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Mechanism of Low Exposure Radon Radiation on human body immunity

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Abstract: *Ionizing radiation particulates from natural origins are present in the nature surrounding us.High radiation exposure can impact on human health which leads to death. This paper suggests that the effects of Radon radiation and exposure should be further tested for their effects on the human immune system to get more accurate explanation about the process and mechanism.This paper will show that low doses of exposure can bring effect to human immune system. The methods for this paper is collecting and surveying 57 literature related about Radon radiation to get new information through some steps: (a) identifying the topic of Radon exposure from surveyed literature; (b) determining the extent of Radon exposure to human body immunity to find interpretable trends or patterns from the published papers; (c) aggregating empirical findings related to a narrow research question to support evidence of the positive and negative effects of Radon exposure on human body immunity including the scientific data or tested information from the body of literature. The analysis result from the reviewed epidemiological data shows that low doses of exposure can impact to human immune responses. There are certain mechanism to shape the problems which caused from low doses of exposure. Hence, this paper showed there has positive and negative effects of Radon radiation and its exposure to human immune system. However, there are more negative effect caused by the exposure that can damage the human immune response through molecular function as pathological indicators.*

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I. Introduction

Radon can impacts on human body immunity. Radon radiation produces free radicals that are capable of transforming important molecules in human cell body, chromosomes, and DNA.[1–4]Some scholars have debated about the benefit and loss of Radon radiation. For example, the Radon radiation can be used as therapy tool of Balnotherapy.[5–7] The therapy has been legalized in Japan that uses Radon as a therapeutic tool to improve the immune system and reduce rheumatoid arthritis.[6,8,9]This argument is Radon therapy with passive and self-directed was useful for US elderly patients. The therapy is used for patients experiencing chronic diseases and reduced drug effectiveness. In other hand, Radon radiation has negative effect in long-term exposure that causing pneumonia and lung cancer.[6,8] However, the mechanism to stop or reduce the effect is dispersed with lack of confirmation and external validation. Therefore, this paper will summarize the information from body of literature about the mechanisms of Radon radiation on human immune system.

Based on the problem above, this paper will summarize the recent literature to describe the positive and negative effects of Radon radiation. This paper will shows the literature body about relationship and information of the effects of Radon radiation and their exposures to impact human immune system. Based on the secondary data from literature, we also compare the source of exposure, mechanism and its doses of the exposure.

II. Review

Ionizing radiation particulates from natural origins are present in the nature surrounding us. Apart from cosmic radiation, ionizing radiations are also produced as a consequence of the presence of radioactive materials in the Earth's crust. Three-quarters of the radioactivity in the environment comes from natural elements.[4,10]

There is various level of radioactivity of the ionizing radiation particulates such as Radon. In some areas of India, for example, Radon radioactivity is 10 times greater than the European average. The Alps and other mountain ranges also have a relatively high level of radioactivity due to the composition of their granite. Besides geographical variation, there are other activities which increasing the doses of exposure such as, ceramics manufacturing, fertilizers production and the extraction of gas and petroleum.[11]

In our homes, radioactivity may also exist, mainly from Radon gas. This gas is produced as a consequence of the uranium decay from rocks. The amount of Radon gas that accumulates in a house depends on its location. Radon can emanate from rocks and accumulates in air with closed ventilation, so it is highly

recommendable that homes and workplaces are well ventilated. Besides natural radioactivity, the radiation background has been increased artificially due to urban industrialization.[3,12,13]

Among the medicine sources of ionization radiation, medicine radiodiagnostic (roentgen) has a dominant position as sources of secondary radiation. Patients from a major part of the population are irradiated by relatively low doses. The average whole-body radiation exposure of an individual obtained from medicinal sources of normal ionization radiation is estimated as 0,6 mSv/annually.[4,14]

Other artificial sources also comes from nuclear weapons testing (mainly in the atmosphere) resulted in a radioactive particulate fall that spread practically around the whole globe. It peaked at the end of 1962 when nuclear powers USSR and USA carried out a lot of test explosions of thermonuclear weapons. Since that time the amount of nuclear arm tests has decreased, however, unfortunately, even these days tests are carried out in certain countries (India, Pakistan, and China). The radiation exposure resulting from nuclear explosions is higher by a factor of more than two than the exposure from natural sources.

III. Radon

Radon is a natural radioactive gas with transparent and without odor originating from radioactive decay of Uranium elements. Through inhalation, it spreads free radicals which leads to disturbing human body immune and DNA mutation.[4,15,16] After Radon gas is inhaled into human lung, it changes the mechanism of hormonal function bring risk to normal lung function. The presence of Radon is also found in the hot water springs in mountain areas.[9] There are concentrations that reach 1,000-10,000 times the concentration of Radon gas in the normal natural atmosphere.[1,3]

Radon is an element with number list of 86 in the periodic table. As shown in Table 1.1 ^{222}Rn originates in the ^{236}U decay series and has a half-life of 3.82 days. Radon has various types of radiological characters, for example, ^{220}Rn (Thoron) is in the 232Th chain with a half-life of 55.6 sec and, ^{219}Rn (Actinon) is in the ^{235}U series with its half-life of 4.0s. All the Radon types are alpha particle emitters. Compared to other elements such as Actinon, ^{219}Rn, due to its short half-life and the comparative scarcity of its long-lived parent, 235U, can usually be omitted from any radiological considerations.[3,7,17]The isotopes of Radon have decay series ranging from ^{199}Rn to ^{226}Rn. The longest lived of these is ^{211}Rin (15 hr) and most decay via alpha emission but beta emission and orbital electron capture are included. Radon is a colorless gas with a density of 9.73 g/1 under standard conditions making it the heaviest gas in nature. When cooled below its freezing point, it has bright phosphorescence which becomes yellow at lower temperatures and orange-red at the temperature of liquid air. It was this property that led Radon to be called niton (the shining one) at the time of its discovery.[18,19]

Radon atom possesses a stable closed shell electronic configuration which gives it the chemical properties of a noble-gas element. It behaves as expected by comparison with the other inert gases in the periodic table including Helium, Neon, Argon, Krypton, and Xenon. The electronic configuration of neutral Radon atoms in the ground state is 5s2 5p6 5d10 6s2 6p6 ('SO). The spectrum of Radon resembles that of the other closed shell elements.The relatively high solubility of Radon in water (230 cm3 kg-2 at 20°C) accounts for its presence at substantial amounts in certain spring waters.[20] A detailed list of the physical properties of Radon is given in Table 1.

The effect of Radon radiation has been studied by observing participant working in mining areas. Uranium mining and processing are associated with a wide range of potential adverse human health risks.[21–23] Some of these risks arise out of aspects of uranium mining and processing specific to that enterprise, whereas other risks apply to the mining sector generally and still others are linked more broadly to large-scale industrial or construction activities. These health risks typically are most relevant to individuals occupationally exposed in this industry but certain exposures and their associated risks can extend via environmental pathways to the general population. Underground uranium miners are exposed to the highest levels of Radon and its decay products. Other underground workers and certain mineral processing workers may also be exposed to significant levels. [3,17,24]

A cohort study has reported that miners were vulnerable from uranium and radium which are the basic ingredients of the soil and mining rocks which with half-life of 1 Bq/m3 or equivalent to 1.3x 10-8.[3,25,26]The miners were exposed to the radiation source and experienced lung cancer with high exposures. Although the vast majority of people are exposed to low or moderate Radon concentrations; from time to time; there are homes found with very high concentrations of Radon. Among those living in homes with very high Radon concentrations, it is typically parents of young children that demonstrate a great deal of concern. They want to know the equivalent risk in terms of the lifetime relative risk of developing lung cancer when a child has lived in a home with high Radon for a few years.[27–29] As Radon radiation has a long half-life, it is deposited in blood and lung which lead to long term exposure and high fraction exposure will lead to pulmonary diseases such as lung cancer. Radon radiation with high or low exposures has potential to impact on the human immune system with various mechanisms.[30–33]

Table 1. Physical properties of ^{222}rn[4,34]

Name	Conclusion
Density at 0°C and 1 atm	**9.73 g 1-1**
Boiling point, normal (1 atm)	**-62°C**
Density of liquid at normal boiling point	**4.4g cm-3**
Diffusion coefficient in free air	**0.1 cm2 sec-1**
Viscosity at 1 atrn pressure and 20'C	**229.0 micropoise**
Critical pressure	**62 atrn**
Critical temperatures	**105°C**
Solubility in water at 1 atm partial Solubility in various liquids at 1 atm	**230 cm3 (STP) kg-1 water**
Solubility in various liquids at 1 atm pressure and 18°C	
Glycerine	**0.21 cm3 kg-1 liquid**
ethyl alcohol	**7.4 cm3 kg-1 liquid**
petroleum (liquid paraffin)	**9.2 cm3 kg-1 liquid**
toluene	**13.2 cm3 kg-1 liquid**
carbon disulfide	**23.1 cm3 kg-1 liquid**
olive oil	**29.0 cm3 kg-1 liquid**

IV. Radon radiation and Human Immune System

There are various effects of radiation doses toward human body and tissues which measured by a unit called gray (Gy). The potential damage from an absorbed dose depends on the type of radiation and the sensitivity of different tissues and organs. Beyond certain thresholds, radiation can impair the functioning of human organs to produce acute effects such as skin redness, hair loss, radiation burns, or acute radiation syndrome. These effects are more severe at higher doses and higher dose rates. For instance, the dose threshold for acute radiation syndrome is about 1 Sv (1000 mSv).[35,36]

If the radiation dose is low and delivered over a long period of time (low dose rate), the risk is substantially lower because there is a greater likelihood of repairing the damage. However, there is still a risk of long-term effects (i.e., cancer) that may appear years or even decades later. The effects of this type will not always occur, but their likelihood is proportional to the radiation dose. This risk is higher for children and adolescents, as they are significantly more sensitive to radiation exposure than adults.

Scholars have recognized that Radon radiation can expose to human body immune with various effects.[16] Through inhalation or swallowing, Radon is deposited into pulmonary especially in bronchus, bone and adipose tissue resulting in respiratory diseases.3,4 Radon radiation elements of α-particle become main elements of irradiation exposing pulmonary tissues with high linear energy ignition (LET) and bringing a risk of cancer lungs, leukemia and DNA mutation18. Besides alpha radiation, Radon has two other elements, e.g., beta β and γ-rays emission. From these elements, alpha radiation is the most dangerous and higher impacts.[10,16,37] Therefore, this paper will focus on the alpha radiation. The alpha radiation is measured by biodosimeter to provide biodosimetric data evaluating health risks.[10,32,38,39]

Previous studies have provided various explanations about the relationship of Radon and immune system.[40,41] For example, there are various effects of low radiation exposures as well as their mechanism of action. The low-level exposure radiation acts on the immune system that can play a key role in cancer ranging 0.1-2.0 Gy (> 2 Gy) to damage normal tissue, inhibits immune function, and increases the risk of secondary neoplasms. [40,42,43]However, other scholars provide positive effect of Radon radiation for therapy. It has proved that low-exposure radiation hormones were effective for cancer and ulcerative colitis treatment.33 The treatment was also successful to cure ankylosingspondyloarthritis, chronic rheumatic polyarthritis, osteoarthritis, asthma, and atopic dermatitis. Other scholar has examined low-exposure radiation (10 cGy x 15 for 5 weeks = 1.5 Gy total) and compare the standard radiation therapy to radical exposure of tumors treatments causing prolonged lifeamong patients.[44] Their study expands our knowledge about the mechanism of Radon gas especially in low exposures is more likely to be beneficial than dangerous. The mechanisms are summarized in the Table 2.

From the Table 2, we found that Radon radiation tends to impact on human immune system which leads to health disorder.[45] The human immune system consists of a non-specific immune system and a specific immune system. The non-specific immune system is responsible for identifying and recognizing foreign objects, activating the complement system, and activating the specific immune system. Phagocyte cells (macrophages, monocytes, and polymorphonuclear) trigger the release of fundamental proteins that mediating inflammatory regulators of cytokines. The cytokines will takes time to recognize antigens before giving a response. The cell responses are mediated by T and B lymphocytes. Such disturbance to the cell response will damage the cells especially the blood cell and impaired protein synthesis. As a result, the total number of lymphocytes and antibodies in the human body will reduce immune system level.[46,47]

Table 2. Previous studies on the relationship of radon and immune system

Name	Purpose	Conclusion
Janiak, et al., (2017)	Reporting low-level ionizing radiation as key role in cancer immunotherapy.	This effect is induced by moderate (0.1-2.0 Gy) or high (> 2 Gy) exposures of ionizing radiation which can damage normal tissue, inhibits immune function, and increases the risk of secondary neoplasms.
Kojima, et al., (2017)	Providing evidence that low-exposure radiation is effective for the treatment of cancer and ulcerative colitis.	Radon treatment is reported to be effective in patients with ankylosingspondyloarthritis, chronicrheumatic polyarthritis, osteoarthritis, asthma, and atopic dermatitis.
Doss (2016)	Examining the Low-exposure Radiation	Examining the Low-exposure Radiation as treatment (10 cGy x 15 for 5 weeks = 1.5 Gy total) and comparing the standard radiation therapy treatments to tumors to improve patient wellness and survival.
Scott (2017)	Examining the mechanism of natural barriers to cancer at the molecular, cellular, tissue, organ, and whole body levels.	Low exposures of ionizing radiation are more likely to be beneficial than dangerous. These exposures increase our natural cancer barriers rather than reduce them, in contrast to the effects of high exposures.

At initial stage, when human body is exposed to Radon radiation, the body starts initial responses into tissue cells and organs. Even though low exposures, the radiation can start the destruction of DNA with linear effect.[16,48,49]In the initial exposures, it has led to genotype mutation and cause a phenotype mutagenic response. If the exposure prolonged, it will mispair cell mutation and even apoptosis, disturbing protective function of cell membrane.[50,51] For certain study case, scholars reported that low exposures radiation (LDR) will have a positive effect on lymphocyte cells. [52]

In the second stage, the lymphocytes will response to infection. The second type of lymphocytes is Helper T cells as activators. Whereas the third type of lymphocytes are Cell B and macrophages as mediators to stop the bleeding. The activation of T lymphocytes is in response to antigen recognition and antigen binding. The activation will increase intracellular Ca++ and protein-kinase concentration. Their high concentration is initial expression of biomarkers, e.g., c-fos gene and c-myc, interferon gamma, interleukin 1 and 2 and transferrin. They are important for T cell proliferation.[53]Some scholars have duplicated the mechanisms for low exposure radiation in experimental studies (controlled trials) where the immune response to radiation involving intracellular calcium and protein-kinase C.[27,54,55] The study provides similar results of causing c-fox gene transcription and interleukin-2 production to activate T cells.[55,56]

V. Cancer Growth

Low-exposure radiation has been linked to cancer growth. However, the relationship between the exposure and cancer growth has involved complex interactions. Some studies have given new light to the complex interactions of ionizing radiation (IR) which has recently been recognized with cancer-related immunity. This, in turn, has led to the development of new radiotherapy schemes based on the idea that local exposure at moderate levels (between 0.1 and 2.0 Gy) of adsorption during acute exposure or even high exposures (more than 2.0 Gy) radiation can improve immunotherapy results since it stimulating anti-neoplastic immune reactions.[57] The mechanism of low exposures and cancer growth is described in the table 3 below. The table also included the exposures used by previous studies. At the first stage, the up-regulation of Rae1 and other ligands of the NKG2D receptor will activate NK cells.[10,46]

Certain scholars have proposed ideal exposures (<0.1 Gy or <0.1 Gy/min) for neoplasm treatment.[57] The result is reasonable since effects of radiation can occur at the organ, cell and molecular level. The Radon effect in a small amount of activity (from nature), is probabilistic (stochastic), meaning that the chance or effect is not having a threshold exposure.[16,53,58]

Even though low exposure below 0.1 Gy will drive higher cancer risk, it still need more information about the indicator of the effects. In normal cells, there is a balance between free radical formation and destruction. If the formation of free radicals becomes excessive, the antioxidant content will be reduced. This situation is called oxidative stress which becomes indicators of higher cancer risk.[10,15,59]Other study provided different result through controlled trials with animal. They reported mammary tumors that develop spontaneously in female mice. In any cell, prolonged oxidative stress results in serious cell damage. The oxidative stress has a major role in the development of chronic and degenerative diseases, such as cancer, joint inflammation, aging, autoimmune diseases, cardiovascular, lung, eye, psychological stress on the fetus, diabetes and infertility in men.[56,60,61]

New study has provided information about low exposure radiation (2 Gy-0.075 Gy) can reduce tumor mass and pulmonary metastases in mice implanted with Ehrlich tumor cells.[58,59]This becomes main evidence that Radon effect was found for lung cancer, emphysema, and pulmonary fibrosis. However, the study did not mention the mechanism of molecular reactivity to lose electrons turn into new radicals and eventually cause cell damage, cell function disorders, and even cell death.

Other doses have been tested in-vivo in animal with low exposures (0.5 Gy-2 Gy). They reported the radiation can suppresses colony formation in the lungs in a model of melanoma B16 pulmonary metastases in rats.[62] This provide cross external validation that important molecules in the body that are susceptible to damage by free radicals are deoxyribonucleic acid (DNA), fat, and protein.[63,64]To understand the exposure range, we give explanation about the low exposure radiation in Table 3.

Table 3. Low Exposure Radiation interval

Clinical study	Low Exposure Radiation	Exposure range	Investigated
Janiak, et al., (2017)	Yes	(<0.1 Gy or <0.1 Gy / min)	Neoplasm
Jaworowski (2004)	Yes	below 0.1 Gy	Increases risk cancer
Cuttler, J. M. (2006)	Yes	(0.001 to 0.3 Gy)	Produces a small amount of damage
Jin, et al., (2007)	Yes	(2 Gy-0.075 Gy)	Reduced tumor mass and pulmonary metastases
Kojima, et al., (2004,2006)	Yes	(0.5 Gy-2 Gy)	G-irradiation significantly slows tumor growth in mice implanted with Ehrlich tumor cells Suppresses colony formation in the lungs in a model of melanoma B16 pulmonary metastases in rats

Generally, free radicals can cause various changes in DNA, e.g., hydroxylation of thymine and cytosine bases. The free radicals can impact the opening of nucleus of purines and pyrimidine and DNA phosphodiester chain breakdown. DNA chains breakdown are intermittent in various places which lead to shorter replication and causes mutations. This means that a longer radiation exposure will produce free radicals in histological level.[65,66]

VI. Free Radical And Enzyme Activity

The effects of free radicals can be detected by measuring the enzyme activity of superoxide dismutase (SOD), catalase and glutathione peroxidase (GSH-PX) in erythrocytes. The work of SOD is to suppress oxidative damage by catalyzing the dismutation reaction of superoxide anion (O2 +) to H2O2. H2O2 is a strong oxidizing agent. SOD can also increase the growth of T cells and B cells and have anti-tumor effects on the body. Radon inhalation will significantly increase SOD levels in the liver and kidneys because SOD acts as a stimulant. It was a three-fold increase compared to the control area in people exposed to Radon 54 bq/m3 and 16 bq/m3. In the other region, the level of SOD in human body will increase concentration to 24.8 ± 29 bq/m3. This is due to a decrease in the total cell life of the lymphoid and lymphatic organs.[22,67] However, other study proposed that 16.6 ± 24 bq/m3 as safe low exposure. The dose can increase the production of T cells and B cells and other cells this is reasonable since such high concentration will cause a response to low-exposure radiation (LDR) and produce cellular responses. The exposure effect will decrease cell capacity for adaptation and reduce lymphocytes adaptability. The decrease of lymphocytes is indicator of reduce human immunity.8,9

In the exposure doses of 3.56 ul/ml and 1.65 ul/ml, the radiation will have indirect effects on human immune. The low SOD activity indicated a high level of free radical.9 In normal circumstances, necrosis and reduce the stability of the cell membrane and disrupt functional proteins. The disruption is early marker of molecular function changes and pathological indicator of apoptosis. The impact of radiation is reduced ability of genes that induce cell proliferation that lead to apoptosis.[16,56]

The apoptosis can be responded physiologically, adaptively and pathologically depending on the function of the controlling protein. Apoptosis is controlled by various proteins in cells, especially the Bcl-2 protein group.[68,69]The Bcl-2 protein group consists of pro-apoptotic proteins such as Bax, Bad and Bid; and anti-apoptotic proteins such as Bcl-2 and Bcl-x and p53. [64,70–72]

VII. Discussion

There is immune response generated by radon exposure on the body. There are various mechanisms of Radon effects on the body with different total exposure response. The exposure variants provides new paradigm in the research of Radon radiation toward immune effect. Our analysis result showed that the exposure will trigger free radical in the histological level and lead to instability of molecular function as pathological indicator of leucocytes apoptosis.

This result has been tested by other study by involving patients with auto immunity disorders by reporting that low radiation exposures can be used radiotherapy as an anticancer or cancer treatment with negative effects on premature cell apoptosis. Research in China on low and high levels of natural Radon

ionizing radiation shows high levels of interleukin 2 at high Radon levels studied in lymphocytes in peripheral blood cells can impact immune system both positive and detrimental effect.[36,52,58] Radiation effects on the immune system are detrimental even though it is low exposure rate. Therefore, setting of low exposure of Radon radiation must be based of low exposure within short duration.[55]However, our review does not find significant result between timing of duration with radiation effect.

In addition, our review provides information that radiation can disturb cell function and lead to leucocyte apoptosis which drive incidence of lymphoma after malignancy. This was previously done where there was a decrease in spontaneity of lymphoma 48.6% at 150 mgG irradiation which was exposed twice a day for 40 weeks. Even though radiation can be used as antitumor therapy, however, Radon usage for the tumor therapy is still in experimental level using animals.[27]

In mice experiments, CD8 + T cells and cytokine modulation and expression of adhesion molecules were activated on endothelial cells and leukocytes since the production of nitric oxide activated by macrophages and granulocytes which lead to carcinogenesis. This is reasonable since the adaptive response to carcinogenesis can inhibit the tumor in immune stimulation when the patient undergoes radiotherapy.[59]

VIII. Conclusion

Radon has potential for treatment with low exposure strategy. Low exposures radiation will increase the production of free radicals in the body as a form of defense mechanism and the body's immune system through activating the endogenous antioxidant defense system and endogenous antioxidants of SOD. SOD as enzyme activity of superoxide dismutase has characteristics of reducing oxidative stress. However, the information and scheme about the mechanism is still unexplained in this paper.

Further study can expand our conclusion by studying molecular level of Radon radiation effects into Nrf2 (erythoid 2 related factor) and oxidative stress to trigger changes in the expression of antioxidant genes such as hemeoxygenase, SOD, GSH and catalase.8 Since Nrf2 binds to antioxidants in DNA (antioxidant response element (ARE)), Nrf2 play an important role in irradiation resistance and tumor response during clinical procedures for radiotherapy.

Finally, further study can expand our conclusion by studying molecular level of Radon radiation effects into a lower exposure of radiation below 0.05 Gy and its effects on cell apoptosis especially in leucocyte cells. As Radon can penetrate the endocrine organs and modify hormone production so, therefore, future study must examine the duration of treatment and radiation to modulate target cells that trigger immune status improvement. The mechanism duration of irradiation is important to understand how Radon can trigger hormonal changes that stimulate T cells.

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