BIOLOGICAL EFFECTS OF HIGH BACKGROUND NATURAL RADIATIONS IN HUMANS

Rashmi Priya[1,2], Vinay Jain[1,2], Divyalakshmi Saini[1,2], PR Vivek Kumar[1], Deepak Sharma[1,2] and Tapan Kumar Ghanty[2,3]
[1]Radiation Biology & Health Sciences Division,
Bio-Science Group, Bhabha Atomic Research Centre,
Trombay, Mumbai-400085, India.
[2]Homi Bhabha National Institute, Anushaktinagar Mumbai-400094, India.
[3]Bio-Science Group, Bhabha Atomic Research Centre,
Trombay, Mumbai-400085, India.

E-mail: tapang@barc.gov.in

Abstract:
Life on earth has evolved around ionizing radiation (IR) emerging from radioactive elements present in cosmos, soil, air and water. Humans are exposed to IR from space, earth, food, drinking water, medical sources, nuclear fallout and other living organisms. Understanding the health effects of IR in relation to dose and dose-rate is important for work safety, fostering appropriate public perception and establishing radiation protection policies. Life-long expsure to chronic high background natural radiation has been shown to extend life-expectancy by ~2.5 years in the US population. Epidemiological studies have shown that IR-induced extension of lifespan is associated with lower cancer mortality. High level natural radiation does not increase birth defects or cancer risk in people residing in South-West coast of Kerala, India. On the contrary, acute exposure to similar doses of IR during CT scan and atomic bomb survivors increased cancer risk. A few mechanistic studies have shown activation of DNA repair genes, antioxidant systems and immunity in response to chronic low dose radiation which may be responsible for the observed health beneficial effects. This chapter summarizes the global research on biological and health effects of high background natural radiation on human populations.

Introduction:

Ionizing radiation (IR) is an inevitable part of the lives of all living beings. As per United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), natural background radiation is a measure of the IR in the environment at a certain area without any intentional introduction of radiation sources. The natural radiation is derived mainly from cosmic and terrestrial sources. Uranium, Thorium and Radium are the main naturally occuring radioactive materials in the Earth's crust. Radon is the major gaseous contributor for natural background radiation and internal exposure. Potassium-40 isotope found in the food materials also contributes to daily dose of IR. The global average annual radiation exposure from different natural sources is around 2.4 millisievert/year (mSv/yr, Fig. 1). Along with natural background radiation, human beings are also exposed to man-made (artificial) radiation sources [1]. Exposure to low doses of IR can happen during diagnostic / therapeutic procedures and also in the occupational workers (nuclear power plant workers, miners, pilots, radiologist, astronauts). Acute exposures to different doses of IR (few mGy to few Gy) have been reported from incidents like atomic bombing in Hiroshima and Nagasaki, accidents at Chernobyl and Fukushima Daiichi nuclear plants. In the last few years, medical exposure has become a major man-made source of radiation and the incidences and total doses are increasing with the time. During 2009–2018, more than 4.0 billion medical radiological examinations were performed. The use of CT scan for diagnostic purpose has replaced many older, less intensive radiological processes, leading to the overall increase in medical exposures [2].

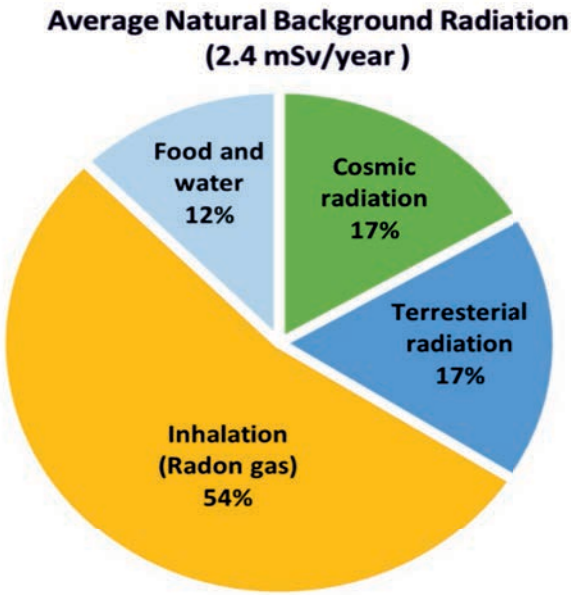

Fig. 1: Sources of Natural Radiation (UNSCEAR 2020/2021 Report Vol 1)

There are several High-Level Natural Radiation Areas (HLNRAs) around the world where the natural background radiation is higher than the global average (2.4mSv/year). These areas contain high concentration of radioactive elements like Uranium, Radium and Thorium. Four

prominent HLNRAs are present in Kerala (India), Guarapari (Brazil), Yangjiang (China) and Ramsar (Iran) (figure 2). The highest average exposure levels measured is in Ramsar, Iran which comes from radium (Ra^{226}) and its decay products in hot springs. The maximum dose is up to 260.0 mGy/yr but the area is sparsely populated[3].

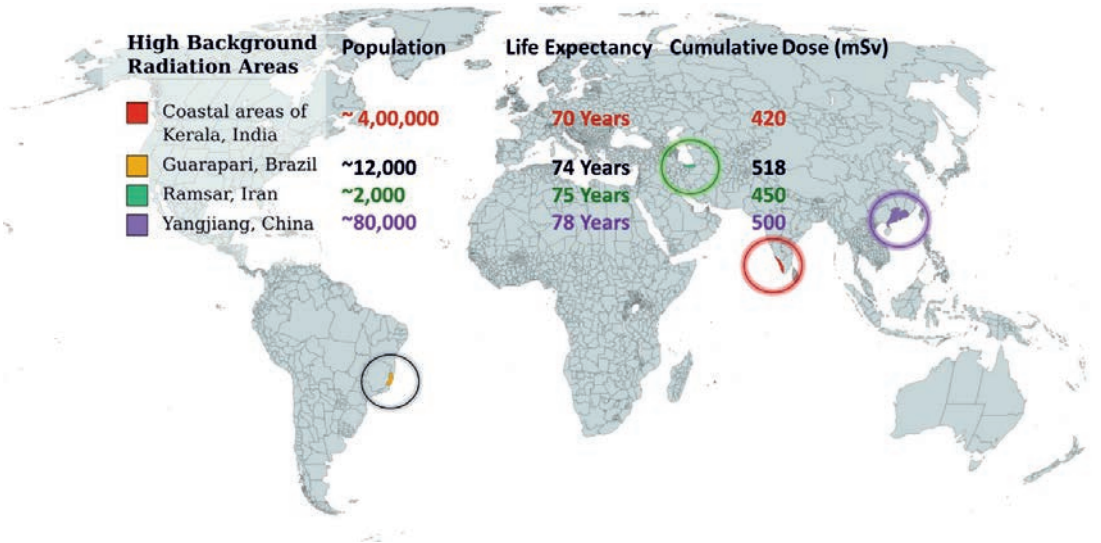

Fig. 2: World map showing four most prominent High-Level Natural Radiation Areas with their population size and average lifetime cumulative dose.

In Kerala (India), the background radiation is due to monazite sand containing radioactive thorium and its decay products. The largest radiation exposed population of almost 4,00,000 individuals lives in HLNRAs of Kerala and it has been extensively studied using various health, cytogenetic and molecular parameters to determine the effect of chronic high background radiation on humans. The background radiation dose in Karunagapally Taluk, part of HLNRA of Kerala, India is between 0.5 mGy/yr to more than 45.0 mGy/yr. In certain pockets, the radiation level is more than 70.0 mGy/yr. Over the past four decades, several studies on biological and health parameters have been carried out in this population. These studies have provided important insights on the effects of chronic low dose/dose rate exposures directly on humans.

A). Health effects of chronic low dose radiation in HLNRA Kerala, India and other countries:

1. Incidence of cancer in HLNRA:

A recently published epidemiological study spanning over 3 decades on a cohort of 149,585 residents aged 30-84 yr showed that there was no significant increase in the relative risk of any of the cancers due to high background radiation in the people who received a cumulative radiation dose of up to 617 mGy (Fig. 3). However, a negative excess relative risk [ERR = -0.05/Gy (95% CI: -0.33 to 0.29)] was reported for solid cancer in HLNRA, Kerala [4].

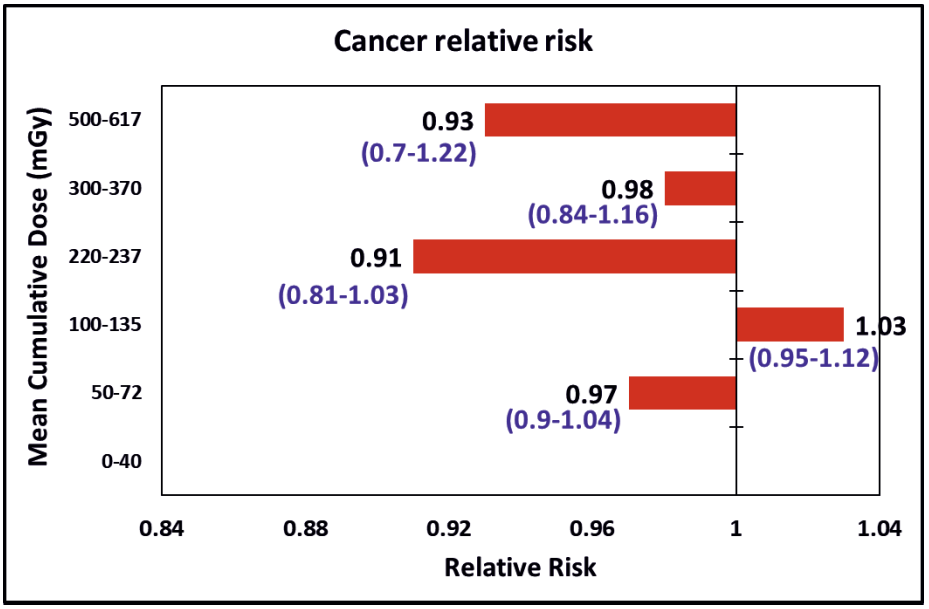

Fig. 3: Relative risk of cancer in population exposed to different cumulative doses of background radiation in Kerala. Confidence interval is shown in blue (adapted from Ref. 4).

Similarly, in HLNRA of Yangjiang, China, in a cohort size of over 1,00,000 individuals exposed to annual effective dose of 6.4 mSv, the cancer related deaths were not increased. Moreover, overall deaths caused by different types of cancers were also lower and ERR/Sv for solid cancer was reported as -0.11 (95% CI: -0.67 to 0.69)[5]. In Ramsar, Iran, no statistically significant increase was observed in cancer mortality ratio and incidence ratio. Further, the report suggested a negative correlation between local radon concentration and incidence of lung cancer[3]. The individuals included in above studies had received a cumulative dose of > 500 mGy and they did not show any increase in cancer risk.

In US, radon gas can contribute significantly to background radiation. In a recent epidemiological study encompassing entire US population (320 million), it was shown that life expectancy of population exposed to high background radiation (>1.8 mGy/yr) was almost 2.5 years more than the population exposed to lower doses (<1.0 mGy/yr). The gender based stratification analysis indicated that background radiation negatively correlated with cancer deaths in both males ($r = -0.90$ and $r = -0.77$), as well as females ($p < 0.001$; 95% CI)[6].

On the contrary, acute exposure to radiation has been unequivocally shown to increase cancer risk. In the long term follow up study of atomic bomb survivors from Japan (cohort size >100,000), it was reported that radiation exposure enhanced solid cancer risk (ERR of 0.40, 95% CI: −0.58 to 2.59) [7]. Similarly, two independent studies comprising of cohort size of more than 11 million young patients exposed to acute radiation through CT scan showed that exposure to 25mGy to 60 mGy can cause a small but significant increase in cancer risk (about 25 per 10,000) [8, 9]. Thus, biological effects of acute and chronic low dose radiation in human populations show contrasting results.

2. Non-cancer diseases in HLNRA:

Limited studies on non-cancer diseases in HLNRA have been carried out. In Yangjiang, China, the populations living in HLNRA was compared with neighboring areas with normal background radiation and a significant effect on non-cancer mortality was reported[3]. Several diseases such as cerebro-vascular diseases, tuberculosis, viral infections, digestive system etc were included. However, these studies lack scientific standing since they did not take into the account other risk factors associated with these diseases.

In Kerala, India, Health audit survey has been carried out to study the prevalence of late onset diseases and life style diseases including circulatory diseases and diabetes in HLNRA and control areas. So far, no increase in the prevalence of these diseases has been seen in people living in high background radiation areas (unpublished data).

3. Hereditary and congenital diseases in HLNRA:

In HLNRA of Kerala, a comprehensive study was carried out to evaluate the prevalence of congenital malformations such as Down's syndrome, cleft lip, microcephaly, polydactyly etc. in the infants born to parents residing in HLNRA as well as NLNRA. More than 1, 90,000 newborns have been analyzed for prevalence of congenital malformation and stillbirth with respect to maternal and paternal cumulative doses. The results demonstrated that there was no significant increase in any of the malformations with cumulative dose of radiation to mothers or fathers (Fig 4). No influence of high background radiation on sex ratio at birth was observed. Recently, in a hospital based prospective study on prevalence of Congenital Heart Diseases (CHD) among the live newborns of HLNRA and NLNRA, a significant reduction in prevalence of CHDs among the newborns from HLNRA was observed.[10-16]

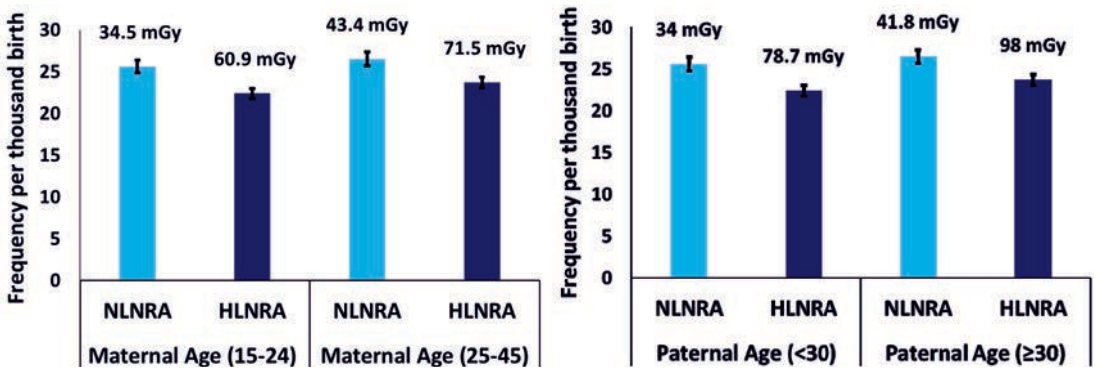

Fig. 4: Frequency of congenital abnormalities between NLNRA and HLNRA: Effect of Maternal (left) Paternal radiation dose (right) is graphed. Mean cumulative dose is shown above each bar.

In Yangjiang, China, the rate of congenital/hereditary diseases (31 different diseases) was studied in 13,000 children from HLNRA. Similar rate of congenital diseases was observed between the children from HLNRA and those from control areas [17].

B). Biological effects of chronic low dose radiation prevailing in HLNRA.

Apart from epidemiological studies, several mechanistic studies using cytogenetic and molecular markers have been carried out in HLNRA of Kerala coast.

1. Cytogenetic studies:

Cytogenetic investigation including karyotype anomalies (numerical and structural) and chromosomal aberrations (translocation/inversions/dicentrics) was carried out in over 27,000 newborns. None of the endpoint showed significant difference between HLNRA and control population (NLNRA). The frequency of micronuclei (MN) among the newborns as well as adults was comparable between these two populations. [18-20]. Similar studies have been conducted in other HLNRAs. In Yangjiang, China, a significant increase in unstable type aberrations (dicentric and rings) was observed in HLNRA individuals in comparison to control group, whereas no significant increase in frequency of translocations was seen. In Ramsar, Iran, two studies have shown contradictory results. One study reported no difference in chromosomal aberration frequency between HLNRA and control areas whereas another study carried out in 80 adults showed significant increase in unstable and stable chromosomal aberrations[3].

2. Molecular studies:

Spontaneous/basal level frequency of DNA double strand breaks (DSBs) was measured using gamma-H2AX, a phosphorylated form of Histone H2AX protein which is a sensitive and surrogate marker of DNA DSBs. The study was carried out in 200 individuals and the cumulative dose received by these individuals varied from 37.6 mGy to > 800 mGy. No linear increase in DNA DSBs was observed upto >800 mGy cumulative dose [21, 22]. In another study, single strand breaks and oxidized bases were measured and no significant difference in two populations was observed[23]. Further, an efficient and improved repair of DNA strand breaks was observed in HLNRA individuals [24, 25]. Telomere length analysis was carried out in the healthy adults and it was found that a cumulative dose of 41 mGy to 663 mGy did not affect telomere length in humans [26, 27]. Transcriptome and proteomics analysis carried out in individuals residing in different background radiation dose groups revealed that a large number of genes/proteins involved in DNA repair mechanisms, epigenetic modifications and survival pathways were activated in HLNRA individuals [28,29]. The activation of these pathways may be the plausible reason for adaptation in response to background radiation.

Further, Germline mutations were studied in a cohort of 200 families using over 40 mini and microsatellite markers. There was no noticeable increase in mutation rates observed in HLNRA population. Similar findings were reported in children of atomic bomb survivors [30]. In a recently published study, where whole genome sequencing was carried out in 130 children of cleanup workers exposed during Chernobyl nuclear accident, the results did not show any increase in de-novo mutations [31].

Conclusion and Future Directions:

Understanding the health risks associated with low dose ionizing radiation is of great relevance for regulatory purposes, building public perception and designing various radiation based therapeutic and diagnostic regimens. As mentioned in UNSCEAR 2020 report, comprehensive studies are required to understand molecular mechanisms active at low doses

and dose-rates. The HLNRA of Kerala coast, being the nature's own laboratory provides unique opportunity to study radiation effects directly on humans. Epidemiological studies on cancer incidence and congenital abnormalities as well as different biological endpoints have not shown any adverse effect of chronic low dose radiation. Studies have been initiated to evaluate the effect of high background natural radiation on lifespan of people residing in Kerala. Detailed mechanistic studies in the individuals who have received cumulative dose of >200 mGy background radiation may provide important insights into biological adaptations associated with healthy ageing.

References:

1. UNSCEAR *Sources and Effects of Ionizing Radiation, United Nations Scientific Committee on the Effects of Atomic Radiation*; New York: United Nations., 2000.
2. UNSCEAR, Biological mechanisms relevant for the inference of cancer risks from low-dose and low-dose-rate radiation. *UNSCEAR 2020/2021 Report Volume III scientific annex C* **2020/2021**.
3. Hendry, J. H.; Simon, S. L.; Wojcik, A.; Sohrabi, M.; Burkart, W.; Cardis, E.; Laurier, D.; Tirmarche, M.; Hayata, I., Human exposure to high natural background radiation: what can it teach us about radiation risks? *Journal of radiological protection : official journal of the Society for Radiological Protection* **2009,** *29* (2a), A29-42.
4. Amma, J. P.; Nair, R. A.; Nair, R. R. K.; Hoel, D. G.; Akiba, S.; Nakamura, S.; Endo, K., Background Radiation and Cancer Excluding Leukemia in Kerala, India – Karunagappally Cohort Study. *Radiation Environment and Medicine* **2021,** *10* (2), 74-81.
5. Tao, Z.; Zha, Y.; Akiba, S.; Sun, Q.; Zou, J.; Li, J.; Liu, Y.; Kato, H.; Sugahara, T.; Wei, L., Cancer mortality in the high background radiation areas of Yangjiang, China during the period between 1979 and 1995. *J Radiat Res* **2000,** *41 Suppl*, 31-41.
6. David, E.; Wolfson, M.; Fraifeld, V. E., Background radiation impacts human longevity and cancer mortality: reconsidering the linear no-threshold paradigm. *Biogerontology* **2021,** *22* (2), 189-195.
7. Brenner, A. V.; Sugiyama, H.; Preston, D. L.; Sakata, R.; French, B.; Sadakane, A.; Cahoon, E. K.; Utada, M.; Mabuchi, K.; Ozasa, K., Radiation risk of central nervous system tumors in the Life Span Study of atomic bomb survivors, 1958-2009. *Eur J Epidemiol* **2020,** *35* (6), 591-600.
8. Pearce, M. S.; Salotti, J. A.; Little, M. P.; McHugh, K.; Lee, C.; Kim, K. P.; Howe, N. L.; Ronckers, C. M.; Rajaraman, P.; Sir Craft, A. W.; Parker, L.; Berrington de González, A., Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. *Lancet (London, England)* **2012,** *380* (9840), 499-505.
9. Mathews, J. D.; Forsythe, A. V.; Brady, Z.; Butler, M. W.; Goergen, S. K.; Byrnes, G. B.; Giles, G. G.; Wallace, A. B.; Anderson, P. R.; Guiver, T. A.; McGale, P.; Cain, T. M.; Dowty, J. G.; Bickerstaffe, A. C.; Darby, S. C., Cancer risk in 680,000 people exposed to computed tomography scans in childhood or adolescence: data linkage study of 11 million Australians. *Bmj* **2013,** *346*, f2360.

10. Jaikrishan, G.; Andrews, V. J.; Thampi, M. V.; Koya, P. K.; Rajan, V. K.; Chauhan, P. S., Genetic monitoring of the human population from high-level natural radiation areas of Kerala on the southwest coast of India. I. Prevalence of congenital malformations in newborns. *Radiat Res* **1999,** *152* (6 Suppl), S149-53.
11. Jaikrishan, G.; Sudheer, K. R.; Andrews, V. J.; Koya, P. K.; Madhusoodhanan, M.; Jagadeesan, C. K.; Seshadri, M., Study of stillbirth and major congenital anomaly among newborns in the high-level natural radiation areas of Kerala, India. *J Community Genet* **2013,** *4* (1), 21-31.
12. Koya, P. K.; Chougaonkar, M. P.; Predeep, P.; Jojo, P. J.; Cheriyan, V. D.; Mayya, Y. S.; Seshadri, M., Effect of low and chronic radiation exposure: a case-control study of mental retardation and cleft lip/palate in the monazite-bearing coastal areas of southern Kerala. *Radiat Res* **2012,** *177* (1), 109-16.
13. Koya, P. K.; Jaikrishan, G.; Sudheer, K. R.; Andrews, V. J.; Madhusoodhanan, M.; Jagadeesan, C. K.; Das, B., Sex ratio at birth: scenario from normal- and high-level natural radiation areas of Kerala coast in south-west India. *Radiation and environmental biophysics* **2015,** *54* (4), 453-63.
14. Cheriyan, V. D.; Kurien, C. J.; Das, B.; Ramachandran, E. N.; Karuppasamy, C. V.; Thampi, M. V.; George, K. P.; Kesavan, P. C.; Koya, P. K.; Chauhan, P. S., Genetic monitoring of the human population from high-level natural radiation areas of Kerala on the southwest coast of India. II. Incidence of numerical and structural chromosomal aberrations in the lymphocytes of newborns. *Radiat Res* **1999,** *152* (6 Suppl), S154-8.
15. Ramachandran, E. N.; Karuppasamy, C. V.; Cheriyan, V. D.; Soren, D. C.; Das, B.; Anilkumar, V.; Koya, P. K.; Seshadri, M., Cytogenetic studies on newborns from high and normal level natural radiation areas of Kerala in southwest coast of India. *Int J Radiat Biol* **2013,** *89* (4), 259-67.
16. Sudheer, K. R.; Mohammad Koya, P. K.; Prakash, A. J.; Prakash, A. M.; Manoj Kumar, R.; Shyni, S.; Jagadeesan, C. K.; Jaikrishan, G.; Das, B., Evaluation of risk due to chronic low dose ionizing radiation exposure on the birth prevalence of congenital heart diseases (CHD) among the newborns from high-level natural radiation areas of Kerala coast, India. *Genes Environ* **2022,** *44* (1), 1.
17. Wei, L. X.; Zha, Y. R.; Tao, Z. F.; He, W. H.; Chen, D. Q.; Yuan, Y. L., Epidemiological investigation of radiological effects in high background radiation areas of Yangjiang, China. *J Radiat Res* **1990,** *31* (1), 119-36.
18. Das, B.; Karuppasamy, C. V., Spontaneous frequency of micronuclei among the newborns from high level natural radiation areas of Kerala in the southwest coast of India. *Int J Radiat Biol* **2009,** *85* (3), 272-80.
19. Karuppasamy, C. V.; Ramachandran, E. N.; Kumar, V. A.; Kumar, P. R.; Koya, P. K.; Jaikrishan, G.; Das, B., Peripheral blood lymphocyte micronucleus frequencies in men from areas of Kerala, India, with high vs normal levels of natural background ionizing radiation. *Mutation research. Genetic toxicology and environmental mutagenesis* **2016,** *800-801*, 40-5.
20. Ramachandran, E. N.; Karuppasamy, C. V.; Kumar, V. A.; Soren, D. C.; Kumar, P. R. V.; Koya, P. K. M.; Jaikrishan, G.; Das, B., Radio-adaptive response in peripheral blood

lymphocytes of individuals residing in high-level natural radiation areas of Kerala in the southwest coast of India. *Mutagenesis* **2017,** *32* (2), 267-273.

21. Jain, V.; Kumar, P. R.; Koya, P. K.; Jaikrishan, G.; Das, B., Lack of increased DNA double-strand breaks in peripheral blood mononuclear cells of individuals from high level natural radiation areas of Kerala coast in India. *Mutat Res* **2016,** *788*, 50-7.
22. Jain, V.; Saini, D.; Soren, D. C.; Kumar, V. A.; Vivek Kumar, P. R.; Koya, P. K. M.; Jaikrishan, G.; Das, B., Non-linear dose response of DNA double strand breaks in response to chronic low dose radiation in individuals from high level natural radiation areas of Kerala coast. *Genes and Environment* **2023,** *45* (1), 16.
23. Kumar, P. R.; Cheriyan, V. D.; Seshadri, M., Evaluation of spontaneous DNA damage in lymphocytes of healthy adult individuals from high-level natural radiation areas of Kerala in India. *Radiat Res* **2012,** *177* (5), 643-50.
24. Kumar, P. R.; Seshadri, M.; Jaikrishan, G.; Das, B., Effect of chronic low dose natural radiation in human peripheral blood mononuclear cells: Evaluation of DNA damage and repair using the alkaline comet assay. *Mutat Res* **2015,** *775*, 59-65.
25. Jain, V.; Saini, D.; Kumar, P. R. V.; Jaikrishan, G.; Das, B., Efficient repair of DNA double strand breaks in individuals from high level natural radiation areas of Kerala coast, south-west India. *Mutat Res* **2017,** *806*, 39-50.
26. Das, B.; Saini, D.; Seshadri, M., Telomere length in human adults and high level natural background radiation. *PLoS One* **2009,** *4* (12), e8440.
27. Saini, D.; Jain, V.; Das, B., Evaluation of natural chronic low dose radiation exposure on telomere length and transcriptional response of shelterin complex in individuals residing in Kerala coast, India. *Mutat Res* **2022,** *825*, 111797.
28. Jain, V.; Das, B., Global transcriptome profile reveals abundance of DNA damage response and repair genes in individuals from high level natural radiation areas of Kerala coast. *PLoS One* **2017,** *12* (11), e0187274.
29. Nishad, S., Chauhan, P.K., Sowdhamini, R. Ghosh, A. Chronic exposure of humans to high level natural background radiation leads to robust expression of protective stress response proteins. Sci Rep 11, 1777 (2021). https://doi.org/10.1038/s41598-020-80405-y
30. Kodaira, M.; Izumi, S.; Takahashi, N.; Nakamura, N., No evidence of radiation effect on mutation rates at hypervariable minisatellite loci in the germ cells of atomic bomb survivors. *Radiat Res* **2004,** *162* (4), 350-6.
31. Yeager, M.; Machiela, M. J.; Kothiyal, P.; Dean, M.; Bodelon, C.; Suman, S.; Wang, M.; Mirabello, L.; Nelson, C. W.; Zhou, W.; Palmer, C.; Ballew, B.; Colli, L. M.; Freedman, N. D.; Dagnall, C.; Hutchinson, A.; Vij, V.; Maruvka, Y.; Hatch, M.; Illienko, I.; Belayev, Y.; Nakamura, N.; Chumak, V.; Bakhanova, E.; Belyi, D.; Kryuchkov, V.; Golovanov, I.; Gudzenko, N.; Cahoon, E. K.; Albert, P.; Drozdovitch, V.; Little, M. P.; Mabuchi, K.; Stewart, C.; Getz, G.; Bazyka, D.; Berrington de Gonzalez, A.; Chanock, S. J., Lack of transgenerational effects of ionizing radiation exposure from the Chernobyl accident. *Science* **2021,** *372* (6543), 725-729.