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♦ *Letter*

Can recent Berkeley findings help us to find a solution to the paradox of cancer incidence in high natural background radiation areas of Ramsar, Iran?

According to the report published by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) in 2000, Ramsar city in northern Iran, has some inhabited areas with the highest known natural background radiation levels in the world (1). The annual radiation absorbed dose in high background radiation areas (HBRAs) of Ramsar is extraordinary high, reaching 260 mSv that is 13 times higher than the current annual dose limit of 20 mSv suggested by the ICRP for radiation workers. On the other hand, indoor radon concentration in some regions of HBRAs of Ramsar is up to 31 kBq m^{-3}(2), a concentration that is much higher than the action level recommended by the U.S. Environmental Protection Agency (EPA) (148 Bq m^{-3} or 4 pCi/L). Considering high levels of public exposures to ionizing radiation in the residents of HBRAs of Ramsar, some experts have recently suggested the need for an effective remedial action program (2). The residents of HBRAs of Ramsar and their ancestors have been exposed to extraordinary levels of natural radiation over many generations. Therefore, if a radiation dose reaching 260 mSv y^{-1} is detrimental to health causing genetic abnormalities or an increased risk of cancer, it should be evident in these people. The first report on the induction of biopositive biological responses (i.e. adaptive response) in the residents of HBRAs dates back to 2002 (3). Mortazavi *et al.* have previously shown that the highest lung cancer mortality rate in HBRAs of Ramsar was in a district with normal levels of radon while the lowest lung cancer mortality rate was in another district with the highest concentrations of radon in the dwellings (4). However, it should be noted that due to the statistical limitations of the cancer studies in HBRAs of Ramsar, only a long-term study can provide considerable number of person-years of observation (the population who live in the HBRAs of Ramsar is estimated to be about 2000 individuals) (5, 6).

In another high background radiation area, Yangjiang, China, Tao *et al.* investigated the health effects of high background radiation on mortality during the period 1979-1998. Their findings showed that the cumulative high background radiation dose was not linked to the mortality due to cancer or all non-cancer (7). As telomere length can be considered as a biomarker of aging, stress and cancer, Das *et al.* determined the telomere length in the residents of HBRAs of Kerala coast in Southwest India and the adjacent normal background radiation areas (NBRAs) and found that above-the-background levels of natural radiation had no significant effect on telomere length (8). In a cohort study performed in 2009 in Kerala, India, it was shown that no cancer site was significantly linked to cumulative radiation dose. Leukemia was not also significantly associated to high background radiation levels. In this study, although Nair *et al.* believed that the statistical power, due to the low levels of dose, was not possibly adequate, their cancer incidence data along with previously reported cancer mortality studies in the HBRAs of Yangjiang, China, cannot confirm that estimates of risk at low doses are substantially greater than the currently believed levels (9). Therefore, we believe that to some extent, our previous findings may be affected by the small population sample size that limits the statistical power and emphasizes the role of the confounding factors such as smoking and diet. To further investigate the shape of the dose-response curve for leukemia and solid tumors in HBRAs of Ramsar, some studies have been started by our research team in recent years. However, it is too early to draw firm conclusions from these research projects. Scientists from the U.S. Department of Energy's Lawrence Berkeley National Laboratory (Berkeley Lab) have recently shown that the risk of cancer from low-dose radiation in most of the mice exposed to a single, whole body, low dose radiation was not increased. Interestingly, a small minority of mice was actually protected from cancer development by low-dose radiation and only a small minority became more susceptible (7). In mice that were susceptible to cancer from low-dose radiation, they identified more than a dozen regions in their genomes that contributed to an individual's sensitivity to low-dose radiation. Considering these findings, as mice and humans share many genes, it can be hypothesized that low dose radiation is possibly not carcinogen by itself and the genetic makeup of the living organisms possibly plays a significant role in the carcinogenesis of low levels of ionizing radiation. It is worth mentioning that in a study on the level of eight biomarkers in the residents of HBRAs of Ramsar and a nearby NBRA it was revealed that the means of PSA, CA15.3, CA125, CA19.9 and AFP were not significantly different. However, significant increases were found in Cyfra21, CEA and Tag72 in HBRA group compared to those of the NBRA group. Moreover, the external gamma dose as well as indoor radon level were linked to the concentration of CEA, Cyfra-21 and TAG 72. This study clearly showed that chronic exposure to high background radiation caused significant alterations in Cyfra21, CEA and Tag72 levels [10].

Therefore, it seems that the majority of the residents of high background radiation areas are the people whose genetic makeup has made them to some extent resistant to the detrimental effects of low levels of ionizing radiation. This new concept along with the old reports which showed that low doses of ionizing radiation possibly trigger the transcription of many genes and the activation of numerous signaling pathways which leads to cell defenses such as more efficient detoxification of free radicals, DNA repair systems, induction of new proteins in irradiated cells with a conditioning dose, and enhanced antioxidant production [8], can explain the low rate of cancer in HBRAs of Ramsar. Due to the complexity of humans, and uncertainties in extrapolating data from animals to humans, further research is needed to confirm these hypotheses. In this light, we believe that the findings of Berkeley Lab can help us find a solution to the paradox of cancer incidence in high background radiation areas of Ramsar.

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