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Experimental insights into high background radiation: reduced cancer risks in a murine model study

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ABSTRACT

Background: Natural background radiation varies geographically and has potential implications for cancer development. High-level natural radiation areas (HLNRAs), like Ramsar, Iran, offer unique opportunities to study the biological effects of radiation exposure. This study investigates the relationship between high background radiation and tumor progression in a murine model. ***Materials and Methods:*** Thirty-two C57BL/6 mice were exposed to varying levels of natural radiation (0.097 µSv/h to 9.24 µSv/h) for two months, simulating conditions in Ramsar. Mice were divided into four groups based on radiation intensity. After exposure, 1^{106} B16-F10 melanoma cells were injected subcutaneously, and tumor growth was monitored for 24 days. Tumor morphology was assessed using Magnetic Resonance Imaging (MRI), and survival rates were recorded. Statistical analyses included mixed-model and Kaplan-Meier methods. ***Results:*** Tumor volume and growth rates were significantly reduced in groups exposed to the highest radiation levels (100X Bkg). Mice in this group also exhibited the highest survival rates (100%) compared to the control group (55.6%). Tumor reduction and disintegration were observed, especially in female mice, suggesting a potential protective effect of elevated radiation exposure against melanoma progression. ***Conclusion:*** Findings challenge the Linear No-Threshold (LNT) model by demonstrating that high background radiation may not correlate with increased cancer risk. Instead, elevated radiation levels appear to confer protective effects against tumor growth in this murine model. These results highlight the need to reassess radiation safety standards and explore the complex interplay between radiation and cancer biology.

INTRODUCTION

Specific regions around the world have notably elevated background radiation levels due to geological and geochemical conditions, which enhance terrestrial radiation [1, 2]. For instance, certain geographic regions are characterized by high natural background radiation due to unique geological formations[3-5]. One such area is the monazite-rich sand deposits in places like Guarapari in Brazil, which contribute to elevated levels of gamma radiation from thorium decay. Similarly, the coastal belt of Kerala in southern India contains monazite sands that emit significant levels of radiation, primarily due to high concentrations of thorium-232. Yangjiang in China is another region with elevated background radiation, where uranium and thorium decay products in the soil and rocks increase exposure for local populations. In addition to these areas, Ramsar in Iran stands out for its

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exceptionally high natural radiation levels, which are some of the highest recorded in residential areas worldwide. This elevated radiation in Ramsar is primarily due to radium and radon emanating from local hot springs and geological deposits rich in uranium and thorium series radionuclides. The radium-laden water and high radon concentrations in the air contribute to radiation exposure levels far exceeding typical background levels, with residents in certain zones of Ramsar experiencing exposure rates up to 260 mSv per year, which is many times the global average. These unique high-radiation environments provide valuable natural laboratories for studying the effects of chronic low-dose radiation exposure on biological systems and public health [6-14]. Ramsar, in particular, is known for having radiation levels 55 to 200 times the global average, making it one of the most densely populated high-radiation zones in the world [2, 15-17].

The International Commission on Radiation Protection (ICRP) established a global annual radiation exposure limit of 1 mSv to safeguard humans and wildlife [18]. Contrastingly, in Ramsar, where natural radiation levels are exceptionally high, residents can experience annual exposure rates as high as 260 mSv, with an average dose rate of about 10 mGy for its roughly 2,000 inhabitants [19-21]. The radon levels in certain Ramsar sites can reach up to 31,000 Bq/m3, significantly higher than less affected areas where levels are below 148 Bq/m^3. The residents of these areas are also being exposed to elevated levels of alpha activity through ingestion of radium and its decay products, as some residents consume vegetables and fruits grown in local hot soil. Consequently, annual radiation exposure levels for some residents far exceed the ICRP's occupational dose limit of 20 mSv/year [18].

Living in areas with high radiation exposure has posed significant health concerns across generations. If annual radiation levels in the hundreds of mSv range were detrimental, leading to genetic abnormalities or an increased risk of cancer, evidence of such effects would be apparent in the local populations [19]. However, reports suggest no significant increase in cancer mortality or incidence in Ramsar, with some studies even indicating a decrease in cancer rates among high background radiation area (HBRA) residents [22, 23]. Yet, the challenge remains to gather sufficient long-term epidemiological data from about 2,000 residents to obtain statistically reliable data, due to the small population living in the most affected areas.

The health effects of cobalt-60 exposure in Taiwan's contaminated apartments challenge traditional radiation protection paradigms, offering unexpected insights into chronic low-dose radiation exposure. Residents who received an average dose of 0.4 Sv over 9–20 years exhibited cancer mortality rates approximately 2.5% of the general population's rates and significantly lower incidences of congenital malformations, at about 5–7% of the general public [24]. However, reproductive health concerns were observed, with prolonged time to pregnancy and a fecundability ratio of 0.75 during exposure, particularly among mothers [25]. These findings challenge the linear no-threshold (LNT) model, suggesting the need for a reassessment of radiation safety standards based on potential health benefits of chronic low-dose exposure [24]. Nonetheless, the long-term risks of such exposure remain contentious, warranting further research to clarify its implications for public health.

A study conducted by Mortazavi *et al*. in 2014, was aimed to assess whether short-term exposure to high natural radiation induces oxidative stress in Wistar rats [26]. In this study, fifty-three rats were divided into groups exposed to normal or elevated radiation for 7 days, with oxidative stress biomarkers, catalase (CAT) activity and malondialdehyde (MDA) levels, measured on days 7 and 9. After a lethal gamma radiation dose on day 8, biomarker levels were compared. Results showed no significant differences in CAT (P=0.69) or MDA (P=0.05) across groups after exposure, nor after the lethal dose (P=0.054, P=0.163). The findings suggested short-term exposure to high natural radiation did not induce oxidative stress, warranting further research into long-term effects and adaptive responses [26].

Another study by the same team investigating the effects of short-term exposure to high natural gamma radiation in Ramsar, Iran, found no evidence of a survival adaptive response [17]. The study involved 50 male NMRI mice and 53 Wistar rats, which were exposed to elevated radiation levels for 7 days before being subjected to a lethal 8 Gy gamma radiation dose. The survival rates 30 days after exposure revealed that while control groups had a 40% survival rate, animals exposed to high radiation in Ramsar showed no significant improvement. For mice, survival rates ranged from 20% to 35%, and for rats, from 20% to 60%. The results suggested that short-term exposure to natural radiation, even at levels up to 196 times the normal background, does not induce a survival adaptive response [17].

This lack of long-term epidemiological data raises numerous public health policy issues [27], such as whether to relocate inhabitants to areas with lower natural background radiation levels and the financial and emotional costs associated with such relocation. The unique conditions in Ramsar offer invaluable insights into the epidemiological impacts of low-dose radiation exposure, an area still not fully understood. Thus, studying the potential health risks, particularly cancer, in high radiation background areas like Ramsar is crucial, not only for expanding our knowledge on low-dose radiation effects but also for assessing the specific cancer risks associated with

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such environments. Given that Ramsar has the highest levels of background radiation among residential areas worldwide, the significance of investigating the causal relationship between high background radiation and cancer incidence is unequivocally critical.

This study is novel in its approach by directly investigating the paradoxical relationship between high natural background radiation and tumor progression using a well-controlled murine model. By simulating radiation levels akin to those found in Ramsar-one of the highest natural radiation areas-the research challenges the traditional linear no-threshold model, suggesting that elevated radiation may actually inhibit melanoma growth and enhance survival. Additionally, the integration of advanced imaging techniques and rigorous survival analyses provides new insights into the biological effects of chronic low-dose radiation exposure, paving the way for a potential reassessment of current radiation safety standards.

MATERIALS AND METHODS

Animals

In this study, 32 C57BL/6 mice (male and female) weighing 18-20 g, aged 4-5 weeks were purchased from the Comparative and Experimental Medicine Center at Shiraz University of Medical Sciences. The animals were randomly assigned to four groups of 7-9 mice each. They were housed under controlled conditions with a 12-hour light/dark cycle at a temperature of 21±1°C, with ad libitum access to food and water. All experimental protocols adhered to the guidelines set by on the care of laboratory animals and their use for scientific purposes of Shiraz University of Medical Sciences (SUMS). The study was approved by the Medical Ethics Committee of Shiraz University of Medical Sciences (Approval Code: IR.SUMS.AEC.1403.011).

Exposure to naturally elevated levels of radiation

The first group (designated as Normal Bkg) was exposed to normal background radiation (0.097 µSv/h) in a standard room for approximately two months. The second, the third, and the fourth groups were exposed to higher levels of gamma radiation in indoor environments that could mimic high background radiation areas of Ramsar. The dose rates were 3.85 µSv/h (~40X Bkg), 6.66 µSv/h (~65X Bkg), and 9.24 µSv/h (~100X Bkg), respectively. The third group (65X Bkg) also experienced elevated radon levels, achieved by housing the mice in a cage with Ramsar radioactive soil to artificially increase Rn-220 levels, resulting in an average radon concentration of 681.84 Bq/m^3, compared to 40 Bq/m^3 in the laboratory environment. Radon levels were monitored using a PRASSI portable radon gas survey meter. The cages were designed to allow radon accumulation, and gamma radiation was measured with a calibrated RDS 110 survey meter positioned about 1 meter above the ground at each location.

Cell culture

Murine melanoma cells (B16F10 line) were obtained from the Transplant Research Center, Shiraz University of Medical Sciences. These cells were cultured in RPMI (Shellmax, China) medium supplemented with 10% fetal bovine serum (FBS) (Shellmax, China) at 37°C in an atmosphere of 5% CO_2 and 95% humidity. Cell viability was assessed using trypan blue (Shellmax, China) exclusion.

Induction of B16-F10 melanoma in mice

After approximately 5 weeks of radiation exposure, each mouse received an injection of 1×10^6 B16-F10 cells suspended in 200 µL of Ringer's solution into the shaved left flank. Tumor growth was monitored by measuring the size of tumors at regular intervals. Measurements were taken using calipers on days 14, 17, 20, and 24 post-injections, recording the shortest and longest tumor diameters. Tumor volume was calculated using the equation 1:

$$\text{volume } (cm^3) = \frac{\pi}{6}(\text{width}^2 \times \text{length}) \quad (1)$$

This method[28-30] provides a consistent and reliable assessment of tumor volume, correlating well with other evaluation metrics like tumor weight to carcass weight ratios [28].

MRI study protocol

The MRI study protocol involved acquiring images using the following sequences: axial T1_FLASH with fat suppression, axial T1_SE, coronal T2_HASTE, and axial T2_HASTE_STIR. The MRI machine used is a Siemens Avanto model with a 1.5 Tesla magnetic field strength. MRI was performed using various sequences as outlined in table 1.

Survival analysis

Table 1. MRI sequencing parameters.

Sequence	Number of Slices	Slice Thickness (mm)	Gap (%)	FOV (mm)	TR and TE (msec)	TI	FA	Matrix Size	NsA
Axial T1-FLASH-Fs	18	3	0	200× 200	91, 4.76	-	70°	128× 128	4
Axial T1-SE	18	3	0	200× 200	500, 17	-	90°	128× 128	2
Coronal T2-HASTE	15	3	0	200× 200	2000, 81	-	90°	128× 128	4
Axial T2-HASTE-STIR	18	3	0	200× 200	1500, 82	160	90°	128× 128	7

FOV: Field of View; TR: Repetition Time; TE: Echo Time; TI: Inversion Ti. FA: Flip Angle; NsA: Number of Signal Averages

Survival rates were analyzed using the Kaplan-Meier method. The time to event (death) and event status (1 = death, 0 = censored) were recorded for each animal. Survival probabilities were calculated, and comparisons between groups were performed using the log-rank test. Results were presented as survival curves with associated p-values to highlight

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differences in survival outcomes among the experimental groups.

Statistical analysis

Statistical analyses were performed using SPSS software (Version 21.0, IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp.) and GraphPad PRISM 9 (GraphPad Software, Boston, Massachusetts USA).

Survival analysis was conducted using the Kaplan-Meier method, with log-rank tests employed to compare survival curves between the different exposure groups. A p-value of less than 0.05 was considered statistically significant for all tests. All statistical tests were two-sided.

RESULTS

Tumor volume analysis

On the 24th day post-injection, the mean tumor sizes in mixed gender groups treated with Bkg (control), 40X Bkg, 65X Bkg with radon gas, and 100X Bkg were 3.57 cm^3, 3.30 cm^3, 1.63 cm^3, and 1.62 cm^3 respectively (Table 2). Analyzing by gender, the mean tumor sizes for male mice were 2.17 cm^3, 6.10 cm^3, 1.24 cm^3, and 2.17 cm^3 in the Bkg, 40X Bkg, 65X Bkg with radon gas (Rn), and 100X Bkg groups respectively. In female mice, the corresponding sizes were 9.16 cm^3, 0.51 cm^3, 1.89 cm^3, and 0.92 cm^3. A non-significant difference in tumor volume was observed between the 100X Bkg and control groups in female mice, indicating potential interactions between radiation exposure levels and tumor growth in these specific setups.

In some instances, tumor disintegration and volume reduction were observed in the 100X Bkg and 65X Bkg with Rn groups, whereas no decrease was noted in the Bkg and 40X Bkg groups, where tumor volume increased in all mice.

Table 2. The mean tumour volumes in different groups.

Group	Average Tumor Volume at Day 24 in Females (cm^3)	Average Tumor Volume at Day 24 in Males (cm^3)	Average Tumor Volume at Day 24, All Animals (cm^3)
Normal Bkg	9.16±0	2.17±0.52	3.57±3.15
40X Bkg	0.51±0.18	6.10±0.63	3.30±3.25
100X Bkg	0.92±1.76	2.17±2.20	1.62±2.01
65X Bkg + Rn	1.89±2.23	1.24±1.75	1.63±1.84
F-value	0.560	1.257	1.472
P-value	0.651	0.335	0.243

Regression analysis

As illustrated in Figure 1, the slope of the regression lines for the normal Bkg, 40X Bkg, 65X Bkg with Rn, and 100X Bkg groups were recorded as 0.807, 0.591, 0.347, and 0.420, respectively. These values represent the daily rate of tumor volume increase, highlighting the highest growth in the normal Bkg group and the lowest in the 100X Bkg group.

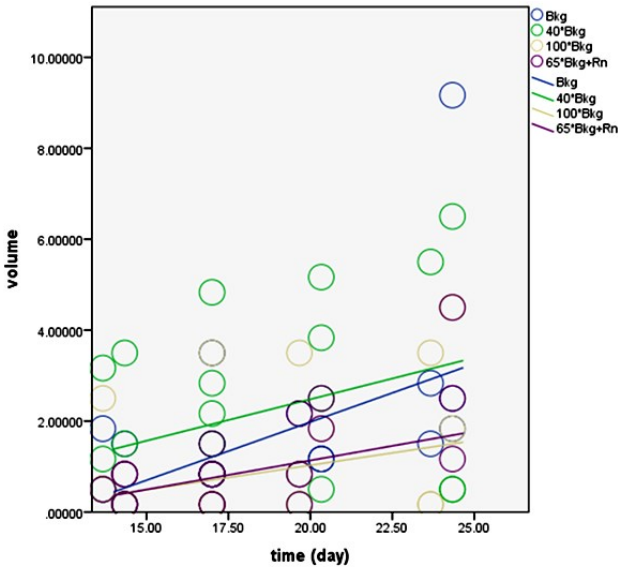

Figure 1. The slope of the regression lines in the normal Bkg, 40X Bkg, "65X Bkg + Rn", and 100X Bkg groups.

Figure 2 illustrates the incremental tumor growth in male and female mice across different exposure groups, demonstrating variable rates of tumor progression influenced by radiation exposure levels. Figure 3 illustrates the tumor growth in all mice (male and female mice) across different exposure groups

Figure 4 shows the survival rates of mice across different radiation exposure groups, with marked differences between those exposed to the highest and lower radiation levels. The statistical analysis confirms the significance of these differences, underscoring the potential protective or adaptive responses in the highest exposure group.

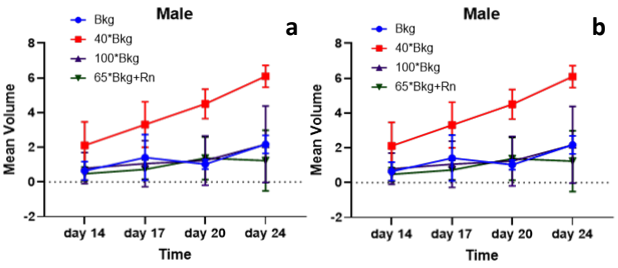

Figure 2. Mean+/-SD tumor volume in **a**. female and **b**. male C57BL/6 mice.

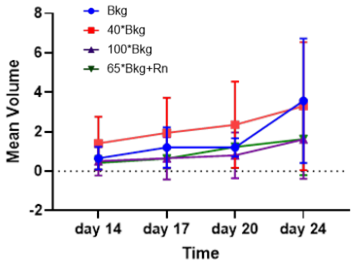

Figure 3. Mean+/-SD analysis of tumor growth in all C57BL/6 mice (males and females).

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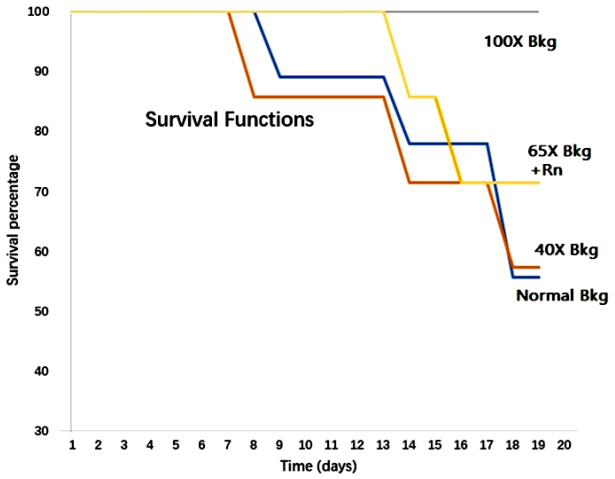

Figure 4. Survival analysis of B16F10 murine melanoma in C57BL/6 mice.

Survival analysis

The survival rates on the 24th day post-injection for the normal Bkg, 40X Bkg, 65X Bkg with Rn, and 100X Bkg groups were 55.56%, 57.14%, 71.42%, and 100% respectively. The survival difference between the 100X Bkg and both the control (normal Bkg) and 40X Bkg groups was statistically significant (P=0.02 and P=0.03, respectively).

The data demonstrate significant effects of radiation exposure on tumor growth dynamics and survival rates, highlighting potential biological impacts of environmental radiation variations.

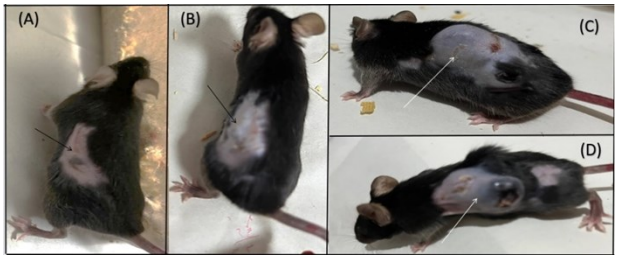

Figure 5. Melanoma tumor growth in mice. Panels **(A)** and **(B)** show the 100X Bkg group where tumor size reduction and tumor disintegration were observed, indicated by arrows. Panels **(C)** and **(D)** display the control (Bkg) group.

Figure 5 illustrates melanoma progression in mice, with panels (A) and (B) showing the 100X Bkg group where tumor size reduction and tumor disintegration were observed, indicated by arrows. Panels (C) and (D) display the control (Bkg) group, where tumors have grown, also highlighted by arrows. These images represent tumor conditions at day 20 post intradermal injection of B16-F10 melanoma cells. Moreover, as illustrated in Figure 6, a series of magnetic resonance images showcases various stages of skin cancer in C57BL/6 mice: (a) T2 coronal image of a mouse from the 65X Bkg with radon gas group showing tumor disintegration. (b, c) Images of skin cancer in a mouse from the Bkg (control) group. (d, e) Images from a mouse in the 100X Bkg group. (f, g) Skin cancer in a mouse from the 40X Bkg group. All images were taken with a field of view of 200 × 200 mm and an acquisition matrix size of 128×128, ensuring a spatial resolution with a 3-mm slice thickness.

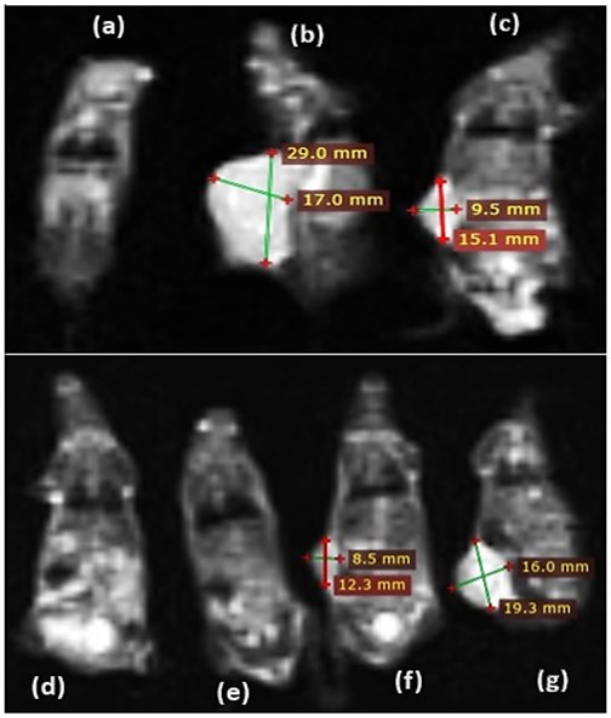

Figure 6. MR Images of skin cancer in C57BL/6 mice: **(a)** T2 coronal image of a mouse from the 65X Bkg with radon gas group showing tumor disintegration. **(b, c)** Images of skin cancer in a mouse from the Bkg (control) group. **(d, e)** Images from a mouse in the 100X Bkg group. **(f, g)** Skin cancer in a mouse from the 40X Bkg group. All images were taken with a field of view of 200 × 200 mm and an acquisition matrix size of 128 × 128, ensuring a spatial resolution with a 3-mm slice thickness.

DISCUSSION

The results of this study showed that tumor volume and growth rates were significantly reduced in the groups exposed to the highest radiation levels (100X Bkg). Mice in this group demonstrated the highest survival rates (100%), in stark contrast to the control group, which had a survival rate of 55.6%. Notably, tumor reduction and disintegration were observed, particularly among female mice, indicating a potential protective effect of elevated radiation exposure against melanoma progression. From a broader perspective, the findings of our study align with current research on the relationship between radiation dose and cancer risk [31]. Animal studies generally suggest that the linear no-threshold (LNT) model overestimates the risk associated with low radiation levels. This observation largely holds true for human data as well, with the exception of cases involving very high dose rates. Evidence further suggests that as radiation dose decreases, the interval between exposure and cancer mortality

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extends. This implies that, at lower radiation levels, individuals are more likely to die of natural causes before developing radiation-induced cancer, supporting the notion of an effective threshold [31]. Moreover, in India, data indicates an inverse correlation between environmental radiation levels and cancer incidence rates, supporting the hormesis hypothesis [32]. However, a statistically significant positive correlation has been reported between environmental radiation levels and the incidence of cancer in other studies [33].

The ALARA principle, advocating that all ionizing radiation exposure should be kept as low as reasonably achievable, is based on the assumption that any level of exposure carries some risk. This principle underpins regulations that lead to spending hundreds of billions of dollars annually worldwide to maintain low radiation levels [34]. However, our findings suggest a need to reassess the Linear No-Threshold (LNT) paradigm, particularly within the scope of natural background radiation levels.

As reported by other investigators [35-37], our results reveal that the highest levels of natural background radiation not only cause no harm compared to the lowest levels but also appear to confer beneficial health effects. This is particularly evident when comparing the control group and the 100X Bkg group in our study. In the 100X Bkg group, which was exposed to substantially higher radiation levels, out of the four female mice in the 100X Bkg group showed tumor reduction and volume decrease while one female mouse in this group showed an increase in tumor volume. Given this consideration, tumor size reduction and tumor disintegration were noted, contrasting sharply with the control group, where normal background radiation was associated with tumor growth.

These findings suggest that the protective effects observed at higher radiation exposures might prompt a reevaluation of current radiation safety standards and the underlying radiobiological models.

Our study found a significant difference in tumor progression between female and male mice, with notable findings in the female subset. Gender is an important factor in tumor volume based on the observed results because males and females may respond differently to radiation exposure due to physiological, hormonal, and genetic differences. In the normal background radiation group, females showed significantly higher tumor volumes compared to males, which could be due to hormonal influences, such as estrogen, which has been linked to increased tumor growth in certain cancer types. In contrast, males exhibited higher tumor volumes at the 40X background radiation level, suggesting that sex-specific factors may affect how radiation influences tumor progression. The observed differences between sexes across various radiation exposure groups highlight the potential role of sex hormones, immune system responses, and genetic factors in modulating tumor growth. Although the statistical analysis did not find significant differences, these trends emphasize the need to consider gender as a key variable in studies of radiation-induced tumor progression, as males and females may have distinct biological responses to radiation that could impact tumor development.

This radiation-induced extension of lifespan may largely be attributable to a reduction in cancer mortality observed in high-level radiation (HLR) areas for several types of cancer, including lung, pancreas, colon, brain, and bladder cancers. Similar trends of lower cancer mortality rates in regions with higher background radiation have also been reported in human populations in India [38] , Iran, and China [38, 39]. While these studies involve human subjects, our animal-based research aligns with these findings [40-43].

However, human studies face significant limitations. The effects of low radiation levels, comparable to natural background levels, on human health and longevity are challenging to determine due to the small population sizes typically studied, which complicates the ability to achieve statistically significant observations [44-46]. Furthermore, confounding factors such as income level, lifestyle choices like smoking, and other carcinogenic exposures or socioeconomic conditions can significantly influence life expectancy and health status in human studies.

Given the complexities of low dose radiation induced carcinogenesis [47], our study utilized an animal model to provide a controlled environment for observing the effects of radiation. Our findings indicate that high levels of natural radiation can impede cancer growth, showing that mice in areas with radiation levels higher than normal exhibit increased resistance to cancer compared to those in the control group. This suggests potential adaptive responses to elevated radiation levels, highlighting a complex interplay between radiation exposure and biological outcomes.

CONCLUSION

This study demonstrates that higher levels of natural background radiation may have a protective effect against melanoma growth in C57BL/6 mice, as evidenced by reduced tumor sizes and improved survival rates in the highest radiation exposure group. These findings challenge the Linear No-Threshold (LNT) model and suggest the possibility of a threshold or hormetic effect, where elevated radiation levels could provide biological benefits. The results provide a foundation for reevaluating radiation safety standards and underscore the need for further experimental and epidemiological studies

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to explore the complex relationship between radiation exposure and cancer progression. By highlighting the potential for beneficial effects of natural radiation, this study contributes valuable insights into radiobiology and cancer research.

***Conflict of Interest*:** The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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***Ethical Consideration*:** The study was approved by the Medical Ethics Committee of Shiraz University of Medical Sciences (Approval Code: IR.SUMS.AEC.1403.011).

***Authors' Contribution*:** SMJ.M.: Conceptualization, Supervision, Methodology, Writing – Original Draft. N.A., L.S.: Supervision, Validation, Writing – Review & Editing. M.A.: Investigation, Data Curation, Visualization. H.M.: Project Consultant. S.N.: Data Analysis. All other authors: Writing – Review & Editing. All authors reviewed and approved the final manuscript.

***AI Usage*:** AI tools, including ChatGPT and DeepSeek were used for language editing.

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