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Radiation Hormesis in Humans Exposed to Low Level Ionizing Radiation

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Through various researches and investigations it has been established that high doses of ionizing radiation are harmful to health. There is substantial controversy regarding the effects of low doses of ionizing radiation despite the large amount of work carried out (both laboratory and epidemiological). According to the linear no-threshold (LNT) hypothesis, any amount, however small, of radiation is potentially harmful, even down to zero levels. The threshold hypothesis, on the other hand, emphasizes that below a certain threshold level of radiation exposure, any deleterious effects are absent. At the same time, there are strong arguments, both experimental and epidemiological, which support the radiation hormesis (beneficial effects of low-level ionizing radiation). These effects cannot be anticipated by extrapolating from harmful effects noted at high doses. The choice of the approximate dose-response model for use in estimating the health effects of small doses of ionizing radiation remains controversial. In the present work, a comprehensive study of the available literature, data and reports of various radiation exposure and protection studies is presented. In conclusion, we find that the radiation hormesis contradicts the predictions made by the LNT hypothesis regarding the health effects of ionizing radiation in the low dose region.

Key Words: Hormesis, Adaptive response, Health, Radon, Epidemiological

INTRODUCTION

The study of impact of low-level ionizing radiation on environment and possible health effects on future generations has been a cause of concern in recent years with the increasing use of radiation in health facilities, scientific research, industry and agriculture[1]. Through various researches and investigations it has been established that high doses of ionizing radiation are harmful to health and there is a linear relationship between dose and the effect. There is substantial controversy regarding the biological and health effects of low doses of ionizing radiation in humans and the biota, in vitro and in vivo despite the large amount of work carried out (both laboratory and epidemiological). By low-level exposure, we mean the exposure to radiation levels comparable to those encountered in the natural environment (ambient radiation level). There are two schools of thought regarding the health effects of low –level –exposure to ionizing radiation one emphasising the harmful effects on health, no matter how small be the level of ionizing radiation exposure (LNT), while other school of thought believes in the beneficial features of such a low-level-exposure[2-4]. Both schools quote epidemiological studies on human beings as well as the laboratory research using experimental animals. The first one favours the LNT hypothesis adopted by major scientific, official and governmental organizations, such as ICRP, NCRP, the NAS-NRC etc. for risk assessment. According to the linear no-threshold (LNT) hypothesis, any amount, however small, of radiation is potentially harmful, even down to zero levels. The basic assumption in the LNT hypothesis- notably the linear extrapolation of cancer risk down to zero dose with no-threshold are increasingly being questioned[5]. The threshold hypothesis, on the other hand, emphasizes that below a certain threshold level of radiation exposure, any deleterious effects are absent. At the same time, there are strong arguments, both experimental and epidemiological, which support the radiation hormesis (beneficial effects of low-level ionizing radiation). According to the hypothesis, very low doses of ionizing radiation may not be harmful after all or may even have net beneficial effects, i.e., radiation can stimulate certain biological activities, in vitro and in vivo, including anti-oxidative capacity, the process of apoptosis and immune responses. There is some evidence that low doses radiation may induce or activate DNA repair functions, the so-called adaptive responses[6-7]. Many studies show that laboratory animals exposed to low doses of radiation outlive unexposed animals[8]. These effects cannot be anticipated by extrapolating from harmful effects noted at high doses. Current radiation risk estimates drawn by linear extrapolation, from high dose and dose rate of radiation to zero dose, to calculate the effects of small doses, clearly ignore the effects of the repair of DNA- the target of radiation damage. If the hormetic effect is added to the effect predicted by the LNT hypothesis, the resultant effect will be somewhat different from that predicted by the LNT hypothesis alone. The choice of the approximate dose-response model for use in estimating the health effects of small doses of ionizing radiation remains controversial.

In the present work, a comprehensive study of the available literature, data and reports of various radiation exposure and protection studies is presented. In conclusion, we find that the radiation hormesis contradicts the predictions made by the LNT hypothesis regarding the health effects of ionizing radiation in the low dose region. To account for the adaptive repair and the non-linear kinetics, a mathematical model has also been given.

RADIATION HORMESIS

The term refers to a process whereby low doses of ionizing radiation may result in beneficial or stimulatory effects. The underlying property is a physiological effect that cannot be anticipated by linear downward extrapolation from the toxic levels of exposure[9-10].

RADIATION HORMESIS IN HUMANS: EPIDEMIOLOGICAL EVIDENCES

There is large amount of literature supported by statistically significant epidemiological studies that speaks in favour of radiation hormesis. There exist reports of various epidemiological studies, which have demonstrated that exposure to LLIR have apparently resulted in positive health effects (Discussed in details elsewhere)[4, 11]. The hormetic argument that whole body exposure to LLIR may actually decrease cancer risk is based primarily on the analysis of occupational and environmental data of various related studies. The information comes from at least nine large studies (Los Alamos National Laboratory (LANL) Study, US Bomb Observers Study, US Nuclear Weapons Plant Workers Study, Canadian Military Study, Canadian Nuclear Workers Study, British Radiation Workers Study, Ontario Nuclear Workers Study, Indian Nuclear Workers Study, Radium Dial Painters Study), of populations exposed to various forms of radioactive materials and from more limited studies of occupational and environmental exposures to plutonium, radium and radon (Details can be found elsewhere)[4]. There exist reports of various epidemiological studies, which have demonstrated a negative correlation of lung cancer risk with radon in dwellings which shows that exposure to LLIAR (Low Level Ionizing Alpha Radiation) have apparently resulted in positive health effects[12-18]. Recently a negative correlation between radon level and age adjusted overall cancer death rate; and lung and bronchus cancer deaths in Rockey Mountain States (R.M.S.) and Gulf Coast States (G.C.S.) has been reported by Jagger[19]. The relative risk (RRs) from nine lung cancer cases control studies (Finland-I, Finland-II, Sweden, Stockholm, Cornwall, Shenyang, Winnipeg, Missouri-I, and New Jersey) of indoor radon plotted as a function of radon concentration show that there is a protective effect of radon in the range 22 to 291 Bq /m^3 [20-21].

All these reports and studies mentioned above advocate in favour of the non-linearity of the dose- response curve and speak in favor of protective effect of low dose exposures. Such observations strongly suggest departure from LNT theory.

ADAPTIVE RESPONSE AND EXPERIMENTAL EVIDENCES

The term adaptive response is used to refer to the possibility that a prior exposure to small dose of radiation- which is variously referred to as the conditioning, adapting or priming dose may mitigate the severity of effect due to subsequent high dose or challenging dose of ionizing radiation. Studies have established the existence of an adaptive response to radiation in human lymphocytes[22-25]. Evidence of increased numbers of lymphocytes in laboratory animals after exposure to low-dose radiation has been presented by several investigators[26-27]. Under proper conditions, pre irradiated cells at about 0.01 Gy of low LET radiation protects them from a subsequent dose of about 1 Gy, as measured by a lower yield of chromosome aberrations, genetic mutations, cell transformation and resistance to cell killing. The protection is apparently mediated by newly synthesized enzymes involved in DNA repair[23]. Recently it has been shown that low doses of restriction enzymes are able to induce the adaptive response, suggesting that double strand breaks may provide a critical trigger for the response[28]. Mitchel[29] has shown that there is a higher rate of repair of DNA double strand breaks in cells given a protracted adapting dose. Azzam *et al.*[30] observed a 75-80% reduction in spontaneous transformation frequency in C3H10T1/2 cells following irradiation with 1mGy of ^{60}Co gamma rays. Mitchel *et al.*[31] has reported that the adapting treatments modified the life shortening effect of leukemia by increasing the latent period in CBA/H mice. In a recent study it has been reported that the tumor induction in pre-irradiated mice with 20-methyl cholanthrene (MC) dissolved in olive oil was significantly less than in controls[32]. It indicates the tumor suppressive effect of low dose irradiation.

HORMESIS MODEL

As per evidences (epidemiological and experimental), it is now established that radiation hormesis is a widely observed and accepted phenomenon. To account for the adaptive repair and the non-linear kinetics, that results into a biphasic (non monotonic) dose-response curve (U-shaped or J shaped and inverted U-shaped (β-curve) depending upon the end point), we have modified the linear quadratic model so as to account for the situations that recognize hormesis and biological repairs. It is a linear quadratic model and its general mathematical form for enhanced and reduced bio-functions or effect on account of exposure to LLIR has been given.

For enhanced biological functions like longevity, immunity, reproduction, growth and development etc., the dose-response curve is inverted U-shaped (β-curve) and the linear quadratic mathematical model is given by equation (1).

$$y = a_0 + a_1 x - a_2 x^2; \text{ where } a_i > 0;\ i = 1, 2. \qquad (1)$$

For reduced biological functions or incidences like cancer mortality/morbidity and other disease incidence the dose-response curve is U-shaped or J shaped and the linear quadratic mathematical model is given in equation (2).

$$y = a_0 - a_1 x + a_2 x^2; \text{ where } a_i > 0;\ i = 1, 2. \qquad (2)$$

The equation (1) and (2) state that at low levels of ionizing radiation, the beneficial effects predominate. As exposure level increases, the detrimental effects eventually overcome the beneficial effects. Thus the mathematical models given by equation (1) and (2) may describe the reality more accurately than by general linear quadratic equation.

For optimum dose ($x_{optimum}$):

The dose of ionizing radiation for which the response is optimum (i.e. minimum) when the dose-response curve is U-shaped or J-shaped and maximum when the dose-response curve is inverted U-shaped or β-curve. It can be obtained by putting

$dy/dx = 0$, or

$a_1 + 2 a_2 x = 0$, or

$$\mathbf{x_{optimum} = - a_1/ 2a_2} \quad (3)$$

Zero Equivalent Dose (ZED):

The dose of ionizing radiation for which the response or effect equals the effect at background dose.

From equation (1 & 2), $y = a_0$, when $x = 0$, and therefore

$$\mathbf{ZED = a_1/ a_2} \quad (4)$$

REALIZATION OF THE MODEL

To realize a linear quadratic model allowing for hormesis, we have selected the data of an epidemiological study carried out by our group in the Haryana State of India with higher radon concentrations upto 135.21Bq/m^3 that has demonstrated a negative correlation of lung cancer (Karl Pearson's Coefficient of correlation (r) yielded the value as –0.16) with radon concentration[33].

A linear quadratic model allowing for hormesis for the data is given in equation (5). An inverted U-shaped curve as expected is shown in fig. 1 (B). Fig. 1 (A) gives normal data curve.

$$y = -7.8086 + 0.2785\, x – 0.0016\, x^2 \quad (5)$$

By knowing a_0, a_1 and a_2 from equation (5), for obtaining the values of optimum dose ($x_{optimum}$), zero equivalent dose (ZED), one can use equation (3) and (4) respectively.

Conclusions

Analyses of a number of experimental studies reveals that there appears to be apparent beneficial effects of low doses of radiation, coupled with an apparently increased in longevity. Statistically significant epidemiological studies of the Japanese atomic bomb survivors and other nuclear workers exposed to low-level radiation suggest that the linear no- threshold hypothesis (LNT) philosophy is overly stated. The inverse correlation between ionizing radiation and cancer mortality in many populations is in agreement with the evidence that whole body exposure to LLIR does not cause cancer. Cancer mortality, which is the most important concern when we consider the effects of low dose radiation, is lowest

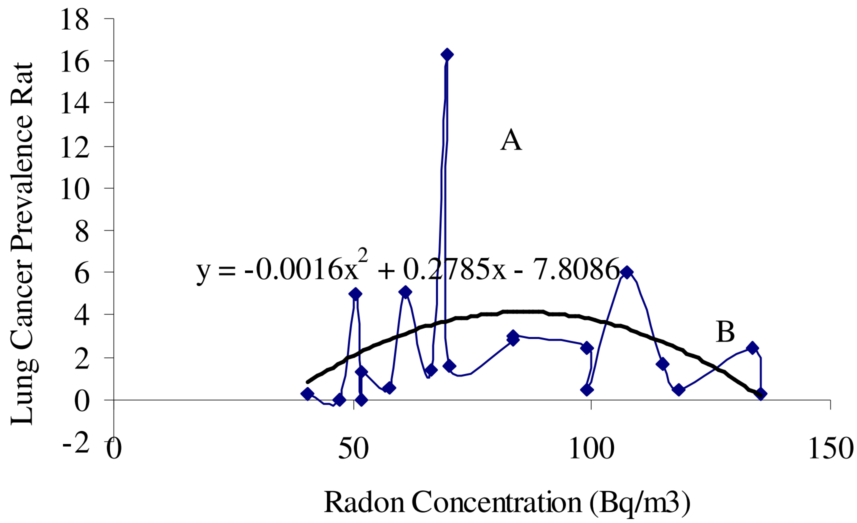

Fig. 1 Average lung cancer prevalence per million population per year in Haryana

where background radiation levels are high. Epidemiological evidence agrees with the data from occupational workers, medical use of radionuclides, and exposure to acute doses from atom bombs. This conclusion is consistent with the results from experimental animals. In this light the traditional assumption that essentially all exposures to ionizing radiation is measurably detrimental and that the health effects of low level exposure may be directly inferred from linearly scaled deleterious high level effects, require careful consideration.

In fact, the present work shows that

- There is a large amount of literature supported by scientific and empirical evidence, experimental, ecological, and epidemiological studies that very strongly propagates in favour of no- adverse- effect thresholds and of hormesis at below- threshold levels in animals and humans exposed to LLIR.
- Very clear biphasic dose response curves (U-shaped or J shaped and inverted U-shaped (β-curve) depending upon the end point, in many experiments clearly indicate that the radiation hormesis exists.

Such observations strongly favour radiation hormesis and challenge the general validity of the Linear No Threshold theory.

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