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EMPIRICAL MODELS OF RADON-INDUCED LUNG CANCER RISK IN RATS

EMPIRISCHE MODELLE DES RADON-INDUZIERTEN LUNGENKREB-SRISIKOS IN RATTEN

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Zusammenfassung

Der Zweck der hier vorgelegten theoretischen Studie ist die Entwicklung semi-empirischer Modelle zur Beschreibung der Beziehung zwischen der Exposition durch inhalierte Radonzerfallsprodukte und zwei verschiedenenen strahlenbiologischen Effekten in der Lunge, die experimentell in Ratten beobachtet worden sind, und zwar die Lungenkrebsinzidenz und die Verkürzung der Lebenszeit. Unter Verwendung experimenteller Daten aus Untersuchungen an den Battelle Pacific Northwest Laboratories (PNL) wurden empirische Beziehungen zwischen der Lungenkrebsinzidenz und der Lebenszeitverkürzung in Abhängigkeit von der kumulativen Exposition im Bereich von 20 bis 10240 WLM abgeleitet: (i) Die beobachtete Lungenkrebsinzidenz nimmt mit steigender Exposition zu, wobei sogar in der niedrigsten Expositionsgruppe (20 WLM) die Lungenkrebsinzidenz größer ist als in der Kontrollgruppe. (ii) Die Abhängigkeit der Lebenszeit der Ratten von der Höhe der Exposition legt nahe, die Lebenszeitdaten der Ratten in zwei Expositionbereiche zu teilen, einem linear ansteigenden Teil im niedrigsten Expositionsbereich, und einem exponentiell abnehmenden Teil im Bereich mittlerer und hoher Expositionen. Multipliziert man die gemessenen Inzidenzen mit einem linearen Normierungsfaktor, d.h. die Inzidenzen werden auf die mittlere Lebenszeit in der Kontrollgruppe bezogen, so werden dadurch die Inzidenzen in den niedrigsten Expositionen verringert, bzw. in den höchsten Expositionen erhöht.

Abstract

The purpose of this theoretical study is to derive semi-empirical models for the relationship between radon progeny exposure and two different kinds of radiobiological effects in the lungs which have been experimentally observed in laboratory rats, namely lung cancer incidence and life span shortening. Based on recent experimental data from the Battelle Pacific Northwest Laboratories (PNL), empirical expressions have been derived for the lung tumor incidence and the life span as functions of the cumulative radon daughter exposure in the range from 20 to 10240 WLM: (i) The reported lung tumor incidence increases with rising cumulative exposure; even in the lowest exposure group (20 WLM), the incidence of lung tumors is higher than the incidence in the control group. (ii) The dependence of the life span on cumulative exposure suggests to separate the life span data into two exposure regimes, a linearly increasing portion for the lowest exposures, and an exponentially decreasing portion for intermediate and high exposure levels. Hence, the application of a linear life span normalization factor, thereby normalizing the reported incidences to the mean life span in the control group, reduces the experimentally determined lung cancer incidences at the lowest exposures and increases them at the highest exposures.

Key-words: radon, rats, lung cancer, life span

1 Introduction

In principle, two different approaches can be taken to model radon-induced lung cancer risk: (i) mechanistic models derived from cellular radiobiological experiments (e.g. CRAWFORD-BROWN and HOFMANN 1996), or (ii) empirical fits to epidemiological data (e.g. NRC 1988). While models based on *in vitro* cellular radiation effects are imperative for the understanding of mechanisms involved in radon-induced carcinogenesis, the effect of the living organism on the transformation of a normal cell to a malignant cell, e.g. the influence of the immune system, is still largely unknown. Hence, cellular carcinogenesis models are very useful tools for the determination of the relative dependence of lung cancer risk on exposure, i.e., the shape of the dose-effect curve. However, in order to predict absolute values of the lung cancer risk per unit exposure, the construction of semi-empirical models by fitting epidemiological data through mathematical functions may be a more appropriate approach for radiation protection purposes. Thus, in the present work, we have chosen the second approach.

The laboratory rat has successfully been used in the past to assess the carcinogenic risk following exposure to inhaled radon decay products (GILBERT et al. 1996, MONCHAUX et al. 1994). While lung tumors are the most serious consequences of radon progeny inhalation, other lung damages, such as interstitial edema, alveolitis and progressive interstitial fibrosis, have also been reported (ROSENBAUM et al. 1997). However, the observed dose-response relationship for bron-

chogenic carcinomas provides information only about the stochastic effects of radiation, but not about these non-stochastic radiation effects. Indeed, inhalation experiments have shown that the life span of rats can strongly be influenced by radiation-induced damage (CROSS 1988). Therefore, the life span of exposed laboratory rats may be a useful indicator of radon-induced radiation effects, including carcinogenesis, in the lungs.

The purpose of this theoretical study is to derive semi-empirical models for the relationship between radon progeny exposure and two kinds of radiation effects which have been experimentally observed in laboratory rats, namely lung cancer incidence and life span shortening. Based on an extensive compilation of experimental data obtained at the Battelle Pacific Northwest Laboratories (PNL), two semi-empirical expressions of the lung tumor incidence, I, and the life span, LS, respectively, as functions of the cumulative radon daughter exposure will be discussed in the present study.

2 Analysis of experimental data

2.1 Lung cancer data

Radon progeny inhalation experiments in laboratory rats were carried out at Battelle PNL over an extended period of time, providing invaluable experimental information about lung cancer incidence and life span of Wistar rats for a wide range of exposure levels and exposure rates. Our analyses of lung cancer risk and life span shortening in rats exposed to radon progeny will be based on this extensive set of data listed in Tables 1 (lung tumors) and 2 (life span).

Among the 3880 Wistar rats exposed to radon progeny at different exposure levels, 474 animals developed lung tumors (see Table 1). For comparison, only 5 rats with tumors have been observed in the various control groups, consisting of altogether 618 rats. Due to their relevance to human environmental exposures, the two lowest exposure groups are of particular interest. Here, lung tumors were detected in 3 out of 246 rats (in the 20 WLM group), and in 10 out of 445 rats (in the 40 WLM group). There are statistically significant differences between the groups with exposure levels above 80 WLM and the control group ($\chi^2 = 7.48$, $p < 0.01$).

The lung tumor incidence observed in these experiments is plotted in Fig. 1 as a function of the cumulative exposure to ambient radon progeny. In general, the reported lung tumor incidence increases with rising cumulative exposure: it increases rapidly in the lowest exposure categories, while flattening out at the highest cumulative exposures. Even in the lowest exposure group (20 WLM), the incidence of lung tumors is higher than the incidence in the control group. In other words, if lung cancer risk is expressed in terms of relative risk, RR, then RR is always greater than 1 (see Table 1).

Table 1. Lung cancer incidence and relative risk in Wistar rats exposed to varying exposure levels of radon progeny.

Exposure (WLM)	Number of rats exposed	Number of rats with lung tumors	Incidence (%)	Relative risk
0	618	5	0.81	1.00
20	246	3	1.22	1.51
40	445	10	2.25	2.78
80	765	22	2.88	3.55
160	191	9	4.71	5.82
320	658	83	12.61	15.59
640	407	69	16.95	20.96
1280	88	32	36.36	44.95
2560	182	81	44.51	55.01
5120	216	121	56.02	69.24
10240	64	39	60.94	75.32

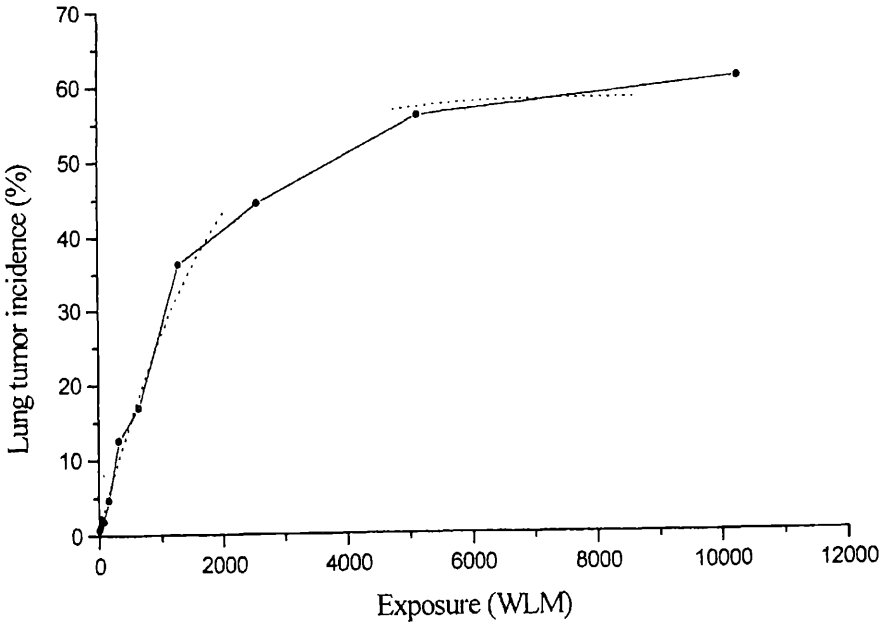

Fig. 1 Lung tumor incidence (in percent) in Wistar rats exposed to radon progeny vs. cumulative exposure (in WLM). The dotted line represents the best fit to the experimental data (equation 1).

The best fit of the lung cancer incidence, I (in percent), as a function of cumulative exposure (in WLM) was obtained by the following mathematical expression (see Fig. 1):

$$I(WLM) = (A_1 \quad A_2)/(1 + \exp((WLM - x_o)/dx)) + A_2 \qquad (1)$$

where A_2 is the observed cancer incidence in the control group , and A_1, x_o and dx are the coefficients obtained by the fitting procedure (A_1 = 75 78, A_2 = 58.27, x_o = - 329.31, and dx = 1127.05).

Since the low exposure data are specifically relevant to human environmental exposures, the same data were also fitted by a logistic function on a log-log plot:

$$\text{Log } I(WLM) = \log N/(1 + WLM/O)^p) + M) \qquad (2)$$

where M is the initial value on the y-axis, N is the final value on the y-axis, O is the center value on the x-axis, and p is a fitting parameter (M = 0.9766, N = 65 14, O = 1267.31, and p = 1.26).

2.2 Life span data

The life spans, LS, of Wistar rats were reported for 3751 animals at 11 exposure levels, including the control group (Tab. 2). The reported mean life spans (in days) in each exposure group are displayed in Fig. 2 as a function of the cumulative exposure (in WLM). With the exception of the two lowest exposure categories (i.e., 20 and 40 WLM), the average LS drops in an exponential manner with increasing exposure. In these two groups, however, the mean LS is significantly higher than the average LS of the control group ($t = 4.66$, $p < 0.01$ for 20 WLM; $t = 3.53$, $p < 0.01$ for 40 WLM). At intermediate exposures, i.e., at 80, 160 and 320 WLM, there are no significant differences between the mean LS and that of the control group ($t = 0.84$, $p > 0.05$ for 80 WLM; $t = 1.83$, $p > 0.05$ for 160 WLM; and $t = 1.15$, $p > 0.05$ for 320 WLM). For all exposures greater than 320 WLM, the mean LS is significantly lower than the LS of the control group ($t = 3.35$, $p < 0.01$). This dependence of the LS (in days) on the cumulative exposure (in WLM) suggests to separate the data into two exposure regimes, a linearly increasing portion for the lowest exposures, and an exponentially decreasing portion for intermediate and high exposure levels (see Fig. 2):

$$LS(WLM) = y + A_s\, WLM \qquad \text{for } WLM \leq 20 \qquad (3)$$

and

$$LS(WLM) = y_1 + A_1 \exp(-(WLM - x_s)/t_1) + A_2 \exp(-(WLM \quad x_o)/t_2) \qquad (4)$$
$$\text{for } WLM > 20$$

where y_o and y_1 are the initial values on the y-axis, x_o is the initial value on the x-axis, and A_o, A_1, A_2, t_1 and t_2 are coefficients obtained by the fitting procedure (y_o = 657, A_o = 1.75, R = 0.8598; y_1 = 386.24, x_o = 20, A_1 = 175.20, A_2 = 113.7, t_1 = 3209, and t_2 = 1.432 E4, χ^2 = 1275.95).

Table 2. Mean life span of Wistar rats exposed to varying exposure levels of radon progeny.

Exposure (WLM)	Number of rats exposed	Life span (days)
0	591	645
20	245	716
40	443	715
80	747	669
160	191	678
320	637	630
640	372	593
1280	87	618
2560	174	573
5120	200	511
10240	64	442

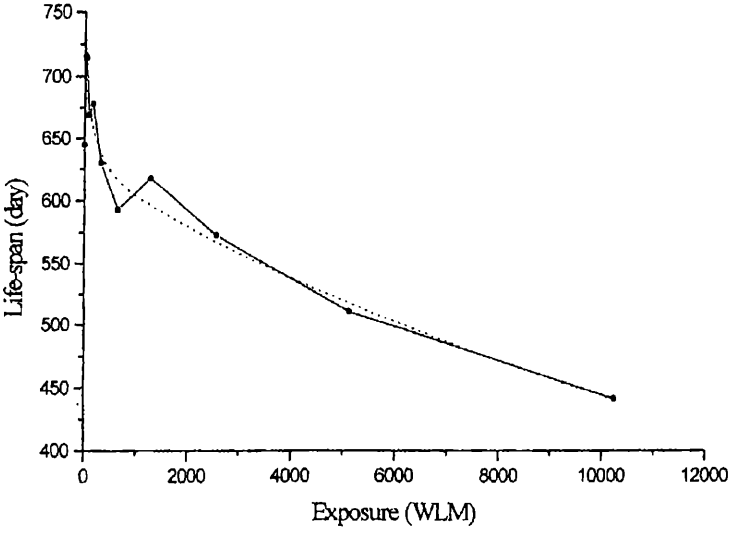

Fig. 2. Mean life span (in days) in Wistar rats exposed to radon progeny vs. cumulative exposure (in WLM). The dotted line represents the best fit to the experimental data (equations 3 and 4)

3 Life span normalization factor

The lifetime of an animal after irradiation is influenced by the occurrence of different post-irradiation lesions, including lung tumors (RAABE 1989). Since the LS of rats after low levels of cumulative exposures is longer than that in the controls, more time is available to give rise to a radon-induced lung tumor before the death of the animal. In contrast, lung tumors may not appear during the lifetime of the animal due to the shorter lifetime of the animal after high levels of cumulative exposures. Hence, the experimentally determined radon-induced lung cancer incidence, I, must be normalized to same mean life span. In the present study, we applied a linear life span normalization factor, β, as defined below:

$$\beta = LS_o/LS_i \tag{5}$$

where LS_o is the mean life span in the control group, and LS_i is the mean life span in cumulative exposure group i. The application of a linear normalization factor is equivalent to the assumption that carcinogenic risk is proportional to attained age. The normalized lung tumor incidence, I* (in percent), in a given exposure category i is then given by:

$$I^* (\%) = \beta \times I_i (\%) \tag{6}$$

where I_i is the reported radon-induced lung tumor incidence in that exposure group.

Through multiplication with the above defined life span normalization factor β, the experimentally determined lung cancer incidences will be reduced at the lowest exposures and increased at the highest exposures, relative to intermediate exposures where life spans are similar to that in the control group.

The normalized lung tumor incidences (in percent) in the various exposure groups (in WLM) are plotted in Fig. 3 and compared with the original data. The best fit to the normalized lung cancer incidences was obtained by a the following function:

$$I (WLM) = p_1 \times WLM/(p_2 + WLM) \tag{7}$$

Here, p_1 and p_2 are the coefficients obtained by the fitting procedure (p_1 = 113.34, and p_2 = 2966.6).

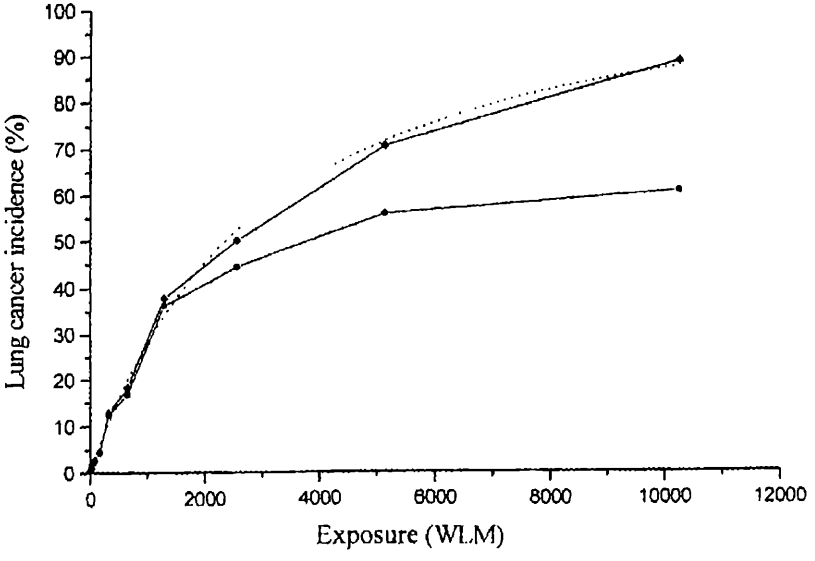

Fig. 3 Normalized lung cancer incidence (♦), obtained by multiplying the experimentally observed lung cancer incidence in the each exposure category by the corresponding life span normalization factor, compared with the original incidences (•). The dotted line represents the best fit to the normalized data.

4 Discussion

The lung cancer incidence function plotted in Fig. 1 suggests that the dose-response relationship may be divided into two parts, a relatively steep linear increase with exposure below about 1280 WLM, and a flattening of the curve above this level. This decrease in carcinogenic potential per unit exposure at higher exposure levels is consistent with the epidemiological findings in uranium miner studies (NRC 1988). Thus, rat inhalation experiments are a valuable complement to human epidemiological studies, having the additional advantage of a much better characterization of the exposure conditions.

The relationship between life span and cumulative exposure, plotted in Fig. 2, shows the interesting result that the LS at 20 and 40 WLM is significantly higher than that in the control group, while dropping subsequently to the control level at about 80 WLM. Application of the LS normalization factor, defined in equation 5, to the lung cancer incidences obtained in the rat inhalation experiments increases the incidences in the highest exposure categories, but decreases them at the lowest exposure levels.

There is sufficient experimental evidence that low dose irradiation often induces biological effects which are different in nature and magnitude from those observed at high doses (KORYSTOV et al. 1996). Low and chronic exposures to ionizing radiation can initiate processes which protect the cell against both naturally occurring and radiation-induced alterations that may ultimately lead to cell transformation. For example, studies on human lymphocytes showed that low doses could protect cells against chromosomal aberrations and radiation-induced mutations (KELSEY et al. 1991). Thus small amounts of radon progeny may not be harmful to rats and, possibly, to human beings too.

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