Non-linear phenomena in biological findings of the residents of high background radiation areas of Ramsar

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► ***Review article***

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ABSTRACT

Some Areas of Ramsar, a city in northern Iran are among the world's well-known inhabited areas with highest levels of natural radiation. Annual exposure levels in these areas are up to 260 mGy y^{-1} and the mean exposure rate is about 10 mGy y^{-1} for a population of about 2000 residents. If elevated levels of natural radiation as high as a few hundred mSv per year is detrimental to health and leads to higher risks of genetic abnormalities and cancer, it should be evident in the residents of areas such as Ramsar. However, it has been reported that no detrimental biological effects have ever been detected in high natural background radiation areas. Some studies indicate that Ramsar residents not only show a significant increase in DNA repair but also demonstrate induction of radioadaptive response. There is currently a great debate over the shape of the dose-response curve for stochastic effects such as mutations and cancer after exposure to low doses of ionizing radiation. Linear-no-threshold (LNT) model predicts that every dose, no matter how low, carries some cancer risk. Lack of any proven detrimental effect in the residents of high natural background radiation areas of Ramsar may be due to the induction of nonlinear dose-response relationships which are not compatible with the widely accepted LNT hypothesis.

Keywords: *Ramsar, High Natural Background Radiation Areas (HNBRAs), Natural Radiation, Non-linearity, Dose-Response*

INTRODUCTION

LNT and the Linearity Paradigm

Life evolved in an environment with greater levels of natural radiation than exists today. Natural background radiation levels on Earth vary by at least two orders of magnitude today. Therefore, all living organisms are exposed to a wide range of background radiation levels (1). Some areas of Ramsar, a city in north Iran, have background dose rates among the highest known in the world. As the biological effects of low doses of radiation are not fully understood (2, 3), the current radiation protection recommendations are based on the predictions of an assumption on the linear non-threshold hypothesis (LNT) relationship between radiation dose and its carcinogenic effects (4, 5). Considering the LNT hypothesis as a scientific fact, there is a general belief that even low levels of radiation as well as exposures to natural sources are harmful [6]. Inhabitants of the high natural background radiation areas (HNBRAs) such as Ramsar (Iran), Guarapari (Brazil), Yangjiang (China), Orissa and Kerala (India), receive radiation doses much greater than the worldwide average background dose for a human being (2.4 mSv per year) [7-10]. It has been reported that no detrimental biological effects have ever been detected in high natural background radiation areas [11]. Among the greatest advantages of radio-epidemiological studies in HNBRAs is the possibility of obtaining results from direct observation on human beings without extrapolating the effects of high doses of radiation to low dose region and from laboratory animals to humans [12]. These studies are of great importance when the study subjects have lived in the HNBRAs for many generations. It should be noted that at present there are no reliable radio-epidemiological data regarding the incidence of cancer in the inhabitants of HNBRAs of Ramsar. However, some of the local physicians strongly believe that the population living in these areas does not reveal increased solid cancer or leukemia incidence. As the majority of the inhabitants of Ramsar have lived there for many generations, an investigation to assess whether there is an apparent lack of radiation susceptibility among residents of the high level natural radiation areas was conducted [9]. On the other hand, moving from elevated levels of natural radiation to other sources of elevated level of environmental radiation such as nuclear accidents, it has been reported that the political, economic, social and psychological impact of the Chernobyl disaster was mainly due to extraordinary fear of radiation caused by the LNT hypothesis [11].

Current Ramsar Findings

•**Dose-Effect Relationship**. Currently, there is a debate over if the so called linear no-threshold (LNT) hypothesis should still serve as the philosophical and practical basis for risk assessment and management of radiation exposures in the environment and workplace [6, 13, 14]. According to LNT, protection of workers and the public from ionizing radiation exposure is based on this assumption that cancer incidence or mortality risk is a linear function of radiation dose, and any dose of radiation, no matter how small, may cause cancer [13]. Currently, there is an ongoing debate on whether the LNT assumption of radiation carcinogenesis, that was introduced more than 50 years ago, and was originally based on experiments that were carried out on fruit flies in the mid-1920s, can be still valid. Now we know that living organisms have defense mechanisms against DNA damage and these mechanisms can be stimulated by low doses [15]. Some investigators believe that although some recent radiobiological findings confirm novel damage and repair processes at low doses, LNT is still supported by findings from both epidemiology and radiobiology [16]. In 2009, Cuttler and Pollycove reported that based upon human data, a single whole body dose of 150 mSv is safe. They also reported that the high background of 700 mSv/year in the city of Ramsar, Iran was also a safe dose limit for continuous chronic exposure [17]. Regarding the bioeffects of exposure to elevated levels of natural radiation, there is a great controversy about the dose-effect relationship in published reports on the frequency of chromosome aberrations induced by chronic exposure to elevated environmental levels of radiation. This controversy exists in studies of residents in areas with elevated levels of natural radiation as well as the residents of areas contaminated by nuclear accidents. Using chromosomal aberrations as the main endpoint, an experiment to assess the dose-effect relationship in the residents of high level natural radiation areas of Ramsar was carried out. A cytogenetic study on 22 healthy inhabitants of the high natural background radiation areas and 33 residents of a nearby control area showed no positive correlation between the frequency of chromosome aberrations and the cumulative dose of the inhabitants [18].

•**DNA damage and Chromosome Aberrations**. We have previously reported that high levels of natural radiation in HNBRAs of Ramsar have not led to a significant alteration in the induction of chromosomal aberrations [9, 19]. However, some reports published recently indicating that elevated levels of natural radiation in HNBRAs of Ramsar caused a significant increase in the frequency of detectable abnormalities in unstable chromosome aberrations [20]. It was also found that the spontaneous level of DNA damage in blood samples of the inhabitants from HNBRAs of Ramsar were considerably higher than those of the control group [21].

•**Hematological Alterations.** It has been reported that in animal models such as mice and rat, total body exposure to moderate doses decreases the number of circulating erythrocytes, platelets, granulocytes, lymphocytes etc. However, data on hematopoieses as a result of exposure to very low doses of ionizing radiation are scarce Lee et al. in a study on 3602 men and women aged 35 and above who lived in a community near two nuclear power installations in Chinshan, Taiwan, showed that those who lived closer to the nuclear power installation had a higher blood cell count. They reported that they were suspect that this could be a type of radiation hormesis [22]. Findings of a study on hematological alterations in the residents of HNBRAs could not show any significant difference in hematological parameters such as counts of leukocytes (WBC), lymphocytes, monocytes, granulocytes, red blood cells (RBC), hemoglobin (Hb), hematocrit (Ht), MCV, MCH, MCHC, RDW, PLT, and MPV between the residents and the control group [9]. In another study three groups of voles were exposed to chronic gamma radiation (2-5×, 50-200× and 40,000× above background levels). Findings of this study showed that hematocrit was greater in the controls (2-5× above background levels) than in irradiated voles [23].

•**Immunological Changes.** The immune system which is composed of cells such as leukocytes and tissues that protect against infections and cancer [24]. It is well known that high doses of ionizing radiation suppress the activity of the immune system [25]. On the other hand, the low-dose radiation can enhance the immunological response [26, 27]. It has been even claimed that low dose radiation can reduce the DNA damage even below the spontaneous level and decrease the probability of neoplastic transformations by stimulating cellular detoxification and repair mechanisms [28-30]. Furthermore, it has been reported that exposure to low doses of ionizing radiation may enhance immune system and eliminate the detrimental effects of higher doses of radiation [31]. To assess whether relatively high doses of natural radiation can alter humoral immune parameters, a study was conducted on the inhabitants of HNBRAs of Ramsar [9]. In 2005 Canadian investigators exposed three groups of voles to chronic gamma radiation controls (2-5×, 50-200× and 40,000× above background levels). They reported that low-dose voles had higher counts of neutrophils than either the controls or high-dose voles; hematocrit was greater in the controls than in irradiated voles. These researchers interpreted their findings as a hormetic response to radiation [23]. We previously selected healthy blood donors from HNBRAs and a neighboring NBRA. Serum concentrations of different immunoglobulin classes were determined by Single Radial Immuno Diffusion (SRID) method. Our findings showed a slight increase in IgA and IgG levels of residents from high, compared to normal, background areas. IgM, C3 and C4 complements were in the normal range for both groups [32]. A report published in 2004 indicated a significant increase of CD69 expression on TCD4+ stimulated cells and a significant increase of total serum IgE in the HNBRAs group compared to the control group (normal background radiation. Other humoral immune parameters, did not show significant differences between the two groups [33]. Attar *et al.* in 2007 reported that the total serum antioxidant level in the residents of HNBRAs of Ramsar was significantly lower than the individuals who lived in areas with normal levels of natural radiation. They reported a higher lymphocyte-induced IL-4 and IL-10 production, and lower IL-2 and IFN-gamma production in HNBRAs group. They also showed that neutrophil NBT, phagocytosis, and locomotion were higher in the HNBRAs group. These investigators came to this conclusion that the immune system of the residents of HNBRAs has adapted to high levels of natural radiation by shifting from a Type 1 to a Type 2 response to promote anti-inflammation [34]. Based on these findings, more research is needed to clarify the mechanisms of the immunological alterations induced by different levels of natural radiation.

•**Radon concerns.** Radon-222 (radon) and radon-220 (thoron) are the most common isotopes of radon. Recent studies show that radon inhalation even at low concentrations poses a risk of developing lung cancer [35]. On the other hand there are published reports indicating that environmental radon exposure may be a risk factor for squamous cell carcinoma [36], or chronic obstructive pulmonary disease (COPD) mortality [37]. It has been reported that the radon health risk is proportional to its concentration, down to the Environmental Protection Agency's action level of 148 Bq m^{-3}. Although naturally occurring isotopes of radon in indoor air are identified as the second leading cause of lung cancer after tobacco smoking [38], there is no large scale data on the incidence of radon-related lung cancers in Iran. It's worth mentioning that, radon levels in some regions of Ramsar are up to 3700 Bq m^{-3}. Mortazavi and his colleagues have previously assessed the association between the radon concentration and frequency of lung cancer in Ramsar. Interestingly, they found a negative association between radon level and the incidence of lung cancer [39]. Our findings are in line with the report of Cohen [40, 41], which indicated that a negative estimate was observed for the regression of county mortality rates for lung cancer on estimated county radon levels. In this light, it seems that the Linear No-Threshold (LNT) model cannot be applied to residential indoor radon levels [42]. Our findings are also in line with those recently reported by Thompson who showed a statistically significant decrease in cancer risk with increased exposure to radon for values ≤ 157 Bq m^{-3} normalized to the reference exposure of 4.4 Bq m^{-3} (the lowest radon concentration measured) [43]. Studies conducted by Cohen and Colditz clearly indicate that LNT overestimates the risk of indoor radon [44].

•**Adaptation to High Levels of Natural Radiation** Radioadaptive response or radiation-induced adaptive response is defined as the acquisition of radiation resistance against irradiation with a high radiation dose in cultured cells or organisms that had been pretreated with a priming low radiation dose. The priming low radiation dose is usually called "adapting dose" or "conditioning dose" while the high radiation dose is called "challenge dose". The induction of radioadaptive response was first reported by Olivieri *et al.* [45] who showed that the frequency of chromatid aberrations were down to 50% less than expected after exposure to 1.5 Gy of X-rays. Many articles have demonstrated radioadaptive response in plant cells [46], insects [47], Chinese hamster V79 cells [48-50], cultured human lymphocytes [32, 51-54], embryonic and HeLa cells [55], occupationally exposed persons [56, 57], cultured animal lymphocytes [58], and *in vivo* studies on laboratory animals [59-62]. However, there are reports indicating lack of radioadaptive response in cultured human lymphocytes [63-65]. Furthermore, long-term follow up studies indicate that lack of radioadaptive response is not a temporary effect and, in contrast with the early reports of Olivieri and Bosi [66], does not depend on transient physiological factors [67].

Radioadaptive responses of the residents who lived in high background radiation areas of Ramsar has been reported previously [32]. It has also been shown that short-term exposure to elevated levels of radon could induce an adaptive response in laboratory animals [68]. Elevated levels of low dose rate natural radiation of Ramsar provide a unique opportunity to study epidemiological effects for the inhabitants. However to obtain reasonable and consistent data for 2000 residents, we need to observe them for long time to acquire considerable number of person-years for reliable statistical data. Recently Mortazavi *et al.*

have shown that short-term exposure to artificially elevated levels of radon may induce an adaptive response in an animal model [68]. In this study we investigate the possible induction of oxidative stress after short-term exposure to extremely high levels of natural radiation. In addition, since there is no report on the induction of adaptive response in short term exposures to high background levels of gamma radiation, the main aim of this study is to verify if exposure of laboratory animals to extremely elevated levels of natural external gamma in high background radiation areas of Ramsar can lead to induction of survival adaptive response.

CONCLUSION

The results presented in this paper indicate that dose-response curve for naturally elevated levels of ionizing radiation are nonlinear. The annual radiation dose to some residents of HNBRAs of Ramsar are much higher than the ICRP recommended dose limit for the general public or even for radiation workers. It has been reported that no detrimental biological effects have ever been detected in high natural background radiation areas. As it was argued the risk from the high levels of natural background radiation found in Ramsar may be less than what is predicted by LNT model. Further studies are required to verify the key mechanisms associated with these non-linear dose-response relationships.

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