in relation to the increase in that for N_2/N_1. In other words, the model predicts that the synergistic enhancement ratio increases with an increase in the ratio of N_2/N_1 until the inequality $p_1N_1>p_2N_2$ holds.

In order to test this prognosis, we used a survey consisting of periodic sputum cytology evaluation and which was performed among 249 underground uranium miners and 123 controls [1]. Cytological sputum samples yielding moderate atypia, marked atypia, or the presence of cancer cells were classified as being abnormal. To estimate the synergistic enhancement ratio, data on both the combined action of the agents and on the separate action of each individual agent is required. Band *et al.* [1] presented data for the combined action of agents and the effects of tobacco smoke inhalation on lung cancer induction in miners for a range of radon concentrations (from less than 2.6 kBq/m^3 to more than 15.7 kBq/m^3). However, if the real epidemiological results for the combined action of radon and tobacco smoke in cancer induction (N_{comb} values) were listed for all 5 conditions investigated (<2.6, 2.7-5.3, 5.4-10.4, 10.5-15.7 and >15.7 kBq/m^3), the data for radon action alone (not smoking miners) was presented only for two concentration levels, and one of them was obtained for the minimal radon concentration when there was no synergistic interaction at all. The residuary point (5.4-10.4 kBq/m^3) may be characterized as follows. In accordance with published results [1], the frequencies of abnormal cytology were 5% after radon exposure alone (N_1), 7% after cigarette smoking alone (N_2) and 28% after combined action of these modalities (N_{comb}). Then the expected frequency should be 12% for independent action of these agents (N_1+N_2) and in terms of the model discussed, the ratio $N_2/N_1=1.4$ and the synergistic enhancement ratio k=2.3. This value was calculated by using equation (1). This point is depicted on the left-hand part of the curve presented in figures 1A and 1B. Having used this result and equation (4), we have p_2= 2.3. Taking into consideration this value and equation (7) that would correct for the condition $p_1N_1>p_2N_2$, the theoretically predicted dependence of the synergistic enhancement ratio on the ratio of N_2/N_1 was calculated. The result is presented

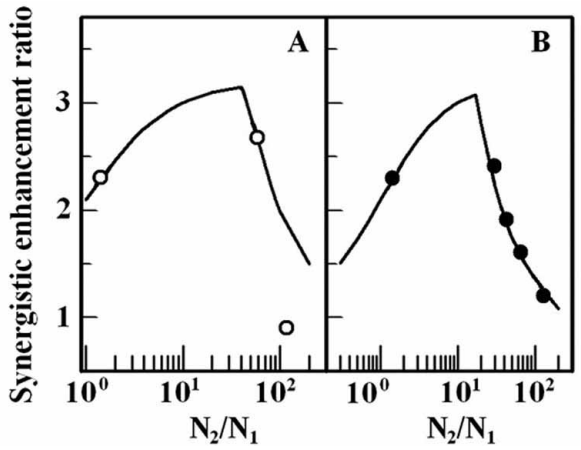

Figure 1. The dependence of the synergistic enhancement ratio on the ratio of the effective damages produced by tobacco smoking (N_2) and radon (N_1).

in figures 1A and 1B by the left-hand part of the solid curve.

The residential study data represent situations in which people are exposed to relatively low radon concentrations, as compared to those of the affected miners. It may be supposed that in this case, tobacco smoke is the main factor responsible for the lung cancer induction. This hypothesis is supported by the data published by Pershagen *et al.* [3]. In this case, $\min\{p_1N_1;p_2N_2\}=p_1N_1$, i.e. tobacco smoke induces a larger amount of precarcinogenic sublesions. Such parameter conditions are necessary to define the model parameter p_1 on the basis of equation (3). The synergistic enhancement ratio in this case can be calculated as

$$k = 1 + \frac{p_1}{1 + N_2/N_1} \qquad (8)$$

According to this Equation, the value for k is decreased in relation to the increase in that for N_2/N_1. In other words, the model predicts that the synergistic enhancement ratio decreases with the increase in the ratio of N_2/N_1 for which the inequality $p_1N_1<p_2N_2$ holds. In order to test this prediction, we used the results published by Pershagen *et al.* [3]. Because of relatively high scattering of the original data [3], we employed two manners to evaluate the parameter of p_1. For the first one, we used two concentrations of radon: 51-80 and >400 Bq/m^3; at the least radon concentration, the synergistic effect was minimal, while for the high radon concentration it had the greatest value. In accordance with the original data [3] for radon concentration >400 Bq/m^3, the relative risk (except for the background risk) was 0.2 after exposure to radon alone (N_1), 11.6 after tobacco smoking alone (N_2) and 31.5 after combined action of both agents (N_{comb}). In this case we assumed the relative risk to be proportional to the number of effective damages responsible for the carcinogenic effects. Under such a supposition all the equations derived above can be applied. Then the expected number of the effective damage should be 11.8 for independent action of these agents (N_1+N_2), the ratio N_2/N_1= 58 and in accord with equation (1), the synergistic enhancement ratio k= 2.7. This data point is depicted on the right-hand part of the curve presented in figure 1A. Having used this result and equation (3), we have p_1=100. Taking into consideration this value and equation (8) that would correct for the condition $p_1N_1<p_2N_2$, the theoretically predicted dependence of the synergistic enhancement ratio on the ratio of N_2/N_1 was calculated. The result is presented in figure 1A by the right-hand part of the solid curve. The second data point at this part of the curve was evaluated by a similar way for radon concentration of 51-80 Bq/m^3. It is

clear that this result does not correspond to the theoretically predicted curve.

The originally published results [3] clearly display linear dose-effect dependence but also reveal some deviations from the general trend. To avoid this we applied a linear extrapolation to the data reflecting lung cancer incidence rate among the residents who were exposed only to radon. Table 1 summarizes the results of such a calculation. The obtained results are depicted by points on the right-hand part of the curve presented in figure 1B. The value of the parameter p_1 of the model can be estimated from any of the data points obtained. For example, by using equation (3) we have p_1=39.5 for a radon concentration of 140-400 Bq/m^3. Taking into consideration this value and equation (8) that would correct for the condition $p_1N_1<p_2N_2$, the theoretically predicted dependence of the synergistic enhancement ratio on the ratio of N_2/N_1 was calculated. The result is shown in figure 1B by the right-hand part of the solid curve. Taking the data presented in figure 1B as a whole, one can conclude that the theoretically predicted curves correspond well with the data points regarding to the dependence of the synergistic enhancement ratio on the ratio of the effective damage produced by tobacco smoking and radon.

Table 1. Model parameters and experimental values of the synergistic enhancement ratio.

Radon concentration, Bq/m^3	Relative risk (except for the background risk)				k_{exp}	N_2/N_1
	Radon	Tobacco smoking	N_{comb}	$N_1 + N_2$		
	N_1	N_2				
<50		9.00				
51-80	0.07		11.3	9.07	1.25	129
81-140	0.15		14.3	9.15	1.56	60
141-400	0.22		17.9	9.22	1.94	41
>400	0.31		22.5	9.31	2.42	29

DISCUSSION

Thus, the data presented here indicated that the mathematical model for synergism which was previously proposed and tested mainly for the description of cell inactivation, can also be used to describe the carcinogenic effects of the combined action of radon exposure and tobacco smoke inhalation. The main difference in the proposed model when compared to the existing ones [8, 9] is the assumption that synergism can be accounted for in terms of the interaction between putative precarcinogenic sublesions, with the frequency of the occurrence of these lesions being proportional to the number of cancer cases. It's important, however, that no attempt is made in the model to apply an assumption on the molecular nature of the precarcinogenic sublesions and the mechanism of their interaction. Nevertheless, the model enables us to obtain some non-trivial results-it predicts the synergistic enhancement ratio for any ratio of the effective damages produced by a combination of tobacco smoking and radon as well as the greatest value of the synergistic effect and the condition under which this is yielded. .

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