Effects of Radon Gas Exposure on Lung Cell Immunity at Low Doses and High Doses: A Review

Azhari[1]*, Ivhatry[2], Bremmy[3], Winni Y[4], Suhardjo S[1]

1. Department of Oral Maxillofacial Radiology, Faculty of Dentistry, Padjadjaran University, Bandung, West Java, Indonesia.
2. Student in Magister in Basic Medical Sciences, Faculty of Medicine Universitas Padjadjaran, Bandung, West Java, Indonesia.
3. Departement Biomelekuler, Faculty of Dentistry Universitas Padjadjaran
4. Departement Histology, Faculty of Dentistry Universitas Padjadjaran

Abstract

Radon as radioactive gas is distributed naturally in free air environments with potential risk to health and cancer disease. Radon with certain radiation exposure dose has both negative and positive effects impacting human cell immunity and protein molecules. The decreased immune cells and molecular proteins caused by radon will impact on lung cancer through unique mechanism and carcinogenesis risk. There is substantial evidence that the dose of radon exposure has effected in human immunity. However, literature body on radon exposure and doses are not systematically arranged. This paper provides a review explaining the exact dose of the exposure systematically. This paper describes the effect of both high and low doses of radon exposure to human body. This paper also summarizes the effect of both doses toward cellular and molecular levels impacting the pulmonary carcinogenesis risks. This paper also explains the mechanism of p53 mutation caused by radon exposure and exposure type toward the patient. We also describe the exposure effect toward patients with background of non-smoking, smoking and uranium miners. Finally, we compare the radon exposure toward human immune mechanism and the genetic responses. This paper provides significant analysis result in explaining radon-induced carcinogenesis as risk identifiers especially at cellular and molecular level.

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Introduction

Radon as radioactive emitter is an inert gas from soil and rock in mining areas[1]. There are many sources of radon such as uranium, radium and asbestos.[2] Many studies has reported significant advantages and disadvantages of the radon exposure. However, there is a debatable issue about the doses of radon exposures to bring negative impacts on human health especially its role in the lung cancer mechanism.[3–6] Many scholars proposed evidence of lung carcinogenesis, especially in the UK and US studies.[7,8] Although lung disease is dominated by smoking behavior, however, cigarette smoke does not have a carcinogenesis effect as strong as radon gas exposure.[8] Other scholars have shown that radon gas can interact with cigarette smoke which strengthens radon exposure to produce aerosols impacting lung carcinogenesis.[9–11] The mechanism of radon exposure is given in Fig.1.Previous epidemiological studies have showed that radon exposure is dominant source of lung cancer risk. In addition, there appears to be a stronger relationship between estimated radon exposure and lung cancer in cases of small cell carcinoma and adenocarcinoma.[12–14]

However, some scholars have faced difficulty determining the safety exposure dose even on lowest dose levels.[15–17] Fortunately, low doses of exposure limit to prevent radiation penetration are between 47 μm and 70 μm depth.[18] This range is important in detecting radon airborne exposure to prevent inhalation into bronchial epithelium and bifurcation site.[19] This lead to a question that radon exposure can have both positive and negative effects in certain range of dose limit. From negative side, such exposure dose can lead to immunity problem in

Corresponding author:
Azhari
Department of Oral Maxillofacial Radiology,
Faculty of Dentistry Padjadjaran University,
Bandung, Indonesia
E-mail: azhari@fkg.unpad.ac.id

human body. The problem is indicated by mutations of mutagenesis events experienced by a cell nucleus of DNA.[20] It is characterized by changes in the DNA mutation and amino acids substitution. Some scholars suggested that radon exposure can penetrate the epidermal layer to a skin depth of 10-40 μm which has the potential to cause non-melanoma skin cancer (NMSC) and squamous cell carcinoma in the skin flesh.[21,22] In addition, although at the lowest dose of 6.0 MeV, there was a rare occurrence of radon gas experienced by some patients such as leukemia, gastrointestinal malignancy.[23,24]

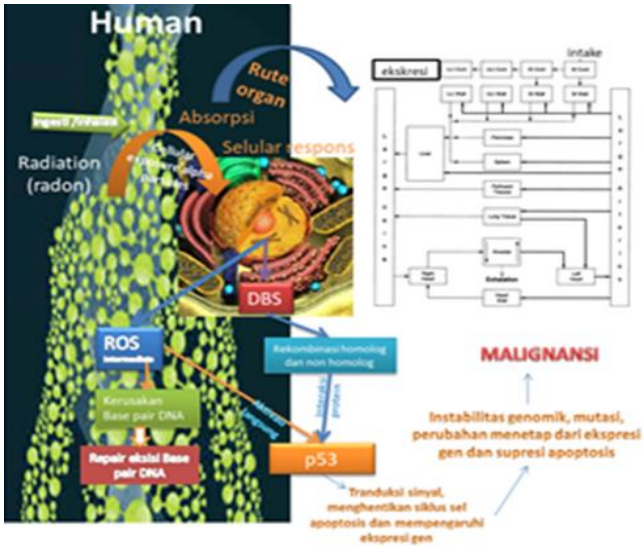

Figure 1. Inhaled and Ingested Mechanism Cellular and Organ Response Caused by Radon Exposure.

From positive side, radon gas has been studied for therapy purposes ,for example radon gas in small doses can reduce perceived pain and increase joint mobility, especially in people with rheumatoid arthritis.[25,26] However, there is a rare validated result to gives more stronger evidence. From the cytogenetic study, it can be seen that radon gas provides cellular and molecular mechanisms that form the elucidation of radon neoplastic potential and affect the nerves to reduce pain even though it is potentially increase mutation event. Despite carcinogenic effects, radon gas is practiced by the cultural community for pain relief therapy. This lead scholar debate about the positive and negative effects of radon as a carcinogen and as a material therapy.[27–29] Some natural springs, thermal pools or aquatic environments have radon based rocks which are all located in areas with very high radon concentrations to thousands of Bqm^{-3}s.[3,9]

Previous studies also have lack of information about the safest lower limit and scarcity of mechanism explanation about the exposure dose limit to impact human immune. This situation leads the authors to observe and compare previous studies and their approach to understand the dose of exposure limit.[29,30] In addition, this paper takes a position to collect information about the evidence of the range of doses and the exposure. We also summarize previous literature about radon exposure and the safe doses limit including the radon exposure toward human immune mechanism and genetic effects even at low exposure levels. Part one consisted of problem formulation and our background in arranging this paper review. Part two explains about the recent literature body of radon exposure and dose limit. Part three explains the methodology we used to search and analysis. Part four provides analysis result and part five contains conclusion and suggestion.

Literature Review

Radon exposure and immune system

In human body, the immune system is mediated by the role of p53 protein as biomarkers.[31–34] The biomarker works as tumor suppressor gene to block cell apoptosis and DNA damage.[19,35,36] When radon exposure reaching to p53 suppressor gene, the gene will mutate which lead to broken DNA chain and activation of p53 mutation.[19] This situation is one of the most common molecular steps in cancer development.[9] The p53 mutation has been identified as starter in human lung cancer [5] with reported prevalence to be highest in small cell carcinoma (> 70%) and lowest in adenocarcinoma (33%).[5,37,38] The main mechanism of p53 mutation which caused by radon exposure is given in Table 1. The studies show the collected results in patients exposed to radon. They showed that only 2% (1 in 50) of the tumors studied showed mutation in codon 249 as evidence of squamous cell carcinoma. Other study also reported that squamous cell has been mutated into carcinoma mutation which experienced by a patient located or working near radiation source hotspot.[39] Other study reported that lung cancer can develop to three levels, namely squamous cell carcinoma, adenocarcinoma

and small cell carcinoma due to the codon mutation of 249g transversion.[5,9] The mutation is mediated by radon exposure. In addition Ruano-Ravina et al., showed that TP53 hotspot mutations can have various effects between mine workers and common population.[36]

Name	P53 Protein	Phase	Conclusion
Rivlin, et al., (2011)[40]	Yes	multistep malignant transformation	Involvement of p53 inactivation at various tumor geneses stages and highlights the specific contribution of p53 mutations at each stage of cancer development after radon exposure.
Wild & Turner (2002)[41]	Yes	Aflatoxin B1	Presenting evidence that aflatoxin B1 induces G: C to T: A transversion in codon 249 of TP53
Guengerich, et al., (2001)[42]	Yes	Aflatoxin B1	Aflatoxin B1 can be enzymatically activated in human hepatocytes of third base of the 249 codon after radon exposure for years.
Hussain, et al., (2007)	Yes	in vitro	Expressions of 249 serine mutations will inhibit p53-dependent apoptosis and transcription decreasing liver cell growth in vitro after radon exposure in residential areas.

Table 1. Review of Mechanism of P53 Mutation Caused by Radon Exposure.

TP53 mutation in non-mine individuals

Radon exposure has alpha emission disturbing cell ability of tumor suppressor genes and tissue homeostasis.[43] The exposure also can reduce the cellular proliferation, terminal differentiation and programmed cell death.[5,9] High dose of radon exposure on p53 tumor suppressor gene will mutate the energy spectrum of p53 etiology leading to cancer pathogenesis.[3-8] This caused 6.5 million cancer cases worldwide per year with 2.4 million tumors are presumed by p53 mutations.[44–46] Such mutation has been related to three types of radon exposure, e.g., high (reaching 200 Bqm^{-3}), low (less than 20 Bqm^{-3}) and mid-level exposures (between 20-200 Bqm^{-3}) (Dixon, 2001). These figures have been studied by Hainaut & Pfeifer, (2001) which provide evidence that p53 mutation hotspot at codon 249 is really happened at 14 smokers or 3 non-smokers with lung cancer. The p53 mutation has been caused by relatively low radon concentrations between 11.1 and 51.8 Bqm^{-3}.[47] Such dose limits are below the mainstream study of radon dose exposure. Therefore, we provide new analysis of the dose limit and radon exposure including the effect toward the patient. The mechanism is summarized in Table 2.

Name	P53 Protein	Smoking (SM), Non-smoking (NS)	Total	Conclusion
Taylor & Stark. (2001)	Mutations in p53 genes	SM and NS	3 or 5 miners	6 (31%) of 52 large cells and squamous cells from miners contained the same AGG as ATG transversion at codon 249, including cancers from 3 or 5 never-smoking-miners
Cho, et al., (2017)	TP53 mutations	SM	28 cases	GS TP53 mutations were more common in GS cases (20/28, 70%) compared to GBM cases (29/90, 32%)

Table 2. Types of Radon Exposure and the Effect Toward the Patients.

Other scholar has reported 126 lung cancers (including adenoid, broncho-aleveolar, squamous, small cell and mixed carcinoma) from ex-smoking (n = 9) and non-smoking (n = 117) women, aged between 41 and 84 at the time of diagnosis. The study showed a higher frequency of p53 mutations in former smokers (67%) than in non-smokers (19%). The lung cancer caused by p53 mutations are experienced by smokers and non-or ex-smokers with various mutation frequencies even though none of them providing statistically significant relationship of p53 mutation and radon exposure.[9] This means that p53 mutation pattern associated with radon exposure was not consistent after comparing the dataset of the non-mining group.

HPRT and BCL-2 mutations in non-mining patients

Hypoxanthine-guanine phosphoribosyl transferase (HPRT) is an indicator of significant positive correlation between mutant frequency and indoor radon exposure. There is a growing

interest to understand the mechanism of radon exposure toward non-mining patients. A possible approach to solving the problem of radon exposure is to look for evidence of somatic cell damage caused by radiation. Population monitoring of genetic damage by analyzing the patient blood samples has been studied for years especially based on cytogenetic approach and gene mutations endpoints.[48] Such approach determines the mutation frequencies in "replacement" genes.

In a UK study, it has reported a higher frequency of the genes mutants has indicated the radon exposure by measuring the hypoxanthine-guanine phosphoribosyl transferase (HPRT) locus in 19 subjects.[49,50] The study concluded a significant positive correlation between mutant frequency and indoor radon exposure in the UK. Similarly, in a German study, an increase in chromosomal aberrations was seen in peripheral lymphocytes from 25 occupants of 9 homes with high indoor radon concentrations.[51] In contrast, smaller studies involving 11 people have found no correlation of radon exposure with low doses of 16- 90 Bqm^{-3}. [52] Other study has taken an ecological study of residential radon exposure to understand the incidence of lung cancer. The study suggested a synergistic effect of high smoking and radon exposure toward lung cancer by observing non-smokers.[53] The study result of observing relationship of HPRT and radon exposure among non-smoking participants is given in Table 2.

From ecological studies there is novel evidence of radon exposure such as leukemia. There is increased trend of leukemia case and other cancers risk in areas with high radon dose especially in residential areas although small case-control studies did not find a relationship between childhood cancer and radon exposure.[54,55] Some reports indicated that the effects can be more pronounced for childhood leukemia, especially myeloid leukemia. Despite the great skepticism with the report validation, however, more rigorous studies of the potential risks associated with radon are growing interest among scholars.[23,51,55]

Fortunately, there is growing evidence of induction of HPRT mutants after exposure, especially in 11 individuals with radon concentration dwellings with inverse association between HPRT mutation and exposure levels. Other scholars have proposed different effect of radon exposure in residential area with concentrations ranging from 50 to 3300 Bqm^{-3} with average concentration of 100 Bqm^{-3} .[55] Similar results of inverse relationship between domestic residential radon exposure and HPRT mutation frequency.[9,49,50] The report recommends that low doses exposure of radon has damaging effect especially toward HPRT mechanism.

Other radon exposure is also reported which showed that flight engineers (n = 28) can be exposed to radon radiation even though it is lack of statistically significant validation on the radon and HPRT mutations relationship.[56] Lack of definitive result of the radon radiation and its frequency of HPRT mutations become main attention among HPRT observer. Shahbazi-Gahrouei et al. suggesting that the lack of statistical significance is caused by weak data validation.[57] Since various individual characteristics and history, there is validated result to support the effect of HPRT mutations for individuals working in flight activity. This result needs more validation to understand the radon exposure and ionizing radiation toward increased frequency of HPRT mutants.[9,50] In addition, it also needs to understand the effect of mutation especially in lymphocytes by using dosimeters over a 72-week period although no correlation was observed in the study.

Chromosome aberrations

Uranium mine has become main source of radon exposure. Many scholars have taken interest in the high frequency of chromosomal aberration (CA) in uranium miners and other radon exposures.[58] Apart from ionizing radiation, there are other agents in underground work environments such as arsenic, diesel exhausts, welding smoke or genotoxic rock.[52,59] Chomosomal abberations had been related to chromatid exchange among non-exposed population.[9,58,60] The mechanism of chromosomal aberration in radon source area is summarized in Table 3.

Name	Chromosome Aberrations	Amount	Age	Exposure	Objectives	Results
Wolf, et al., (2004)	Yes	23 workers	more than 60 years old	peripheral lymphocytes from 66 WUM and 29 RCM	comparing chromosomal aberrations in uranium Wismut (WUM) mineralized lymphocytes and Ruhr coal miners (RCM)	Frequency of chromosomal aberration and chromatid exchange in WUM and RCM is quite similar
Mészáros, G., & Bognár, G. (2004)	Yes	165 uranium miners	35 and 65, 50 and 78	The emission of 1.3 x 105 MeV of potential energy	Chromosome aberration analysis was carried out on blood samples from 165 active underground uranium miners between 1981 and 1985	Acentric frequency, however, decreased significantly, but even the lowest values remained 2-3 times higher than the values in the non-exposed population.
Santa Maria et al., (2007)	Yes	38 miners	45,28,36 and 26 years	Cells were collected by centrifugation, briefly suspended in hypotonic pre-heating 0.075 M KCl and repaired twice in acetic acid / methanol (1: 3, v / v).	Analyzing the frequency of chromosomal aberrations in peripheral lymphocytes from underground miners from Casapalca.	Cytogenetic biomonitoring results are considered as a valuable index for exposure to genotoxic carcinogens

Table 3. Effect of Radiation Exposure Toward Chromosomal Abberations.

There are many studies reporting indicator of chromosomal aberration induced by radiation in the grouping population especially among mining workers. The mining workers have "unstable" cell abberations but only three cells from the controlled patients have a classification of chromosomal changes and acentric fragment type.[51] This finding is consistent with the study conclusion type that the miners' nonpulmonary cells undergo mutation changes as a consequence of radiation exposure encountered from the uranium mine. The difference between the worker and control group in the prevalence of lymphocyte chromosomal aberrations is statistically significant and the magnitude is biological importance. This finding is consistent that workers' nonpulmonary cells has undergo mutation changes as a consequence of radiation exposure from uranium mine.[6,20]

Chromosomal aberration in non-mining patients

Although many studies have reported relationship between frequency of chromosomal aberration and radon exposure, there is lack of validated result for the non-occupational exposure especially in the workers who got blood lymphocytes compared to subjects who had a local residence.[61] A study showed the domestic risk of radon exposure at lower doses. In addition, the increased frequency in chromosomal aberration is higher for occupational exposures than nuclear workers.[62] However, the study did not explain the people background to validate the relationship of high background radiation concentrations and the effects of chromosomal rest. They used self-administered to observe socioeconomic status rather than radiation characteristics to validate the results. An Austrian reported that population can be exposed to high levels of radon radiation even though they are not mining workers.[63] The study gives evidence that a dose-response effect even the low dose exposure can bring chromosomal abberations.

Such abberations in lymphocytes also found by using suitable epidemiological approach.[19,64] The study found case of patient deaths from all types of cancer in higher radiation doses. The study contains validation approach by comparing both control and independent group

especially in the radiation areas and the exposure levels compared to control area. In addition, the study reported higher rates of dysenteric formation, leukemia and lung cancers for both genders. The study provides evidence of dicentric and ring formation in lymphocytes case with radon concentrations known to be 4 to 60 times the German study average of 50 Bqm^{-3}. Other study has different result. For example, a Finnish study found no correlation between domestic radon concentrations (<100 to> 800 Bqm^{-3}) in 84 non- smoker with chromosomal aberrations. However, there is no further evidence for a relationship between high chromosomal aberration frequencies in peripheral blood lymphocytes as indicators of cancer risk this lead to a gap in cancer risk study to understand the frequency of chromosal abberations to compare high and low frequency of radon concentrations toward the abberations in blood lymphocytes.

This approach can be validated and expanded by including children and adolescents, from areas of high radon concentrations to understand the relationship of chromosal aberration and radon exposure mediated by any aberrations of chromosome breaks and acentric fragments.

Low doses of radon exposure

Radon exposures have been studies in many doses to understand the impact of radon gas toward human peripheral lymphocytes. Some studies used in vivo and in vitro have estimated the effect of exposure of 18 cGy radon toward chromosomal aberration and chromatid removal.[65,66,67]

There is a trend that cells exposed to increasing doses will lead to abberations in short term.[9,68] The previous study also showed that about half lower doses toward pre-exposed cells of 2 cGy will show an adaptive effect especially toward haemopoietic cells.[60,69] it has provided evidence that haemopoietic cells with doses of pu-238 will show a higher aberration frequency in clonal offspring.[70] This preliminary evidence still contains debatable results especially on the transgene instability and abnormalities of chromosome bone marrow cells. Other study reported that case was observed in two of the four individuals to impact the chromosomal instability and leukemia chromatid sister exchange.[23] This is reasonable since the study only measured a low dose of 0.31 mGy alpha radiation toward the human pulmonary fibroblast cells. Similar result has been reported. [52,64] Radon doses from 0.4 to 12.9 cGy to estimate number of alpha traversals cellular particles and suggests that alpha particle irradiation was associated with an extranuclear mechanism. A follow-up study in the same cell type also noted that abberations in cells are not directly affected by alpha particles.[60,71] This means that radon exposure only give small effect if the exposure drive extranuclear effect after exposed in superoxide and hydrogen peroxide anions after being exposed to alpha particles.

Direct irradiation and transmission of effects to non-irradiation cells of pulmonary fibroblasts after exposure to cell irradiation also have been confirmed by other studies. Some scholars provided evidence of transformation factor beta 1 (TGF-P1) cytokines as mediators of chromosomal response. Similar results observing promitogenic effects of cell growth augmentation to produce TP53 protein and 1A cyclin kinase-kinase inhibitor (CDKN1A).[72] This result is validated by using Western blotting to measure the decreased cell division control protein 2 (CDC2) after patients are Pu-238 irradiated in years.

However, there is lack of evidence especially of the relationship of chromosomal aberration and diethlyenetriamine pentaacetic acid (DTPA) to prevent external exposure in blood lymphocytes. Low dose of exposure (0.03-41.4 mGy) using polonium-214 toward blood lymphocytes will increase frequency of dicentric and acentric fragments.[70] Similar result that the doses derived from the radon gas apparatus will bring frequency of irregularities if the doses are increased from 0.03 to 0.10 mGy.[73] Certain exposure will have linear dose effect as response to low dose exposure. This result is different by comparing the in vitro study and the synergistic effect of radon and smoking examines in patients of smokers and non-smokers at exposure 0.10-5 Gy. Streffer, et al., also reported that radon exposure on smoker lymphocytes were more unstable even the doses are increased from 0.9 and 5.2 mGy.[74] This means that radon-induced dicent fragments, acentric fragments and chromatid breaks are occurred with very small doses. The results are important since we can determine the quality of radon exposure to measure various effects toward intracellular level.[8,75] In very small doses, radon exposure has

tendency to increase frequency of chromosomal aberration to detect DNA damage in areas of high radiation sources. In addition, it is important to validate the result to understand the incidence of cancer risk and correlation between the abberations and cancer risk.

Methodology

Methodology is useful for directing this paper to be consistent and sequential. The reason we took the title of this paper is to find out the dose of radon exposure on human lung cell immunity.[76,77] We collect information and data from Google Scholar with certain keywords from previous longest years up to the latest years. We also included sources of names and groups of researchers including the reasons for taking the topic. For that we use search engines from Google Scholar, EBSCO, Web of Science, ASSIA via ProQuest, Medline via WoS, and the Cochrane Library. The methodology in this review paper consists of six stages.

The first stage is radon exposure and immune system. This is done by comparing the prediction model for lung cancer and validation studies. We compiled an article search strategy related to radon exposure, dose, and its effects on the human immune system. We use certain search keywords related to "Lung Cancer", "risk models", risk assessment models", and "predicted scores".

In the second stage, to obtain information related to p53 mutation in non-mine patients, we used keywords in the form of "lung cancer and p53 mutation", "lung cancer among non-mine workers", and "lung cancer experienced by non-miners", and "p53 mutation among workers". In the third stage, we would like to look for articles related to HPRT and BCL-2 mutations in non-mining patients. For the purpose, we use key words such as "lung cancer screening", "HPRT after lung cancer incidence", "HPRT among non-mining patients", and "HPRT and BCL-2 mutations for both male and female patients".

In the fourth stage, we want to know information about the effects of radon exposure on chromosome aberrations. To achieve the objective, we typed in a list of keywords including "models of lung cancer and chromosome abberations", "chromosome abberations in male lung cancer", "chromosomal abberations in female lung cancer", and "radon exposure effects on chromosome abberations". In the fifth stage, to find out the prediction model for lung cancer, especially for Chromosomal aberration in non-mining patients, we look for the model title. We also look for validation both internally and externally. This was done by using the keywords such as "predictive model of lung cancer", "chromosomal aberration as a predictive model of lung cancer", and "chromosomal abberations in non-mining patients".

Finally, in the sixth stage, we want to find journals and articles that explain very small low doses of radon exposure. Our goal is to find and compare the less well-known models including their mechanism for identifying lung cancer. We also found a small portion that low exposure can be detected because other researchers have used more accurate technology. However, technology issues of radon measurement are not the scope of our review paper. To find out models of very low dosage of radon exposure, we use the following keywords: "Low doses of radon exposure", "model of radon exposure in low doses", "very small low radon exposure dosage".

Discussion

Low doses, radon gas can interact with fresh air which inhaled into human lung to shape complex chemical compound. The compound is inhaled through certain mechanism. This paper provides evidences from previous studies that the incidence of cancer risk has been increased rapidly with various doses. However, they needs to be validated externally especially through cross validation of the correlation between frequency of chromosomal aberration and cancer risk.

Our analysis result showed that even low doses of radon exposure can have effects on human immune especially the lymphocytes cells with doses between 0.9 and 5.2 mGy. This numbers have been reported in many studies.[9,78] However, the studies lacks of adequate validation and equipment in order to provide qualified measurement. In addition, the studies does not specify the observer competence as limiting factors in the entire results.

Our review provide insightful information that low dose of exposure (0.03-41.4 mGy) can impact on human lymphocytes cell caused by synergistic effect of radon and smoking from both

smokers and non- smokers. This effects are reasonable since there is direct irradiation and transmission of the effects to non-irradiation cells of pulmonary fibroblasts after long exposure to cell irradiation. The irradiation has led to mutate transformation factor beta 1 (TGF-P1) cytokines to reduce the ability of p53 protein and 1A cyclin kinase-kinase inhibitor (CDKN1A) especially in patients irradiated in years.[9,79–81]

Finally, our analysis result provides new insight that pre-exposed cells with very small doses of 2 cGy will show an adaptive effect especially toward haemopoietic cells. A at small low doses of exposure, the haemopoietic cells will impact chromosomal instability and chromatid sister exchange in leukemia. From the literature review, the extranuclear mechanism in cells is not directly affected by alpha particles. The radon exposure only gives small effect toward extranuclear SCE since it can increase superoxide and hydrogen peroxide anions after the exposure. The result has been studied and observed which lead us to know that a small dose will result in a reduction in the number of exposed cells without changing the condition and mechanism.[82–84]

Our review result showed that chromosomal delinquency in non-mining individuals can occur after the patients are exposed in years.[59] The patients can suffer from blood lymphocytes even though they are not nuclear miners or smokers. Our review also gives evidence that a dose-response above limiting exposure can bring abberations as experienced by miners group exposed to low dose of radon levels.

There is role of p53 biomarkers as tumor suppressor gene containing p53 protein to block cell apoptosis and DNA damage. As suppressor gene, p53 protein has role in the tumor-suppressor activity mechanism to reduce cancer development. However, the radon exposure can lead to p53 mutation in human lung cancer.[36,85] Our review showed that the mechanism work in multistep malignant transformation through inactivation of p53 which then lead to carcinoma, adenocarcinoma and small cell carcinoma. The cancers are occurred even though the exposure reaching as low as 20 Bqm^{-3} for both smoker and non-smoker.[44,86–88]

We also review the patient background especially who works as uranium workers (miners). Our review shows that p53 gene mutation was observed in most of respondent populations. This is reasonable since the mutations in exon 5-8 p53 genes are induced by radon exposure which lead to lung cancers (including adenoid, broncho-aleveolar, squamous, small cell and mixed carcinoma) experienced by both ex-smoking and non-smoking workers.[9,36,47]

Conclusion and suggestion

The mechanism of radon exposure among the smokers, non-smokers and uranium miner has been explained in this paper review. There is clear evidence and explanation that the mechanism is triggered by radon exposure which changes the gene activity. In addition, the exposure toward the cytogenetic endpoints will change the chromatid exchanges, micronuclei-chromosomal aberration and incidence of lung cancer. Such mutagenic effect is experienced by patient after exposed from a low dose of 200 Bqm^{-3} to start translocations in lymphocytes for both smoking and non-smoking workers. However the effect of radon exposure to lead leukemia is not as big as lung cancer. Therefore, we concluded that radon exposure will create higher effect to lung cancer risk than to leukemia or other mutagenesis-related disease.[11,31,74]

Finally, we conclude that radon exposure can lead to lung cancer risk with various doses ranging from 50 to 3300 Bqm^{-3} with average concentration of 100 Bqm^{-3}. For such doses, it can lead to chromosome aberrations and genotoxic carcinogens the chromosomal changes are indications of cancer risks. Therefore, an increase in cancer risk emphasizees a conclusion that radon exposure has great role in the pulmonary carcinogenesis.[9]

Exposure to radon and its offspring can induce various cellular and molecular cytogenetic affects both in vitro and in vivo levels. Our review demonstrates the risk of radon gas to induce cell damage even in small low dose still representing significant public health risks. In the future, the low dose ranges must be measured with more sophisticated technology and tools in order to get more accurate result. This study does not explain the cellular response and the full risk of ionizing radiation technology experienced by the general population.[11]

Even though our study is deterministic on its basis, we want to provide multicellular basis on the threshold dose and the mechanism to explain the mutagenesis and carcinogenesis comes from radon exposure. For future study, it is suggested to measure carcinogenesis risk and

neoplasms testing by observing the monoclonal as well as the observation of the role of single traversal alpha particle and how the particle can induce significant cell damage in order the role can be clear in the advanced research.

References

1. EPA. A Citizen's Guide to Radon, The Guide to Protecting Yourself and Your Family from Radon Indoor. US; EPA 402/K-12/002, 2012:3-5-10.
2. Saha JMU, Sonon PTL, Lynch GWD, Holland K, Hold H. Your Household Water Quality: Radon in Your Water Uga Extension Circular. UGA extension. US, Georgia: EPA. 2015;16:1–4.
3. Field R, Steck D, Smith B, Brus C, Fisher E, Neuberger J, *et al*. Residentiol Radon Gas Exposure and Lung Cancer. Am J Epidemiol. 2000;151(11):1091–102.
4. Springs CC, Diego S. Lung Cell Immune System Response Due to Irradiation by Alpha Particles Lung Cell Immune System Response Due to Irradiation by Alpha. (May 2015).
5. Hinojosa OR, Garza D, Sanín LH, Elena M, Cabrera M, Ivette K, *et al*. Lung Cancer Mortality and Radon Concentration in a Chronically Exposed Neighborhood in Chihuahua, Mexico: A Geospatial Analysis. 2014.
6. Hall S, Nwako P. Exploring Knowledge, Beliefs and Practices of Radon Gas Exposure Among Public Health Workers. Setin Hall. 2016.
7. Al-Jundi J, Li WB, Abusini M, Tschiersch J, Hoeschen C, Oeh U. Inhalation dose assessment of indoor radon progeny using biokinetic and dosimetric modeling and its application to Jordanian population. J Environ Radioact. 2011;102(6):574–80.
8. Rattan S, Le Bourg É. Hormesis in Health and Disease. 2014;382.
9. Robertson A, Allen J, Laney R, Curnow A. The cellular and molecular carcinogenic effects of radon exposure: A review. Int J Mol Sci. 2013;14(7):14024–63.
10. Chahine T, Schultz BD, Zartarian VG, Xue J. Modeling Joint Exposures and Health Outcomes for Cumulative Risk Assessment: The Case of Radon and Smoking. 2011;3688–711.
11. National Research Council of The National Academies. Health Risks from Exposure to Low Levels of Ionizing Radiation BEIR II. 2nd ed. MONSON RR, editor. wahington DC: The National Academic Press; 2006. 385.
12. Mirzaie-Joniani H, Eriksson D, Sheikholvaezin A, Johansson A, Lfroth P-O, Johansson L, *et al*. Apoptosis induced by low-dose and low-dose-rate radiation. Cancer. 2002;94(S4):1210–4.
13. Bersimbaev RI, Bulgakova O. The health effects of radon and uranium on the population of Kazakhstan. Genes and Environment. 2015;37(1):1–10.
14. Malinovsky G, Yarmoshenko I, Zhukovsky M. factors in ecological studies Ac ce pt us. Int J Radiat Biol. 2018;0(0):000.
15. Soto J, Sainz C, González-Lamuño D, Cos S. Low doses of alpha particle irradiation modify the expression of genes regulating apoptosis in human MCF-7 breast cancer cells. Oncol Rep. 2006;15(10):577–81.
16. Yu H, Song A, Fei C, Wang Z, Qiu W. Effects of Low Dose Radiation on Tumor Apoptosis, Cell Cycle and Apoptosis-Related Protein Bcl-2 in Tumor-Bearing Mice. Chinese-German J Clin Oncol. 2005;4(2):89–92.
17. McLean AR, Adlen EK, Cardis E, Elliott A, Goodhead DT, Harms-Ringdahl M, *et al*. A restatement of the natural science evidence base concerning the health effects of low-level ionizing radiation. Proc Royal Soc B: Biolog Sci. 2017;284(1862):20171070.
18. Red FA, Ettler M, JR, MD, MPH, George L, Voelz MD, Ajor M. Radiation exposure-What expectation and how to respond.N Engl J Med Rev. 2009;51(2):144–70.
19. Li BY, Sun J, Wei H, Cheng YZ, Xue L, Cheng ZH, *et al*. Radon-induced reduced apoptosis in human bronchial epithelial cells with knockdown of mitochondria DNA. J Toxicol Environ Health-Part A: Curr Issues. 2012;75(18):1111–9.
20. Madas BG, Balásházy I. Mutation induction by inhaled radon progeny modeled at the tissue level. Radiat Environ Biophys. 2011;50(4):553–70.
21. DW, Donnelly ATG, HC. Cancer in Ireland 1994-2004: A summary report. ireland; 2004.
22. Burke LS, Hyland PL, Pfeiffer RM, Prescott J, Wheeler W, Mirabello L, et al. Telomere length and the risk of cutaneous malignant melanoma in melanoma-prone families with and without CDKN2A mutations. PloS one. 2013;8(8):1–7.
23. Xin Y, Zhang H-B, Tang T-Y, Liu G-H, Wang J-S, Jiang G, et al. Low-dose radiation-induced apoptosis in human leukemia K562 cells through mitochondrial pathways. Mol Med Rep. 2014;10(3):1569–75.
24. Monie T. The innate immune system: a compositional and functional perspective. 2017.
25. Strupler FP, Protection R, Spondylitis A, Society I, League E, Rheumatism A. Opinion concerning radon therapy for ankylosing spondylitis 3. Opinion Commission. 2014;(December):1–2.
26. Hahn Y-S, Kim J-G. Pathogenesis and clinical manifestations of juvenile rheumatoid arthritis. Korean J Pediatr. 2010;53(11):921.
27. Madas BG. Radon Exposure and the Definition of Low Doses-The Problem of Spatial Dose Distribution. Health Phys. 2016;111(1):47–51.
28. Erickson BE. The therapeutic use of radon: a biomedical treatment in europe; an "alternative" remedy in the united states. 2007;(714):48–62.
29. Grass GD, Krishna N, Kim S. The immune mechanisms of abscopal effect in radiation therapy. Curr Probl Cancer. 2016;40(1):10–24.
30. Cui J, Yang G, Pan Z, Zhao Y, Liang X, Li W, *et al*. Hormetic response to low-dose radiation: Focus on the immune system and its clinical implications. Int J Mol Sci. 2017;18(2).
31. Sam Keith, M.S., C.H.P. John R. Doyle, M.P.A. Carolyn Harper, Ph.D. Moiz Mumtaz PDOT. Draft Toxicological Profile for Radon: Agency for Toxic Substances and Disease Registry (ATSDR). 3rd ed. Christopher J. Portier, editor. ATLANTA GEORGIA: Agency for Toxic Substances and Disease Registry. 2012;9-11:161-167.
32. IAEA. Radiation Protection and Safety of Radiation Sources: International Basic Safety Standards (GSR Part 3). Int Atomic Energy Agency Vienna. 2014;3:471.
33. EPA. Radiation: Facts , Risks and Realities. United States Environmental Protection Agency. 2012;(April).
34. NCRP) NC on RP and M. Radon exposur of the US Population status of the problem. Woodmont Avenue 2016.
35. Bai L, Zhu W. p53 : Structure , Function and Therapeutic Applications. 2006;141–53.
36. Ruano-Ravina A, Faraldo-Vallés MJ, Barros-Dios JM. Is there a specific mutation of p53 gene due to radon exposure? A systematic review. Int J Radiat Biol. 2009;85(7):614–21.
37. Pallis AG, Syrigos KN. Lung cancer in never smokers: Disease characteristics and risk factors. Crit Rev Oncol/Hematol. 2013;88(3):494–503.
38. Sun S, Schiller JH, Gazdar AF. Lung cancer in never smokers-A different disease. Nat Rev Cancer. 2007;7(10):778–90.
39. Song Y, Li L, Ou Y, Gao Z, Li E, Li X, et al. Identification of genomic alterations in oesophageal squamous cell cancer. Nature. 2014;508(7498):91–5.
40. Rivlin N, Brosh R, Oren M, Rotter V. Mutations in the p53 tumor suppressor gene: Important milestones at the various steps of tumorigenesis. Genes Cancer. 2011;2(4):466–74.
41. Wild CP. The toxicology of aflatoxins as a basis for public health decisions. Mutagenesis. 2002;17(6):471–81.
42. Guengerich FP, Cai H, McMahon M, Hayes JD, Sutter TR, Groopman JD, et al. Reduction of Aflatoxin B 1 Dialdehyde by Rat and Human Aldo-keto Reductases. Chem Res Toxicology. 2001;14(6):727–37.
43. Brooks AL, Brooks AL, Zentrum FH, Forschungszentrum D, Superiore I, Sanit GC, et al. Hormesis in Health and Disease. Proc Royal Soc B: Biol Sci. 1928;284(6):382.

44. Husgafvel-Pursiainen K, Boffetta P, Kannio A, Nyberg F, Pershagen G, Mukeria A, et al. P53 Mutations and Exposure to Environmental Tobacco Smoke in a Multicenter Study on Lung Cancer. Cancer Res. 2000;60(0008–5472 SB–IM):2906–11.
45. Lantz PM, Mendez D, Philbert MA. Radon, smoking, and lung cancer: The need to refocus radon control policy. Am J Pub Health. 2013;103(3):443–7.
46. Snyder LA, Bertone ER, Jakowski RM, Dooner MS, Jennings-Ritchie J, Moore AS. P53 Expression and Environmental Tobacco Smoke Exposure in Feline Oral Squamous Cell Carcinoma. Vet Pathol. 2004;41(3):209–14.
47. Hainaut P, Pfeifer GP. Patterns of p53 G→T transversions in lung cancers reflect the primary mutagenic signature of DNA-damage by tobacco smoke. Carcinogenesis. 2001;22(3):367–74.
48. Bonassi S, Ugolini D, Kirsch-Volders M, Strömberg U, Vermeulen R, Tucker JD. Human population studies with cytogenetic biomarkers: Review of the literature and future prospectives. Environ Mol Mutagen. 2005;45(2–3):258–70.
49. Hackman P, Hou SM, Nyberg F, Pershagen G, Lambert B. Mutational spectra at the hypoxanthine-guanine phosphoribosyltransferase (HPRT) locus in T-lymphocytes of nonsmoking and smoking lung cancer patients. Mutation Res-Genetic Toxicol Environ Mutagen. 2000;468(1):45–61.
50. Alanazi M, Al-Arfaj AS, Abduljaleel Z, Fahad Al-Arfaj H, Reddy Parine N, Purusottapatnam Shaik J, et al. Novel hypoxanthine guanine phosphoribosyltransferase gene mutations in Saudi Arabian hyperuricemia patients. BioMed Res Int. 2014;2014.
51. Al-Zoughool M, Krewski D. Health effects of radon: A review of the literature. Int J Radiat Biol. 2009;85(1):57–69.
52. Hughes MF, Beck BD, Chen Y, Lewis AS, Thomas DJ. Arsenic exposure and toxicology: A historical perspective. Toxicol Sci. 2011;123(2):305–32.
53. Sethi TK, El-Ghamry MN, Kloecker GH. Radon and lung cancer. Clin Adv Hematol Oncol. 2012;10(3):157–64.
54. Kendall GM, Little MP, Wakeford R, Kathryn J, Miles JCH, Vincent TJ, et al. A record-based case-control study of natural background radiation and the incidence of childhood leukaemia and other cancers in Great Britain during 1980–2006. Leukemia. 2013;27(1):3–9.
55. Tong J, Qin L, Cao Y, Li J, Zhang J, Nie J, et al. Environmental radon exposure and childhood leukemia. Journal of Toxicology and Environ Health-Part B: Crit Rev. 2012;15(5):332–47.
56. Radiation S, Risk C, Visit NA, Press NA. Technical Evaluation of the NASA Model for Cancer Risk to Astronauts Due to Space Radiation. SciencesNew York. 2012;1-93.
57. Shahbazi-Gahrouei D, Setayandeh S, Gholami M. A review on natural background radiation. Adv Biomed Res. 2013;2(1):65.
58. Bonassi S, Znaor A, Norppa H, Hagmar L. Chromosomal aberrations and risk of cancer in humans: An epidemiologic perspective. Cytogenet Genome Res. 2004;104(1–4):376–82.
59. Kumar A, Vij R, Gupta M, Sharma S, Singh S. Risk assessment of exposure to radon concentration and heavy metal analysis in drinking water samples in some areas of Jammu & Kashmir, India. J Radioanal Nuc Chem. 2015;304(3):1009–16.
60. Han W, Yu KN. Response of Cells to Ionizing Radiation. In: S C Tjong, editor. Advances in Biomedical Sciences and Engineering. Hongkong: Bentham Sci Pub. 2012 :204–62.
61. Azhari, Silviana D. The effects of X-rays radiation on active and passive transport of erythrocytes membrane. J Int Dental Med Res. 2018;11(1):261–4.
62. Brenner DJ, Doll R, Goodhead DT, Hall EJ, Land CE, Little JB, et al. Cancer risks attributable to low doses of ionizing radiation: Assessing what we really know. Proc National Acad Sci. 2003;100(24):13761–6.
63. Friedmann H. Final results of the Austrian Radon Project. Health Phys. 2005;89(4):339–48.
64. Ding L-H, Shingyoji M, Chen F, Hwang J-J, Burma S, Lee C, *et al*. Gene Expression Profiles of Normal Human Fibroblasts after Exposure to Ionizing Radiation: A Comparative Study of Low and High Doses. Radiat Res. 2009;26:17–26.
65. Morgan WF, Sowa MB. Non-targeted effects induced by ionizing radiation: Mechanisms and potential impact on radiation induced health effects. Cancer Lett. 2015;356(1):17–21.
66. Ciorba D, Morariu V, Cosma C, Neamţu S, Cuceu C. Quantification of Dna Damage in Human Lymphocytes by Comet Assay, During in Vitro Ageing in the Presence of Radon. 2014;20(2):137–48.
67. Ciorba D, Truta A, Science E, Faculty E, Faculty B. Cytotoxic exposure of green algas chlamydomonas peterfii gerloff in radon aerosols*. 2013;58:1–11.
68. US EPA. Environmental Protection Agency Radon Radon in Drinking Water Health Risk Reduction and Cost Analysis; Notice part II. US, 1999;64.
69. Seong J, Kim SH, Pyo HR, Chung EJ, Suh CO. Effect of low-dose irradiation on induction of an apoptotic adaptive response in the murine system. Radiat Environ Biophys. 2001;40(4):335–9.
70. Que T, Duy P, Luyen BK. Calibration curve for dicentric chromosomes induced in human blood lymphocytes exposed to gamma rays at a dose rate of 12.5 mgy/s. Genome Integrity. 2016;7(1):2.
71. Furlong H, Mothersill C, Lyng FM, Howe O. Apoptosis is signalled early by low doses of ionising radiation in a radiation-induced bystander effect. Mutation Res-Fundam Mol Mech Mutagenesis. 2013;741–742:35–43.
72. Woo Lee J, Ning Qi W, Scully SP. The involvement of β1 integrin in the modulation by collagen of chondrocyte-response to transforming growth factor-β1. J Orthop Res. 2002;20(1):66–75.
73. Lee C, Rajaraman P, De AB. Cancer Risks Associated with External Radiation from Diagnostic Imaging Procedures. CA Cancer J Clin. 2012;62(2):75–100.
74. International Commision on Radiological Protection (ICRP). Low Dose Exposures in the Environment: Dose-Effect Relations and Risk Evaluation. 3rd ed. R.cox, editor. oxford UK, UK: Elsevier; 2006: 1–141.
75. Short SC, Bourne S, Martindale C, Woodcock M, Jackson SP. DNA damage responses at low radiation doses. Radiat Res. 2005;164(3):292–302.
76. Laura S, Larsson, M.P.H. BSN. Risk ‐ reduction strategies to expand radon care planning with vulnerable groups. Public Health Nursing. HHS Pub Access. 2015;91(2):165−71.
77. Baskaran M. Radon: A Human Health Hazard in the Environment. In Radon: A Tracer for Geological, Geophysical and Geochemical Studies. Porcelli D, editor. USA: Springer Geochemistry. 2016:229-254.
78. Cavalcanti MB, Fernandes TS, Silva EB, Amaral A. Correlation between radiation dose and p53 protein expression levels in human lymphocytes. Anais da Academia Brasileira de Ciencias. 2015;87(3):1783–90.
79. Scott BR, Di Palma J. Sparsely Ionizing Diagnostic and Natural Background Radiations are Likely Preventing Cancer and other Genomic-Instability-Associated Diseases. Dose-Response. 2007;5(3): 45-55.
80. Kumar A, Chandna S. Evidence for a radiation-responsive “p53 gateway” contributing significantly to the radioresistance of lepidopteran insect cells. Sci Rep. 2018;8(1):1–14.
81. Tungjai M, Phathakanon N, Rithidech KN. Effects of Medical Diagnostic Low-dose X Rays on Human Lymphocytes. Health Phys. 2017;112(5):458–64.
82. Balásházy I, Farkas Á, Madas BG, Hofmann W. Non-linear relationship of cell hit and transformation probabilities in a low dose of inhaled radon progenies. J Radiol Prot. 2009;29(2):147–62.
83. Ray K, Stick M. Radiation and Health Effects. In: Stick KR and M, editor. Handbook of Toxicology of Chemical Warfare Agents: Second Edition. II. Elsevier Inc.;2015 :431–46.
84. Vogiannis EG, Nikolopoulos D. Radon Sources and Associated Risk in Terms of Exposure and Dose. Frontiers Pub Health. 2015;2(5):1–10.
85. 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):1–28.

86. Yngveson A, Williams C, Hjerpe A, Lundeberg J, Soderkvist P, Pershagen G. p53 Mutations in lung cancer associated with residential radon exposure. Cancer Epidemiol Biomarkers Prev. 1999;8(5):433–8.
87. Smardova J, Liskova K, Ravcukova B, Malcikova J, Hausnerova J, Svitakova M, et al. Complex analysis of the p53 tumor suppressor in lung carcinoma. Oncology Rep. 2016;35(3):1859–67.
88. Yan W, Wistuba II, Emmert-buck MR, Erickson HS. Review Article Squamous cell carcinoma–similarities and differences among. Am J Cancer Res. 2011;1(3):275–300.