Editorial

Challenging the Mutation-Only Paradigm: Evidence from Ramsar High Background Radiation Areas

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All models are wrong, but some are useful

Natural background radiation varies widely across the globe, with some regions like Ramsar, Iran, exhibiting some of the highest recorded levels, with annual exposures reaching up to 260 mSv [1]. According to classical carcinogenesis theories, such elevated radiation doses should correspond with increased cancer incidence [2]. Surprisingly, epidemiological studies of Ramsar residents have not consistently reported heightened cancer risk, challenging conventional models and prompting deeper investigation into the underlying mechanisms [3,4].

Current Models of Radiation-Induced Carcinogenesis

1. *Accumulation of Mutation Model*

This classical framework asserts that cancer develops through the gradual accumulation of harmful mutations stemming from DNA damage, with ionizing radiation considered a major contributor [5]. Accordingly, higher radiation exposure should lead to increased mutation rates and elevated cancer incidence [6]. Yet, observations from Ramsar — where residents are chronically exposed to naturally high levels of background radiation — challenge this linear expectation. Despite substantial long-term exposure, cancer rates in these populations remain similar to, or even lower than, those in regions with typical radiation backgrounds [4]. These findings highlight the limitations of a strictly mutation-accumulation model in the context of chronic low-dose exposure [7], and imply that adaptive or protective biological mechanisms may modulate radiation effects over time.

2. *Immunological Model*

This model emphasizes the immune system's role in identifying and destroying nascent tumor cells [8]. Chronic low-dose radiation exposure may enhance immune surveillance, enabling effective clearance of potentially malignant cells before tumor establishment. This dynamic immune response could explain the absence of increased cancer risk despite higher mutation potential [9].

3. *Radiation Hormesis and Adaptive Response Models*

These related models propose that low to moderate doses of radiation stimulate protective biological processes—such as improved DNA repair, antioxidant defense, and cellular stress responses—that reduce overall cancer risk. Adaptive responses may condition cells to better tolerate radiation-induced DNA damage, thereby counteracting mutagenic effects [7,10].

The Best-Fitting Explanation: Immunological and Adaptive Response Models

The paradox observed in Ramsar residents is best explained by the interplay of enhanced immune function and adaptive cellular responses induced by chronic low dose radiation exposure. Rather than a linear increase in cancer risk with dose, low-dose chronic radiation appears to trigger compensatory mechanisms that maintain genomic integrity and suppress tumorigenesis [7,10,11].

These mechanisms may include:

- Upregulation of DNA-repair pathways reducing mutation fixation,
- Activation of antioxidant defences mitigating oxidative stress,
- Enhancement of immune surveillance eliminating damaged or transformed cells.

The findings of a study by Borzoueisileh et al. suggest that long-term residence in High Background Radiation Areas (HBRAs) is associated with gradual immune system modulation [11]. Over time, residents exhibited an increase in CD4+ T-cell proportions, indicating enhanced T-helper (Th) cell representation — a population critical for supporting the activation, expansion, and persistence of tissue-destructive CD8+ T cells. Conversely, CD107a+ cell frequencies, a marker of cytotoxic activity in CD8+ T cells and Natural Killer (NK) cells, showed a progressive decline among HBRA inhabitants. This reduction may reflect cumulative radiation exposure effects on cytotoxic immune function [11].

Such a biological balance prevents cancer risk escalation despite continuous exposure to high natural radiation levels [3,4,11].

The lack of increased cancer incidence in high background radiation areas like Ramsar challenges the simplistic dose-mutation-cancer paradigm. Instead, it underscores the importance of the immune system and adaptive protective mechanisms in modulating radiation-induced carcinogenesis. Incorporating these insights into radiological protection frameworks may lead to more biologically accurate risk assessment and proportionate safety standards.

Authors' Contribution

SMJ. Mortazavi and AR. Mehdizadeh contributed to the study conception and manuscript drafting. J. Welsh contributed to the study conception and critical revision of the manuscript, and JJ. Bevelacqua participated in the critical revision of the manuscript. All authors were involved in writing, reviewing, and approving the final version of the manuscript.

Conflict of Interest

AR. Mehdizadeh, Editor-in-Chief and Chairperson, was not involved in the peer-review and decision-making processes for this manuscript. The non-author, Editorial Board and reviewers oversaw the peer review process for this paper. SMJ. Mortazavi and J. Welsh, as the Editorial Board Members, were not involved in the peer-review and decision-making processes for this manuscript.

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