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Review Article

Exploring Non-Genetic Factors in Cancer Resistance among Ramsar Residents: From Medical Geology to the Role of Diet: A Review

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ABSTRACT

Ramsar in northern Iran provides a unique natural setting to investigate the biological effects of exposure to chronic radiation and the potential adaptive mechanisms. It is owing to its exceptional high concentrations of radium in sedimentary rocks, hot springs, and the elevated indoor radon levels. Despite prolonged exposure, available evidences did not demonstrate an increased incidence of cancer among local residents, which may indicate adaptive biological responses or protective lifestyle factors, although a causal relationship has not been established. Beyond potential genetic influences, it can be hypothesized that the predominantly vegetarian diet of Ramsar inhabitants, rich in raw vegetables, fruits, nuts, and garlic, may contribute to the reduced cancer risk through its antioxidant and anti-inflammatory effects. To explore the relatively low cancer incidence observed in this population, this review assessed existing evidences in relation to the potential protective role of diet against cancer and compared these findings with populations consuming acidogenic diets high in processed foods and animal proteins. The evidences collectively suggested that lifestyle and dietary factors may influence the biological impact of environmental stressors such as chronic exposure to natural radiations.

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Introduction

Natural sources of radioactivity, including uranium and its decay products such as radium and radon, are ubiquitous throughout the environment (1-3). Exposures to these elements are clearly increased in areas with uranium deposits, extraction sites, or other locations with special geochemical conditions. One such region is Ramsar in northern Iran that is an area with sedimentary rocks containing up to a millionfold higher concentrations of radium when

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compared to average levels elsewhere (4). It was shown that the actual radiation exposure in Ramsar's high background radiation areas (HBRAs) is lower than previous report with maximum estimated doses around 80 mSv/year rather than 260 mSv/year (5).

Available studies have not reported statistically significant differences in DNA damage, cancer incidence, or aging between HBRA and non-HBRA inhabitants; however, data remained limited (6, 7). It was demonstrated that HBRA residents exhibited fewer induced chromosomal abnormalities following gamma exposure, though findings should be interpreted cautiously based on sample size and methodological limitations. Mortazavi *et al.* confirmed that short-term exposure to extremely high natural radiation levels did not induce oxidative stress in animal studies. Some evidences even suggested an adaptive response, where the lymphocytes of residents were more resistant when challenged with high doses of radiations (5). No real epidemiological data are available to date, but according to local physicians reports, no increase in cancer incidence has been observed among the residents (8). Researchers have demonstrated that longer-term studies are required before any conclusive statements to be made regarding the cancer risk. The research conducted in Ramsar provided unique context for studying chronic radiation exposure and informing discussions on public health and radiation safety standards. These findings have been discussed in the context of the linear no-threshold model and may indicate potential adaptive responses; however, the evidence remains inconclusive (5, 7). Therefore, this review was designed to investigate the remarkably low incidence of cancer among the indigenous population in Ramsar, northern Iran.

Medical Geology of HBRAs in Ramsar

Ramsar, located in northern Iran, is renowned as a HBRA due to its elevated natural radiation levels that is primarily attributed to the presence of radioactive elements in its sedimentary rocks. This region provides a unique setting to study the health implications of long-term exposure to high levels of natural radiation. Radiation exposure occurs through multiple pathways, including soil, water, and air; while radon gas being a critical contributor to indoor radiation. Specific measurements revealed that water samples frequently exceeded the normal radium levels. Pourhabib *et al.* found 11 stream and 8 drinking water samples to be above standard concentrations. Indoor radon measurements illustrated concentrations to range from 100 to 400 Bq/m³ in local dwellings that demonstrate the pervasive nature of this radiation exposure. Notably, these elevated levels result from local geological conditions, particularly high radium content in rocks, soils, and groundwater (9-13). Although locally produced food items contained detectable radioactivity, it was shown that the committed effective doses were within safe limits, which may suggest adaptive tolerance among the residents (14).

Despite the high radiation background, studies to date have not demonstrated clear evidence of increased cancer rates among Ramsar residents. The concept of an 'adaptive response' has been proposed, suggesting that chronic low-dose radiation exposure might influence cellular responses to higher doses, although this remains under investigation. This is of continuing interest, though the mechanisms are unknown and a subject for further research. In a previous study in which Mortazavi and his colleagues used a standard food frequency questionnaire (FFQ) to investigate the diet of the people of Ramsar, the dietary habits of Ramsar residents were rich in antioxidants provided from fruits and vegetables that can play a role in diminishing the effects of radiation-induced oxidative stress (15, 16). Antioxidants from fruits and vegetables have been shown to form a very crucial protective aspect against radiation-induced oxidative stress and related health effects. Free radicals due to radiation exposure can cause membrane damage, enzyme modification, and DNA damage, thereby resulting in a wide range of diseases including cancer (17).

While radon-related studies provided compelling evidences of radiation risks, studies in other areas with high background radiation have been less conclusive. They indicated that residents of areas such as Ramsar, Guarapari, Orissa, Kerala, and Yangjiang have lived for generations without a significant increase in cancer that are challenging linear models without thresholds for radiation risk (18, 19). Restier-Verlet and colleagues undertook a systematic review of 98 studies and collated three main findings of (i) the actual doses from radiation were often much lower than initially estimated, (ii) no significant difference in DNA damage was visible between areas with high and natural background radiation, and (iii) a persistent adaptive response in lymphocytes was noticed when exposed to the high doses. However, these findings demand more rigorous systematic research to clarify the biological interaction of radiation (5).

Adaptive Response in Human Populations

Mortazavi *et al.*'s studies on mice exposed to high levels of natural radiation in Ramsar found that higher radiation exposure was not correlated with increased cancer growth. Instead, mice in the highest radiation group showed reduced tumor size and progression, along with higher survival rates, suggesting a protective effect against melanoma progression (20, 21). The concept of radiation adaptive response, as discussed by Bugała and Fornalski, supports these findings. Their research indicated a reduction in chromosomal aberrations, cancer incidence, and mortality in high background radiation areas, which may indicate an adaptive biological response to chronic radiation (22) .

Study on Ramsar residents using micronucleus assays has shown significant differences in chromosomal damage between residents of high radiation areas and control groups. The findings suggest an adaptive response to radiation, with residents showing less chromosomal damage compared to controls after radiation exposure (23). The adaptive response is further supported by the observation that the frequency of chromosomal aberrations was correlateds with individual radiosensitivity, indicating a complex interaction between radiation exposure and biological adaptation (22).

Conditions in space are thought to be analogous to the chronic high-LET radiation exposure in Ramsar, offering an opportunity to understand the radiobiological hazards to manned space missions. The study brings the importance of research in areas with high levels of radiation and its long-term consequences on human populations. This research highlighted the importance of studying human populations in high radiation areas to better understand the long-term effects of radiation exposure (24). Recent findings also indicated that adaptive mechanisms to chronic radiation are conserved across species. Mortazavi *et al.* compared the residents of Ramsar with Chernobyl's darker-pigmented frogs and found similar protective traits (enhanced DNA repair, melanin-based antioxidant defense) that support a common biological basis of radiation resilience (25).

Although these studies indicated some potential benefits that could be associated with high background radiation, consideration of variability in individual responses to radiation and the need for further researches to understand the mechanisms underlying these adaptive responses is important. The implications for environmental health are profound, in that they challenge the existing radiation safety paradigms and hint at a reevaluation of present standards. With these considerations in mind, high-level radiation exposure is usually associated with an elevated risk of cancer; however, in the case of the indigenous residents of Ramsar, there is a paradoxically low incidence of cancers, especially lung and colorectal cancers. This phenomenon may be influenced by a combination of genetic and lifestyle factors, though definitive conclusions cannot yet be drawn (26).

Dietary Factors and Cancer Resistance

As discussed by Bahrami and Tafrihi, comprehensive examination of cancer's underlying causes, combined with statistical analyses of cancer incidence, indicates that modifying dietary and lifestyle factors along with minimizing exposure to carcinogens can substantially reduce cancer risk (27). Individuals who adhere to balanced and health-conscious diets generally exhibit a lower incidence of cancer compared to those who frequently consume unhealthy foods. Consequently, adopting a natural, balanced diet and a healthy lifestyle that may serve as an effective complementary or adjunctive approach in cancer prevention and therapeutic strategies (27). Nutritional resistance to cancer has great significance in terms of maintaining favorable conditions in cells. Estimates suggest that nutritional factors alone are responsible for 30-35% risk to cancer. Plant nutrients rich in antioxidants are highly protective against cancer. It has been found that consuming plenty of plant foods lessens the risk associated with cancer development (28, 29).

Optimal conditions are essential for cells to function normally. An unfavorable environment causes cells to go into stress, which leads to mutations too. These mutations result in cancer. The diet in Ramsar has been reported to include raw garlic, vegetables, fruits, nuts, and seeds, which are potential sources of dietary antioxidants. On the other hand, diets containing highly acidogenic foods like processed meats, sweet beverages, and refined carbohydrates are associated with increased risks of cancer. Several studies provided preliminary evidence supporting the following observations: (i) eating raw garlic can lower the risk of developing lung cancer because of its effects on oxidative stress (30). (ii) an improved metabolic homeostasis can make carcinogenesis less probable (31). (iii) a diet rich in antioxidants supports cellular functions, leading to an environment less favorable to cancer development (32).

Comparative Analysis: Ramsar vs. Hungary

Hungary's population exhibits high age-standardized rates of lung and colorectal cancers (33). Factors contributing to this include (i) diets characterized by high animal protein and low fruit and vegetable intake (34). (ii) exposure to heavy metals and radiation from natural and industrial sources (35, 36). Hungary exhibits significantly higher cancer rates compared to Ramsar, primarily driven by dietary and environmental factors. Available epidemiological data indicated that Hungary had relatively high lung cancer rates (37). Dietary contributors include high fat consumption and low fruit/vegetable intake (34). In contrast, Mortazavi *et al.* surprisingly found that despite high radiation levels, Ramsar showed lower lung cancer rates (9). Key differentiators include Hungary's nutritional profile including high animal protein consumption, low fruit intake, and an elevated fat consumption (38). While the Ramsar data is limited, the sources suggest that balanced nutrition and environmental factors play crucial roles in cancer risk (39).

Radiation and Adaptation

Ramsar's indigenous residents have adapted over generations to high radiation levels. It has been hypothesized that long-term exposure could influence cellular repair mechanisms and immune responses, potentially affecting cancer susceptibility. Dietary factors may play a complementary role in influencing oxidative stress and DNA repair, though this requires further investigation. Beyond environmental adaptation, the concept of radiation adaptive response has broad biomedical implications. Kanani *et al.* summarized its potential roles in cancer therapy, neuroprotection, and space medicine, emphasizing that controlled low-dose exposure may enhance cellular resilience but requires rigorous validation before clinical translation (40).

Conclusion

The findings of this study suggest a possible interplay between genetic adaptation and lifestyle factors, particularly dietary habits, in contributing to the relatively low cancer incidence among the indigenous population of Ramsar. It can be hypothesized that a diet rich in plant-based foods containing antioxidants may enhance resilience against radiation-induced oxidative stress and carcinogenesis. In contrast, populations consuming diets high in acidogenic foods, such as in Hungary, appear to experience higher cancer rates, potentially influenced by both dietary composition and environmental exposures. Overall, these observations underscore the importance of considering dietary and lifestyle factors when evaluating cancer risks in high-radiation environments. Future research should integrate nutritional, genetic, and environmental data to more comprehensively elucidate the mechanisms underlying cancer resistance and to inform potential preventive strategies.

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Authors' Contribution

S.J.M, S.M.J.M, and H.B conceived and designed the study. P.Z, A.M, H.V, A.A.F, F.Z, and M.A contributed to the literature review and preparation of the initial manuscript draft. All authors participated in the preparation, critical review, and approval of the final manuscript.

Conflict of Interest

None declared.

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