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REVIEW ARTICLE

# Radon induced health effects: A survey report

**Biswajit Das**[1]*

**1** Assistant Professor, Department of Physics, Vidyasagar University, Midnapore, 721102, Paschim Medinipur, West Bengal, India. Tel.: +91-9474751320

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* **Corresponding author**.

Tel: +91-9474751320
biswajitdass100@yahoo.com

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## Abstract

**Background/Objectives**: The main objective of the present study is to find a relationship between radon exposure and the incidence of some malignant or non-malignant diseases. **Methods**: To find risks of occurrence of some diseases associated with radon exposure, this study reviewed published literature reporting the sources of radon, indoor and outdoor radon entry, factors influencing the radon concentrations, and induced health effects associated with radon and its decay products. **Findings**: Health hazards caused by radon ($^{222}$Rn) exposure are mainly due to its decay radionuclides of $^{218}$Po, $^{214}$Po and $^{210}$Po. A high-level radon exposure is a risk factor for lung cancer. It is strongly associated with risks of some cancer in blood, skin, stomach and brain. The link of malignancies in the cardiovascular system, kidney and pancreas with radon exposures is controversial, but cannot be ruled out for the kidney. Radon has a significant effect on the reproductive system and growth of offspring at different gestation periods of women. Radon may also account for some other diseases, including COPD in lungs, diseases in esophageal, and rectum, or colorectal of the digestive system, cancers in the lip, oral cavity, and also pharynx and laryngeal cancers. Radon-induced diseases including cancers are susceptible to race, gender, or children, particularly cancers or diseases in lungs, stomach, brain, pancreas, female breast, and fetus. More systematic studies are required to find a correlation of radon exposure with malignant and non-malignant diseases. The vulnerable population for such exposure (miners and dwellers of colder regions) needs to be identified for protective measures. Of course, the contribution of Radon to the possible background radiation exposure, which may attribute to the hormetic effect, is almost outside the scope of the present study. **Novelty/Applications**: Present study provides some valuable information regarding evidence of some health effects caused by radon and its decay products. This can help researchers and the general population.

**Keywords:** Radon; health effects; cancer; mortality; miners; general population

## 1 Introduction

Radon belongs to group 18 (noble gases) element in the periodic table. It is the only gaseous radioactive element formed by the radioactive decay of radium. Decay products of radon are solid (metallic) radioactive elements. For its colourless, odorless, tasteless, chemically inert activity, radon is not detectable by human's senses.

Generally, radon has three isotopes, namely, $^{222}$Rn (half-life $T_{1/2}$ = 3.825 d, called radon), $^{220}$Rn ($T_{1/2}$ = 55.6 s, called thoron) and $^{219}$Rn ($T_{1/2}$ = 3.96 s, called actinon), which are intermediate radionuclides of three natural radioactive decay series of $^{238}$U, $^{232}$Th and $^{235}$U, respectively, through which uranium and thorium slowly decay to the short-lived radionuclides and finally ending at stable isotopes of lead. The decay products or progeny of radon isotopes are: (i) $^{218}$Po, $^{214}$Pb, $^{218}$At,$^{214}$Bi, $^{214}$Po, $^{210}$Tl, $^{210}$Pb, $^{210}$Bi, $^{210}$Po of $^{222}$Rn family; (ii) $^{216}$Po, $^{212}$Pb, $^{212}$Bi, $^{212}$Po, $^{208}$Tl of $^{220}$Rn family; and (iii) $^{215}$Po, $^{211}$Pb, $^{215}$At,$^{211}$Bi, $^{211}$Po, $^{207}$Tl of $^{219}$Rn family. The radon isotopes of $^{222}$Rn and $^{220}$Rn are mostly available in nature. The availability of $^{219}$Rn isotope in the earth's environment is thought to be very poor because relative abundance of $^{235}$U in nature is 0.7205% on average[(1)]. Among the radon isotopes, radon ($^{222}_{86}Rn$) has significant importance, because the half-life of radon is much greater than half-lives of both thoron and actinon so that it can travel relatively a large distance in a medium.

Radon gas is ubiquitous — outdoors and indoors, as uranium and radium occur widely in soil, rocks and water[(2)]. In our natural environment, there are various sources of radon, of which soil and rocks are the main. The largest source of radon can be found in some areas where uranium, thorium, radium and their corresponding decay products are widely distributed in soil and rocks[(3,4)]. Groundwater provides a secondary source of radon in the environment. The concentrations of radon in groundwater may vary from location to location depending upon the uranium and radium contents in underground rocks and minerals. Relatively high levels of radon in groundwater can be found in certain areas where granite rocks are present[(2)]. Additional sources of radon in the environment are surface water and natural gas. Certain industrial activities are usually involved on some rocks and minerals that contain significant quantities of naturally occurring radioactive materials (NORMs), which are uranium, thorium and any of their decay products such as radium and radon[(5)].

When radon gas is produced within the soil, it is transported through soil mainly by two processes – molecular diffusion and convective (pressure-driven) flow of soil gas[(6)], and then transferred in ambient air. Because of their continued dispersion, radon and its decay progenies are always present with lower levels over the earth's surface. A part of this radon can seep into the indoor spaces and be concentrated with varying amounts depending upon the difference in air pressure at inside and outside spaces, type of soil, the moisture content in the soil, soil permeability, porosity in soil and uranium content in soil[(7)]. It is seen that the radon is typically four or five times more concentrated indoors than outdoor[(8)]. Some industrial and underground workplaces such as phosphate industry, mines, caves and cellars can have significant levels of radon than the indoor radon in other places such as schools, offices, shops, etc. In the phosphate industry, phosphogypsum (a by-product derived from phosphate) can increase the radon concentration in a closed place by a factor of 100 or more[(9)]. Moreover, in some tourist caves radon concentration has been found to vary from levels hardly higher to levels several 1000 times higher than the outdoor air concentrations[(10)]. However, the primary pathway of indoor radon is the soil gas intrusion to dwellings or buildings. The main entry points of the outdoor radon and its short-lived decay products within a building are some openings or cracks in concrete floors, ceiling, walls, construction joints, floor drains, sump pumps, seams, ventilation pipes and other cracks or openings as well as the moderately porous concrete[(9,11,12)]. Several factors that influence the indoor radon levels are – season of the year, weather conditions, ventilation conditions, types of construction materials, emanation power fraction of the materials, materials covering the floors and walls, the thickness of the walls, and the geological structure underneath the buildings[(13–15)].

On the other hand, radon can be found in all water sources and its high level found normally in groundwater. Dissolved radon in groundwater can be released in ambient air through the use of such water for different purposes. Radon in water also become airborne in indoor of a building when such water is used by simple activities of households, such as taking showers, washing dishes, running faucets, floor cleaning, or cooking. This can enhance the levels of radon and its progeny in indoor air, especially when groundwater is used. In areas with high groundwater radon levels, the relative contribution to indoor radon levels will increase accordingly. It is estimated that 95% of radon exposure is from indoor air and about 1% is from drinking water sources[(16)]. However, outdoor air, water and natural gas work out to be 10% of the total rates of radon emission from soils underneath the floors and from building materials[(17)].

The radon and its decay products may be attached or unattached to dust and smoke particles in ambient air. As we breathe air and drink water, radon and its decay products in air and water may be entered into different parts of our body. Within the body, they continue their radioactive decay processes and delivered radiation doses to the affected portions. The worldwide average value of annual effective dose equivalent from natural background radiation is 2.4 $mSv$, of which about 1.4 $mSv$ comes from the radionuclides of both radon and thoron families (1.24 $mSv$ from radon family and 0.18 $mSv$ from thoron family)[(1)]. Hence, more than 58% of the total dose comes from the inhalation of the radon, thoron and their corresponding decay products. It may also clear that radon contributes about 87% of the radiation dose caused by exposure to the radionuclides of both radon and thoron families, whereas that for thoron is only about 13%. That means radon itself is the most dominant exposure and is able to induce several health hazard problems to the human population. United States Environmental Protection Agency (USEPA) estimated that radon and its decay progenies cause many thousands of death each year[18]. According to International Agency for Research on Cancer (IARC), the radon and its decay products are classified as Group 1 carcinogenic element for humans[19]. Therefore, when the concentrations of radon and its decay products in air and drinking water reach high levels, they can able to induce several harmful effects on human health.

## 2 Purpose of the present study

The radon and its decay products are deeply trapped in the lungs and stomach through inhalation and ingestion processes. Once leaves the stomach and lungs, they are normally transported to other organs through body fluids and irradiate the targeted organ's tissues during their radioactive decay processes. The irradiation of the tissues is mostly by the alpha-particles radiations emitted by the respective radionuclides of the radon decay chain. The tissue regions and cell types that are within depths traversable by alpha particles can be susceptible to induce biological damage[20].

Among the decay products of radon, the isotopes $^{218}$Po, $^{214}$Po and $^{210}$Po are assumed to be the most important alpha emitters, because they have short half-lives (a fraction of few microseconds to few days) and their alpha decay energies are relatively high (5.30 $MeV$ to 7.683 $MeV$), so that they can deliver a large amount of energy to a targeted organ in a very short time. So, these polonium radioisotopes can constitute a major health hazard for man[21]. Alpha particles emitted by the decay of $^{218}$Po and $^{214}$Po have respective penetration depths of 48 $\mu m$ and 71 $\mu m$ in tissue, so that they deliver a high density of DNA (deoxyribonucleic acid) damage to cells in these short distances[22]. All the organs are not equally be affected by the same amount of radiation exposure, but it depends upon the concentrations of radon, time of radiation exposure, the solubility of radon along with decay products in the body tissues or organs, radiosensitivity of the organs, age of the consumers, and also on gender. It is found that radon delivers more than 55% of the total radiation dose to the cells of the respiratory system[23].

When the alpha-particles emitters entered the cellular system, the emitted alpha particles [high linear energy transfer (LET) radiation] from them within the cellular systems can interact with DNA molecule and its adjacent molecules. In this ionizing process, the alpha particles can eject electrons from the molecules and simultaneously generate ions along the alpha tracks within the DNA and adjacent molecules. The generated ions can break the intramolecular chemical bond from the DNA molecules[24,25], or can change the structure of other molecules in the cells[26]. This can lead to initiate the relative biological effect (RBE) on DNA, and thereby induce potential damages to DNA[16] and its adjacent molecules. While cells are capable of self-DNA repair, but repeated damage to DNA can result in mutations and lead to uncontrolled cell growth[27]. It is observed that each alpha particle has the potential to induce approximately 16 mutations per DNA genome[20]. A double-strand break (DSB) of the DNA is arguably most dangerous and can be mutagenic since, it can result in cell death if unrepaired and if misrepaired, it can cause chromosomal translocations, deletions, and fusions in the DNA[28,29]. Collectively, all these consequences are referred to as genomic rearrangements and found commonly in cancerous cells[29]. The rate of repair to DNA-damaged cells after alpha exposure is much slower when compared to low LET irradiation such as X-rays[30]. The DNA damage leading to chromosomal aberrations constitutes an important prerequisite for inducing genetic disorders and diseases like cancer[24]. The chromosomal aberrations have been clearly associated with high radon exposures, particularly in the occupational environment[31]. Genotoxicity or genotoxic endpoints of alpha radiations from the radon and its decay progeny have been investigated by several studies on the underground miners and individuals[32]. The complexity of the chromosomal aberrations in blood lymphocytes and the chromosomal instability in bone marrow cells has been seen in some people who are exposed to high levels of alpha-radiations from radon and its progeny[33,34]. It is seen that the chromosome damage in liver cells by alpha particles is about 15 to 20 times greater than that caused by beta or gamma irradiations[35]. So, the alpha radiations emitted from the radon and its decay products can induce a variety of cytogenetic effects that can be biologically damaging and result in an increased risk of carcinogenesis[20].

The carcinogenic health hazard problems associated with radon exposure were first discovered in 1930s during investigations into why half the uranium miners in the Ore Mountains in Czechoslovakia were died from lung cancers[36]. This makes the role of radon determination and measurement of its activity level in the natural environment for monitoring human health and safety. Attention to the health problems associated with environmental radon exposure has thus been growing around the world[2,25,37–41]. Over the last four decades, a large number of scientific and regulatory interest concerning both indoor and outdoor radon problems has been paid by several environmental scientists and organizers worldwide[16,27,31,41–56]. To find the risks of occurrence of some feasible diseases associated with radon exposure, this study reviews some literature that examined and reports the link between radon exposure and some health hazard problems including cancer.

## 3 Methodology

The present review study is performed and reported in accordance with suitable reporting items regarding the radon and its associated health effects. Various search terms, which include radon, sources of radon, radon entry in indoor and outdoor, factors influencing the radon concentrations, induced health effects associated to radon and its decay products, have been used to identify the relevant studies on radon and health effects. By this searching process, this study identified a lot of published research articles, review reports, including PubMed database, which are pertinent to radon studies. All the published literature has been written and published in English and has sufficient data or information for making the present review study complete. Most of these studies are published in different valuable national and international repute journals and books from 1975 to December, 2020. First screened all titles and abstracts of the literatures, and then carefully read the full text of relevant studies. Then extracting relevant data or information regarding the radon sources, the path of radon entry in both indoor and outdoor environments, influencing factors on radon concentrations, and the incidence of health risks associated with radon exposure. From these studies, required information and supporting data have been used in the present study. A few relevant reference lists from the original studies and review articles are also used to identify the additional relevant publications.

## 4 Health hazard problems caused by radon exposure

Exposure to radon and its short-lived decay progeny can occur by ingestion of drinking water, or, more significantly, through inhalation of indoor and outdoor air. Entries of radon and its decay progeny in the human body are mainly via the respiratory tract, skin and gastrointestinal tract. After entered the body, they can primarily be stored much time in lungs, skin and stomach, and then diffuses into the bloodstream and accumulates in fatty tissues[(57)]. As their short half-lives, the radon and its progeny produce their respective decay progeny during this time, and then they are largely deposited in these organs. Before diffusion from these organs, some of the radon and progeny can deliver a significant amount of doses to these organs by depositing alpha decay energies. It is observed that bronchial epithelium tissue receives the highest alpha doses from inhaled radon decay progeny, then upper respiratory tract and skin[(36)], along with other organs including red bone marrow, liver and kidney receive appreciably low doses[(22)]. The kidney is the organ that received highest dose from radon and its decay products outside the respiratory tract[(58)]. On the other hand, the organ that receives the highest alpha radiation dose from radon dissolved in drinking water is the stomach[(59)], then esophagus and other organs of the digestive system. As the radon and its decay products are small in size and are preferentially soluble in tissues with a higher fat content[(34,58)], the fatty tissues in the yellow bone marrow and female breast may receive relatively high doses from the radon and radon's progeny rather than by other organs. Because of the low-fat content in fetus, the fetus receives a dose that is assumed to be similar to that of the maternal muscle and is about $3-4$ orders of magnitude smaller than the dose to the lung[(22)]. As alpha particles have a high ability of LET[(60)], they can induce an intense local ionization in the irradiated tissues by depositing a large amount of energy and thereby damaging the targeted tissues. So, it is clear that high levels of exposure to radon and its decay products for a long-time period can induce various degrees of malignant or nonmalignant health effects in different parts of the human body. Health effects induced by radon and its decay products are primarily by creating local damage as a result of the interaction of alpha-particles with the tissue's atoms or molecules.

Since the early 1970s, evidence has been increasing that radon and its progeny were regarded as radiation health hazards for humans in both mining and non-mining environments[(2)]. The high level of radon-alpha activity in a closed space was recognized as a significant cancer risk for the general population in that time[(9)]. The World Health Organization (WHO) was the first to draw attention to the health effects due to residential radon exposures in 1979, through a European working group on indoor air quality[(41)]. In 1988, the radon and its decay products were designated a human lung carcinogen[(19)]. Now, in this section, it has been tried to find evidence of the relationship between radon exposure and some cancer and non-cancer health effects in man.

### 4.1 Lung cancer and disease

Once $^{222}Rn$ and its decay progeny, particularly $^{218}Po$, $^{214}Po$ and $^{210}Po$, are inhaled into the lungs, they are absorbed by the cells into the bronchial airways and deposited on the respiratory epithelium. During this period, they can irradiate the bronchial tissues of the lungs by emitting alpha radiations[(9,26)] and results in disrupting the DNA of the bronchial tissues. The DNA damage has the potential to be one step in a chain of events that can lead to developing lung cancer[(25)]. For the long-time radon exposure, the relative risk of lung cancer may increase by 16% per 100 $Bq.m^{-3}$ of radon concentration[(16,61)].

On the basis of the experimental evidence and studies on underground miners historically exposed to high levels of the gas, the IARC determined that the radon and its decay products are designated a carcinogen for human lung cancer[(19)]. Analysis of many studies on the mortality risk in the French cohort of uranium miners has been confirmed that the excess risk of death from lung cancer is positively associated with cumulative radon exposure[62–65]. Strong evidence for an increased lung cancer risk after long-term exposure to the low occupational radon exposure rates have been seen among the uranium miners in different countries[66,67].

Radon in groundwater is also associated with lung cancer incidence. The USEPA estimated from NAS (National Academy of Science) report that 89% of lung cancer caused by breathing radon released to the indoor air from water with a high concentration of radon[68]. Few studies in the USA have provided some epidemiological evidence regarding the positive and significant correlations between groundwater radon exposure and the rates of lung cancer incidence[69,70]. It has beenobserved that the water radon levels of 20 to $180,000$ $pCi.l^{-1}$ and the airborne indoor radon levels of 0.05 to 210 $pCi.l^{-1}$ both are significantly correlated with the rates for lung cancer in some counties of Maine[69]. In North Carolina, every 100 $Bq.l^{-1}$ of groundwater, radon increases the incidence rate ratio of 1.03 [95% confidence interval (CI): 1.01-1.06] for lung cancer[70].

Numerous residential case-control studies provided evidence of induced lung cancer due to the long-term residential radon exposure[32]. It is observed that the incidence of respiratory disease exceeds the average in some residential areas where radon level is high[71]. An ecological study showed a significant correlation between lung cancer and domestic radon levels in some areas of Devon and Cornwall[72]. Positive associations between the ecological indicators of residential radon and lung cancer have been found in a large-scale cohort study[73]. Based on the American Cancer Society Cancer Prevention Study II (CPS-II), this study reported that the risk of mortality from lung cancer per each 100 $Bq.m^{-3}$ increase in radon exposure is increased by15%. According to BEIR VI (Biological Effects of Ionizing Radiation) report in 1999 that about $15,000$ lung cancer deaths per year in US are caused by radon[25]. Recently, in 2016, the EPA (Environmental Protection Agency) estimates radon causing $21,000$ lung cancer deaths per year in US, of which about 2,900 deaths occur among people who have never smoked[74]. That means, during 1999 – 2016, the lung cancers caused by radon is increased by a factor of 1.4 in US.

Epidemiological studies conducted in Europe, China, and North America have provided robust evidence regarding the increased risk of lung cancer with the high levels of radon exposure in dwellings[61,75,76]. Many other valuable research outputs have been confirmed that prolonged exposures to high activity levels of radon (indoor) lead to developing lung cancer in many cases[77–79]. In Europe, the risk factor for the annual occurrence of lung cancer caused by radon is 1014%[80]. Recently, a meta-analysis study observed that the radon concentrations below $\sim 1000$ $Bq.m^{-3}$ equivalent to about 20 $mSv.y^{-1}$ of effective dose to the whole body does not support the thesis that radon may be a cause of any statistically significant increase in lung cancer incidence[81]. More recently, a study concluded that the correlation between lung cancer and the radon exposure remains undeniable[82].

Radon exposure causes $3-14\%$ of all lung cancers worldwide, depending on the average radon level and the smoking prevalence in a country[16]. Smokers are estimated to be 25 times more at risk of lung cancer from radon than non-smokers[16]. In a study[83] it has been reported that between 72% and 94% of the cases of registered lung cancers may be attributable to the combined effect of radon inhalation and cigarette smoking. So, the combined effect of radon gas inhalation and tobacco smoking can be enhanced the lung cancer risk effectively[25,84]. Presently, radon is recognized as the number one cause of lung cancer among non-smokers[74,85], and it is the second most important cause of lung cancer after tobacco smoking[41].

The risk for lung cancer incidence is also gender-dependent. A study it has been compared the number of lung cancer cases among both male and female populations in Netherlands and Sweden[83]; this study found that the lung cancer risk for males is slightly lower than for females. Recently, a study conducted in Galicia, Spain[86] has reported a statistical association of the residential or indoor radon with the higher lung cancer in women only. The relative risk (RR) for mortality from lung cancer of 0.958 (95% CI: 0.886-1.037) for men and 1.087 (95% CI: 0.977-1.276) for women has been found in this study.

Other than lung cancer, the incidence of some malignant and non-malignant respiratory diseases in miners may also be induced by exposure to radon progeny[25]. Excess mortality from non-cancer diseases including all non-malignant respiratory diseases such as asthma, bronchitis, pneumoconioses, emphysema, pulmonary fibrosis, interstitial pneumonitis, and tuberculosis has been identified by some studies on miners exposed to radon and its progeny[32]. Smoking habits and respirable dust, especially crystalline silica dust, are likely to be potential confounders for mortalities from non-cancer respiratory diseases[32]. A limited number of evidence of non-cancer lung diseases has been reported in some ecological studies. It has been reported in a study[87] conducted in American Cancer Society CPS-II that a significant positive trend in the mortality from chronic obstructive pulmonary disease (COPD) in lungs is linearly associated with mean county-level residential radon concentrations [hazard ratio (HR) per 100 $Bqm^{-3}$ of radon 1.13, 95% CI: 1.05–1.21]. Later, it is found in a study that there were no clear associations between the residential radon exposure and the non-respiratory mortality in the CPS-II[88]. This study suggests the residential radon is not associated with any other mortality beyond lung cancer or COPD. Recently, a cohort study[89] found 4·49% increase in mortality risk (95% CI, $p < 0.001$) for COPD in some participants and individuals, and the risk is independent of exposure to $PM_{2.5}$.

### 4.2 Skin cancer and disease

The deposition of environmental radon along with its decay products carried by ambient air on the skin is relevant for skin exposure. Particularly, the airborne radon's daughters can adhere to the human skin via electrostatic attraction [90]. When they decay, much of the alpha particles emitted from them will be harmlessly absorbed in the dead outer layers of the epidermis of the human skin. The targeted skin is either able to stop the alpha radiations, or, harmlessly absorbed the alpha decay energy. But, where the skin is thin like as human face and neck, the alpha radiations may be able to reach the sensitive basal cells beneath the epidermis and then deliver the radiation dose. This in turn led to developing different types of skin diseases or skin cancers. The radon's daughters whose alpha decay energy is relatively high can also be able to reach the bottom layer of the epidermis. So, when an individual spends a long time in a radon-containing atmosphere, his/her skin may receive an appreciable amount of alpha radiation doses [36]. A theoretical estimated value of the radon-related annual dose equivalent to the basal layer of face and neck is found as 2.5 (range 1.7 to 17) $mSv.\ y^{-1}$ for the average domestic radon exposure of 20 $Bq.\ m^{-3}$ in UK [91]. The radon daughters, especially $^{218}Po$ and $^{214}Po$, are the potential carcinogenic agents for inducing skin cancer [92]; their alpha decay energy: 5.998 $MeV$ for $^{218}Po$ and 7.683 $MeV$ for $^{214}Po$. Eatough estimates the average radiation dose from $^{218}Po$ to the basal layer of a human face is of the order of 0.5 $mSv/decay/cm^2$ while the dose from $^{214}Po$ is of 1 $mSv/decay/cm^2$ [92].

The basal cell carcinomas (BCC) type skin cancer has been seen in a cohort of uranium miners exposed to radon's daughters [93]. A positive, but not significant, an association of radon with malignant melanoma (MGM) skin cancer has been found in a case-cohort study conducted in Czech uranium miners [94].

Accumulation of the airborne radon's daughters on the skin is suggested to explain the correlation seen for melanoma skin cancer [95]. Using a dosimetry model, a research team [96] has claimed that melanoma skin cancer shows a significant association with radon exposure in the home. Using standard risk factors, it has been estimated that about 13% of skin cancers are theoretically attributed to radon exposure at UK average radon level of 20 $Bq.m^{-3}$ [97]. It has been estimated using radiation risk factors that about 2% (range 1% to 10%) of non-melanoma skin cancer (NMSC) is theoretically linked with equal radon exposure level in UK [98]. An ecological study [72] in Devon and Cornwall has found a significant increase of NMSC in high-radon areas ($\geq$ 100 $Bq.m^{-3}$) than in low-radon areas ($<$ 60 $Bq.m^{-3}$). Regarding the causal link between radon exposure and skin cancer, the theoretical dosimetric calculations reported in a review article have revealed that attributable risk (ATR) $\sim 0.7\%$ ($0.55\%$) of skin cancers are associated with the nominal indoor radon level of 20 $Bq.\ m^{-3}$ in UK [99]. A cohort study in Iceland has shown a significantly increased risk of basal cell carcinoma (BCC) and non-Hodgkin´s lymphoma (NHL) among the residents of high-temperature geothermal areas where the exposure through water can include radon [100]. An association between high radon levels in the environment and skin cancer, particularly squamous cell carcinoma (SCC), has been reported in an ecological study conducted in southwest England [101], but not BCC or MGM at the national level. This study suggests the environmental radon exposure may be a risk factor for inducing SCC type skin cancer. An ecological study in England suggests an association between NMSC and mean household radon, particularly comparing the two highest categories at concentrations $>$ 75 $Bq.m^{-3}$ to the reference category [102]. This study tentatively supported that the environmental radon may be a risk factor for inducing NMSC. Using a large prospective cohort design, it is reported in a study that long-term residential radon exposure is strongly contributing to the development of BCC [103]. A statistically significant increased risk of death from MGM and other skin cancers with residential radon exposure has been seen in adults from the Swiss National Cohort [90]. This study suggests radon exposure is a relevant risk factor for mortality from skin cancer.

### 4.3 Stomach or gastric cancer and diseases

Ingestion of groundwater with a high level of radon is the main route for delivering an alpha radiation dose directly to the stomach. After ingestion, water is absorbed in the gastrointestinal tract comprising the mouth, esophagus, stomach and intestines. Radon in ingested water remains in the stomach for several tens of minutes [104]. A small part of the ingested water is absorbed in the stomach and colon [105], and rest is absorbed mostly in the small intestine after leaving the stomach. Sensitive cells in the stomach are exposed by alpha radiations emitted from the radon and its decay products in the ingested water [106]. Calculations show that dose to the lining of the stomach can be significant and this implies some risk of inducing stomach cancer [58,107]. Based on the NAS (National Academy of Science) report, the EPA estimated that 11% of stomach cancer caused by drinking water with a high concentration of radon [68]. On the other hand, the gastrointestinal tract has also a potential for radon exposure by swallowed air and/or pulmonary secretions [108]. The mathematical and dosimetric models have been used in an epidemiological study to quantify the risk of stomach cancer caused by radon exposure among uranium miners [109].

Elevated levels of stomach cancer have been observed in survivors of the atomic bombs[27] and in 11 cohorts of underground miners exposed to a high level of radon[110], mentioned in an article[58]. But, the study[110] has not found a trend in mortality from stomach cancer caused by radon exposure. A Swedish study on iron miners' cohort has found that the risk for the cancers of stomach and rectum is significantly related to cumulative radon exposure among the miners[111]. This study also found that mortality from stomach cancer is tended to increase slightly with increasing cumulative radon exposure [ratio of observed to expected (O/E) 2.38, for 200 WLM or more], whereas the mortality from rectum cancer is tended to decline slightly with increasing cumulative radon exposure (O/E 2.44, for 200 WLM or more). A study on German miners' cohort[112] reported a significant positive relation between radon exposure and stomach cancer (ERR/WLM=0.021%; 95% CI: 0.0007–0.043%). A study on a cohort of Ontario uranium miners has shown that the statistically increases in diagnosis (incidence) and mortality of stomach and colorectal cancers are significantly associated with exposure to cumulative radon daughters[113]. This study also reported the relative risk (RR) for the diagnosis of stomach and colorectal cancers of 2.30 (95% CI: 1.02-5.17) and 1.56 (95% CI: 1.07-2.27), respectively, when comparing the highest cumulative exposure group (> 40 WLM) to the referent group (0 WLM). The statistically positive, but non-significant, linear relationships between stomach cancer and fine dust (ERR/dust-year=0.0012, 95% CI -0.0020 to 0.0043) and absorbed dose from high-LET alpha radiation (ERR/Gy=22.5, 95% CI -26.5 to 71.5) have been reported in a German miners' cohort study[114]. According to this study the relationship of stomach cancer with arsenic exposure is non-linear with a 2.1-fold higher RR (95% CI: 0.9-3.3) in the exposure category above 500 compared with 0 dust-years.

In a county-scale ecological study in Pennsylvania[115] has reported the significant and positive correlation between indoor air radon levels and stomach cancer incidence in females. In this study, the correlation for mortality from stomach cancer has been found amongst males, females and total population. This study also suggests a relationship between radon levels and gastric cancer mortality. A census based cohort study in Iceland has been reporting an apparent risk of stomach cancer among residents of high temperature geothermal areas where exposure through water can include radon[100]. Results of this study have been shown that the hazard ratio (HR) for stomach cancer are 1.13 (95% CI: 0.53-2.41) and 0.99 (95% CI: 0.46-2.14) for warm reference area and cold reference area, respectively. A case-cohort epidemiologic study in Finland has found the HR of 0.68 for radon exposure at 100 $Bq.l^{-1}$ of water (95% CI: 0.29-1.59)[116]. Results of this study do not indicates an association between the risk of stomach cancer and exposure to radon, even for radon concentrations exceeding 300 $Bq.l^{-1}$. Although this study reported a little indication of an increased risk of stomach cancer associated with high levels of radon, radium or natural uranium combined in drinking water. It has been mentioned in an article that a possible link between gastric cancer and alpha radioactivity in water[117]. Recently, evidences from epidemiological study have been suggested that the radon in groundwater is associated with increased risk of stomach cancer[70]; also incident rate ratio (IRR) per 100 $Bq.l^{-1}$ of groundwater radon has been found as 1.05 (95% CI: 0.99-1.11) for the stomach cancer incidence rate model, while the IRR of 1.24 (95% CI: 1.03-1.49) found for the stomach cancer cluster membership (GEE model). The residential radon level is strongly and significantly associated to incidence of stomach cancer, reported in a cohort study[118]. More recently, a study conducted in Galicia, Spain[86] has showed a statistical association of the residential or indoor radon with the higher stomach cancer [relative risk (RR) 1.17, 95% CI: 1.02-1.32] in women only; the RRs for mortality from stomach cancer are 1.083 (95% CI: 0.952-1.206) for men and 1.142 (95% CI: 1.001-1.301) for women. Authors of this study have suggested the stomach cancer mortality pattern differed between the sexes. It is also observed in this study that the effects of sociodemographic variables, arsenic, and altitudes did not change significantly in the RR for mortality. An ecological research work observed a positive and significant correlation between the residential radon exposure and the esophageal cancer risk and mortality ($p < 0.001$) in males, but not for females[119].

## 4.4 Cardiovascular diseases

Radiation dose to the blood and walls of coronary arteries due to the exposure to radon and its short-lived decay progeny can increase the incidence of cardiovascular diseases (CVDs). The elevated relative risk (RR) of coronary heart disease (CHD) mortality (RR 1.5, 95% CI: 0.77-2.75) for accumulative radon exposure above 1000 $WLM$ has been found among the fluorspar miners of Newfoundland[84]. This study suggests a positive, but not statistically significant, association between CHD and radon exposure. Results of this study indicate the smokers are 1.8 times more likely to die from CHD (95% CI: 1.1-2.8) than the nonsmokers. Some studies do not found significant association between the radon exposure and the mortality from CVD among German uranium miners[41,120]. But, a trend in risk of circulatory diseases with increasing cumulative exposure to radon (ERR/100 WLM 0.0006, 95% CI: -0.004 to 0.006) has been observed among the miners[120]. An association of the cumulative exposure to radon progeny with the CHD has been observed among the Newfoundland fluorspar miners[121]. This study found that the RR of CHD mortality among miners (non-smokers) is 1.19 (95% CI: 0.70–2.03) for cumulative exposure of 1600 WLM or more from radon progeny, compared to 0 WLM of exposure; but after adjusting for lifetime smoking status, the RR value does not change effectively. Results of this study indicate the RR of acute myocardial infarction mortality (RR 1.39, 95% CI: 0.71–

2.69) among the miners (after adjusting for lifetime smoking status) is significantly associated to cumulative radon exposure of 1600 WLM or more. A more recent study on Newfoundland fluorspar miner's cohort has reported that the incidence rate of CHD at higher levels of cumulative radon exposure compared to the lowest levels is 4.97 vs. 3.51 per 1000 person-years amongst miners(122). The hazard ratio (HR) between these two categories of radon exposure is 1.53 (95% CI: 1.07 – 2.18), with no presence of effect-modification by smoking. Authors of this study concluded that long follow-up interval of this cohort provides insight on the risks of coronary heart disease in relation to time-varying aspects of radon exposure. In some residential areas where radon level is high, it has been found that the incidence of cardiovascular system disease exceeds the average(71). A cohort study(89) on some participants and individuals has shown that 4·58% increase in mortality risk (95% CI: 3·88%-5·29%, $p < 0.001$) for congestive heart failure (CHF) is associated with county-level radon exposure, and it is independent of effect of $PM_{2\cdot5}$. But, this study has not found such association for myocardial infarction (also known as heart attack) mortality (mortality risk 0·65%, 95% CI: −1·64%-3·00%, $p < 0{\cdot}099$).

## 4.5 Blood cancer and diseases

The radon and its decay products once transported to bone marrow via bloodstream, they can transmit high levels of alpha-particle doses directly to the bone marrow tissues(96,123), particularly radon itself delivers a higher dose to the bone marrow tissues compared to the radon's decay products(58). Prolonged exposure to alpha radiation doses can damage the bone marrow tissues, and this can lead to develop some immature or abnormal blood cells. Principally, white blood cells are exposed highly than the other blood cells or blood components. The exposed blood cells may undergo a malignant change that may lead to develop a group of cancers in the bone marrow known as leukaemia; it is a cancer of blood. Other cancers in blood are including multiple myeloma (MTM) or plasma cell myeloma, Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL).

A study conducted in West Bohemia has reported that the risk of MTM and the increased risk of mortality from MTM among uranium miners all are associated with cumulative radon exposure, and the ratio of observed to expected (O/E) mortality risk has been found to be greater than unity, but not significant (O/E = 1.08)(124). This study also reported that the mortality from leukaemia is not associated to cumulative radon exposure (O/E = 0.91), but increases with increasing duration of employment in the mines. The increased leukaemia mortality among underground miners is not likely to have been caused by radon, as it is not related to cumulative exposure to radon. This observation has been reported in a large cohort study(110). But a Swedish study on iron miners' cohort(111) found that the risks for MTM incidence and mortality are tended to increase with increasing cumulative exposure (O/E = 4.00 for 200 WLM or more); whereas the leukaemia incidence or mortality is tended to decrease with increasing cumulative radon exposure (O/E = 0.00 for 200 WLM or more). A case-cohort study on Czech uranium miners(125) has reported a positive and significant increased relative risk (RR) of incidence of all leukaemia combined (RR 1.75, 95% confidence interval (CI): 1.10–2.78), especially chronic lymphocytic leukaemia (CLL) (RR 1.98, 95% CI: 1.10–3.59), when compared to highest quintile of cumulative radon exposure (>100 WLM) with lowest (<3 WLM). Authors of this study have not found any apparent relationship of radon exposure with incidence of either non-NHL or MTM, but they have observed that the risk for inducing AML and HL with radon exposure is elevated but nonsignificant. Results of this study also revealed that the increased risk of developing leukaemia among the workers is associated to the exposure to radon and its progeny, particularly CLL is strongly associated to radon exposure. But, two studies on German cohort of uranium miners did not support the hypothesis of an association between exposure to radon progeny and risk for inducing all leukaemia among the miners(112,126), except for incidence of CLL (ERR/WLM=−0.013%; 95% CI: −0.067 to 0.040%), non-CLL (ERR/WLM=0.019%; 95% CI: −0.04 to 0.08%) and acute myeloid leukaemia (AML) (ERR/WLM=0.036%; 95% CI: −0.076 to 0.149%), where, ERR/WLM is the ratio of excess relative risk to working level months(112). So, these two studies provide some evidences of the increased risk of CLL, non-CLL and AML associated with radon exposure. A study on radon exposure and mortality among White and American Indian uranium miners has not found the association between exposure to radon progeny and CLL(127). This study reported that the elevated rates of mortality from MTM and NHL among the miners are not associated with WLM exposure, rather associated to a poor surrogate for uranium dust exposure. No statistically significant association between the exposure to radon decay products and the mortality or incidence of any hematologic cancer, including MTM, HL and non-NHL, has been found among Eldorado uranium workers(128). But, this study observed the consistent but non-statistically significant increased risks of CLL and HL incidence and non-NHL mortality with increasing gamma-ray doses.

A study conducted in some counties in England and Wales for investigating the correlation of indoor radon exposure with incidence of ALL(129). This study reports the incidence of childhood ALL is strongly correlated ($r = 0.56$, $p < 0.01$) with the indoor radon concentration, but the correlation is weaker for adults. A positive correlation of environmental radon concentration with the incidence of AML, chronic myeloid leukaemia (CML), ALL and CLL has been observed by a study(130). The significant positive correlation between radon levels in given regions of a country and leukaemias has not been seen in a study(131). The positive (nonsignificant) associations between the ALL, AML, CLL, and CML leukaemias and the county level radon values within Iowa have been reported in a study[132]. This study observed that the relative risk (RR) associated with 1 $pCi.l^{-1}$ of increased radon for ALL, AML, CLL, and CML are 0.91 (0.78-1.03), 1.01 (0.92-1.12), 1.06 (0.96-1.16), and 1.12 (0.98-1.27), respectively. A cohort study in Iceland has shown that a significant increased hazard risk (HR) is 1.64 (95% CI: 1.00 – 2.66) for all cancers of lymphoid and hematopoietic tissue, and that for non-Hodgkin´s lymphoma (NHL) is 3.25 (95% CI: 1.73 – 6.07) among residents of high-temperature geothermal areas[100]. A study[133] reported a positive and significant correlation between the incidence rates for CLL and the residential radon levels among whites (both genders together and each gender separately; p < 0.005) and among blacks (p < 0.05) in the US at the level of the state. A recent cohort study among the Cancer Prevention cohort has reported a risk of hematologic cancer is increased significantly among women for county-level residential radon exposure; but the risk is not found for men[134]. Authors of this study observed a statistically significant higher risk of hematologic cancer among women living in counties with highest mean radon concentrations ($> 148\ Bq.m^{-3}$) compared to those living in counties with the lowest ($< 74\ Bq.m^{-3}$) radon levels (HR = 1.63, 95% CI: 1.23-2.18), and there was found an evidence of a dose-response relationship ($HR_{continuous}$ = 1.38, 95% CI: 1.15-1.65 per 100 $Bq.m^{-3}$; p = 0.001). A study re-investigated the association between residential radon and CLL incidence rates in the US[135]. This study reported that the incidence rates for CLL are significantly and positively correlated with residential radon at the county level (p < 0.0001), and the p-values for males and females are respectively found as p < 0.0001 and p < 0.0001. This study also found the positive correlations between residential radon exposure and CLL incidence rates for both genders, both together and individually, and suggested that radon plays an etiologic role in CLL.

In case of children exposed to radon, a group of researchers of a study have claimed that the myeloid leukaemia and some childhood cancers such as childhood AML show significant correlation with the indoor radon[96]. Analysis of this study suggests $6-12\%$ of myeloid leukaemias may be attributed to radon and its decay progeny in UK; whereas in Cornwall (where mean radon levels is 110 $Bq.m^{-3}$), the range of incidence of myeloid leukaemia will be $23-43\%$. Authors of this study also reckon that $13-25\%$ of the myeloid leukaemia at all ages may be caused by exposure to radon of 50 $Bq.m^{-3}$, which is the world average radon concentration. A study reported that the incidence of childhood ALL is strongly correlated (r = 0.56, p < 0.01) with the indoor radon concentration[129]. A significant association of the childhood lymphomas and leukaemias with the county levels radon exposure in North Carolina has been reported in a study[136]. This study found that the RR for mortality from both childhood lymphomas and leukaemias is significantly and positively increased with county levels radon exposure. In this study, it is observed for lymphomas that the RR = 1.13 (95% CI: 0.79-1.62) for radon exposure of $229-1375\ pCi.l^{-1}$ and RR = 1.38 (95% CI: 0.95, 2.02) for high radon exposure of $1376-10,692\ pCi.l^{-1}$, compared to low radon level of $0-228\ pCi.l^{-1}$; whereas for leukaemias, the RR = 1.26 (95% CI: 1.08-1.47) for radon exposure of $229-1375\ pCi.l^{-1}$ and RR= 1.33 (95% CI: 1.13-1.57) for high radon exposure of $1376-10,692\ pCi.l^{-1}$, compared to low radon level of $0-228\ pCi.l^{-1}$. But, a study reported that the risk of childhood AML is not associated to the radon exposure, with adjusted odds ratios of 1.2 (95% CI: 0.7–1.8) for $37-100\ Bq.\ m^{-3}$ and 1.1 (95% CI: 0.6–2.0) for $>\ 100\ Bq.\ m^{-3}$, when compared with $<\ 37\ Bq.\ m^{-3}$[137]. Additionally, this study found an increased risk of AML with higher radon exposure among children of ages equal or greater than to 2 year, while an inverse association between radon level and AML risk has been found among children under-age 2 years. A study has shown that the high risk related to develop ALL among children is significantly associated to high level of ground radon exposure[138]. This study reported that the association of the incidence of childhood ALL with the continued residence at normal or high radon levels areas is significant or even stronger than at areas of birth places that classified as low radon level. Authors of this study found a trend in relative risks (RRs) of 1, 6.40 and 10.07 for ALL among children born in low risk ($< 10000\ Bq.m^{-3}$), normal risk ($10000-50000\ Bq.m^{-3}$) and high risk ($50000\ Bq.m^{-3}$) areas, respectively, which suggesting a dose-response relationship. This study also found the standardised mortality ratios (SMRs) of 1.43, 1.17 and 0.25 for ALL among children born in high, normal and low risk areas, respectively. An ecological study found a significant positive association of the indoor radon, range $22-262\ Bq.m^{-3}$, with AML incidence among the children under 15 years of age[139]. A case-control study conducted in Denmark for testing the hypothesis of domestic radon exposure increases the risk for childhood cancer[140]. The results of this study show the risk for ALL is 1.21 (95% CI: 0.98-1.49) for radon exposure of 0.26 to $0.89\times10^3\ Bq.m^{-3}.years$ and that is 1.63 (1.05-2.53) for exposure of $0.89\times10^3\ Bq.m^{-3}.years$ or more, when compared with radon exposure below $0.26\times10^3\ Bq.m^{-3}.years$. This study suggests the domestic radon exposure increases the risk for ALL during childhood but not for other types of childhood cancer. A linear dose-response analysis that has been done in this study showed a 56% (95% CI: 1.05–2.30) increase in the rate of ALL per $10^3\ Bq.m^{-3}.years$ increase in radon exposure, whereas that showed 34% (95% CI: 0.53–3.40) increase in the rate of other leukaemias for equal radon exposure. A group of research team conducted a case-control study of ALL incidence among children under age 15 years in the US in relation to residential radon exposure[141]. The results from this analytic study provide no evidence for an association of indoor radon exposure with ALL among children living in homes with radon concentration levels ranged from 4 $Bq.m^{-3}$ to 2194 $Bq.m^{-3}$. Their calculated RR for ALL incidence is 0.71 (95% CI 4 0.42–1.21) for radon exposure of 300 $Bq.m^{-3}$ to 20 $Bq.m^{-3}$. A census-based cohort study[142] do not support the evidence of the association between domestic radon exposure and childhood leukemia, despite relative high radon levels in Switzerland. Results of this study show adjusted hazard ratios for children with radon exposure 139.9 $Bq.m^{-3}$ or more are 0.95 (95% CI: 0.63, 1.43) for all leukemias and 0.90 (95% CI: 0.56, 1.43) for ALL, in comparing children exposed to a radon concentration below 77.7 $Bq.m^{-3}$.

### 4.6 Diseases and cancer in cerebrovascular and central nervous system:

The central nervous system (CNS) consists of two parts, brain and spinal cord. Cerebrovascular refers to blood flow in the brain. The term cerebrovascular disease includes all disorders in which an area of the brain is temporarily or permanently affected by ischemia or bleeding.

The study on mortality of a cohort of French uranium miners exposed to radon has reported an association of the radon exposure with the cancer of brain and other nervous system in total cohort, and the ratio of observed to expected deaths (O/E) has been found as 1.89 (95% CI: 0.76-3.89) for this cancer[143]. A statistically significant relationship between the brain and CNS cancers and the cumulative radon exposure, with O/E of 2.00 (95% CI 1.09–3.35), has been seen among French sub-cohort of uranium miners[144]. But, a German uranium miners' cohort study does not support the association of the cancers of brain and others with the cumulative radon exposure[112].

A significant increased risk of childhood brain and CNS cancers with the increasing county-specific levels of radon in groundwater has been reported in a study conducted in North Carolina[136]. This study suggested that the relative risk (RR) of mortality from childhood brain and CNS cancers is increased in counties with both medium ($229-1375$ $pCi.l^{-1}$) and high ($1376-10,692$ $pCi.l^{-1}$) radon levels, compared to low radon level of $0-228$ $pCi.l^{-1}$; the estimated values of RR are found as 1.28 (95% CI: 1.00-1.62) for medium and 1.18 (95% CI: 0.90-1.54) for high radon levels. The significant associations and exposure-response patterns have been seen between the long-term residential radon exposure and the risk of primary brain tumour incidence in Danish cohort[145]. Authors of this study have observed that the adjusted IRR (incidence rate-ratios) for primary brain tumour risk of 1.96 (95% CI: 1.07; 3.58) for each 100 $Bq.m^{-3}$ increment with the increase in average long-term residential radon levels, and for each $10^3$ $Bq.m^{-3}.years$ of cumulative radon exposure the adjusted IRR becomes 1.37 (95% CI: 1.03; 1.82). An ecological study[146] in a radon prone area (Galicia, Spain) has reported that a significant possible correlation exist between the residential radon exposure and the brain cancer mortality for males and females, and this correlation observed as higher for females (Spearman's Rho = 0.433, p < 0.001) compared to males (Spearman's Rho = 0.164, p = 0.009) ). Recently, in investigating the association between residential radon levels and mortality from different types of cancer in Galicia, Spain[86], a group of research workers observed a statistical association of the chronic exposure to residential or indoor radon levels with the higher brain cancer [relative risk (RR) 1.28, 95% CI: 1.13, 1.50] in women only; the RRs for mortality from brain cancer have been found as 1.042 (95% CI: 0.932-1.160) for men and 1.220 (95% CI: 1.205-1.244) for women. This indicates the brain cancer mortality pattern differed between the sexes. Authors of this study have observed that effects of sociodemographic variables, arsenic topsoil levels, and altitude can increase the RR values. Studies on the role of short-term exposure to air pollution and mortality have revealed that an incidence of nervous system disease exceeds the average in some residential areas where radon level is high[71]. A study performed in Maine[69] has analyzed the presence of radon in water using an ecological design and this study has not found any association of radon with brain tumors; this observation has been reported in a study[146]. In an ecological study, a research group examined the association between residential radon and non-respiratory mortality in Cancer Prevention Study II[88]. They have not observed the brain cancer mortality for residential radon exposure, with a hazard ratio (HR) of 0.98 per 100 $Bq.m^{-3}$ (95% CI 0.83–1.15). A census-based cohort study does not support the evidence of the association between domestic radon exposure and CNS tumors, despite relative high radon levels in Switzerland[142]. A study investigated the association of the incidence of cancers in brain and spinal cord (CNS) with the mean county-level radon levels in highly populated and radon-enriched states of New Jersey, Wisconsin, Minnesota, Pennsylvania, and Iowa in USA[147]. This study reported that Iowa is the only state where a significant positive association exists between the radon exposure and the brain and spinal cord (CNS) cancers incidence; but no associations have been detected in other states of USA. This study does not provide the evidence regarding radon is a risk factor for CNS cancer.

In investigating cerebrovascular diseases (CeVDs), a French cohort study of uranium miners has shown a significant positive trend of CeVD mortality with the cumulative radon exposure, together with a significant excess relative risk (ERR) per 100 $WLM$ has been found as 0.49 (95% CI: 0.07-1.23)[148]. The cumulative radon exposure is significantly associated with risk of CeVD [ERR/100 WLM = 0.41 (0.04-1.03)] among the French cohort uranium miners[64]. Recently, an update of the French cohort (1946-2007) study[65] reported the significant association between cumulative radon exposure and excess mortality risks for CeVD [ERR per 100 $WLM$ = 0.42 (95% CI = 0.04-1.04)]. But another study[121] has not found the association of the cumulative radon exposure with the risks of inducing CeVD and mortality from CeVD among the Newfoundland fluorspar miners.

Residential or indoor radon exposure can be associated to the risk of Cerebrovascular accident (CVA) or stroke. This evidence has been found in a nationwide cross-section study among participants of South Korean population [149]. This study reported that the indoor radon level is significantly and strongly associated with stroke even after adjusting potential confounding factors [odds ratio (OR): 1.004, 95% CI: 1.001–1.007, P = .010]. This study also found the high indoor radon exposure of 100 $Bq.m^{-3}$ or more is also significantly associated with stroke (OR: 1.242, 95%CI: 1.069–1.444, P = .005). Authors of this study also observed that the participants of age above 76 years also showed a most strong correlation between elevated radon exposure and stroke even after adjusting for physical and socioeconomic variables (OR: 1.872, 95%CI:1.320–2.254, P < .001). But, a cohort study has not found the association between mortality from stroke and radon exposure (mortality risk 4·19%, 95% CI: 1·96%-6·47%, p < 0·168) [89].

### 4.7 Pancreatic cancer

In a collaborative analysis of 11 studies among the uranium miners has been carried out by a research team [110], this team found a correlation of the pancreatic cancer mortality with the cumulative radon exposure (ERR/WLM = 0.07%, 95% CI = 0.01-0.12). A significant correlation between the indoor radon and the incidence of pancreatic cancer (r = 0.259 to 0.3, p < 0.001) among the non-white patients in USA has been reported in a correlation study [150]. This study suggests indoor radon may be a significant risk factor for pancreatic cancer. The significant correlation of overall incidence of pancreatic cancer with the county-levels radon exposure has been found among the African Americans, American Indians and Asian Americans, but not in whites [151]. It is suggested in this report that environmental radon exposure may be a significant risk factor for inducing pancreatic cancer among African Americans, American Indians, and Asian Americans. In a census based cohort study in Iceland has observed a positive and significant risk of pancreatic cancer among the residents of high temperature geothermal areas [100]. Results of this study have been showed that hazard ratio (HR) for pancreatic cancer are 2.57 (95% CI: 1.30-5.07) and 2.85 (95% CI: 1.39-5.86) for the warm and cold reference areas, respectively. A large-scale cohort study conducted in American Cancer Society CPS-II has not found a clear association between the residential radon exposure (100 $Bq.m^{-3}$) and the mortality from pancreatic cancer [88]; the HR for this mortality found as 1.03 (95% CI: 0.92-1.14).

### 4.8 Liver cancer and diseases

It is estimated that about one-half of the 10% of the ingested radon that is absorbed and retained in the body is distributed to the liver, and this amount of ingested radon can deliver alpha radiation dose to the liver. The elevated level of liver cancer (primary and unspecified) incidence or mortality has been seen in combined cohort of underground iron miners exposed to radon [111]. Authors of this study have reported the ratio of observed to expected deaths (O/E) for mortality of 1.93 (95% CI: 0.83-3.81), although, they have not found a trend in mortality from liver cancer due to high level of radon exposure. A study has shown that the risk for mortality from liver cancer (O/E = 1.67) among the uranium miners in West Bohemia is significantly associated to radon exposure [124]. But, the mortality from liver cancer does not increase with duration of employment or with cumulative radon exposure among these miners. A combined analysis of large cohorts of underground miners has not been showed the evidence of an increased risk of liver cancer incidence or mortality due to cumulative radon exposure [110]. A German uranium miners' cohort study reported a significant and positive correlation between radon exposure and liver cancer (ERR/WLM = 0.044%; 95% CI: $-0.008$ to 0.096%), and recorded a statistically significant increased mortality from cancer of liver (O/E = 1.26; 95% CI: 1.07-1.48) [112]. It has been reported in a study that the effects of external gamma-radiation exposure, long-lived radionuclides, arsenic and dust can decreases ERR/WLM, but confounding from alcohol consumption cannot be ruled out [112].

### 4.9 Cancers and diseases of gallbladder and extrahepatic bile ducts

A study conducted among uranium miners in West Bohemia [124] has reported that the increased risk for cancers of both gallbladder and extrahepatic bile ducts is associated with cumulative exposure to radon. Authors of this study have found the risk of mortality from these two cancers [ratio of observed to expected deaths (O/E) = 2.26] is significantly increases with cumulative radon exposure, but not increases with duration of employment underground. A Swedish study on iron miners' cohort has reported that the cancer of the gallbladder and extrahepatic bile ducts among the miners is tended to increase with increasing cumulative exposure [111]. This cohort study reported that the O/E is 1.41 (95% CI: 0.29-4.12) for this cancer, and the value of O/E is tended to increase highly with cumulative radon exposure of at least $200+\ WLM$ (O/E = 5.88). An elevated, but not statistically significant, positive association of radon exposure with gallbladder cancer has been observed in a case-cohort study conducted in Czech uranium miners [94]. By comparing 180 WLM of cumulative lifetime radon exposure to 3 WLM, this study reported the relative risk for gallbladder cancer of 2.39 (95% CI: 0.52 – 10.98).

### 4.10 Kidney cancer and diseases

Kidneys act as a filter for soluble wastes from bloodstream, excess water, or from a variety of other compound. During this filtering process, the radon and its daughters dissolved in blood and excess water can deliver alpha radiation doses to the kidneys through direct interaction of the emitted alpha-particles with the renal cells of the kidneys. The high levels of radon exposure can result in carcinogenic effects on the kidneys and that can be induced kidney cancer[96]. The renal cell carcinoma (RCC) is the most common kind of kidney cancer in adults, and it represents about $90\% - 95\%$ of all renal malignancies. Urine is normally stored in urinary bladder after passing through ureters from kidney, and spent much time in bladder, therefore, the bladder is thought to be exposed relatively long-time than the kidney by same amount of radiation. It has been estimated in a cohort study[152] that kidney cancer risk associated with radon in drinking well water is $0.81\ (0.47 - 1.37)/log\left(100\, Bq.l^{-3}\ of\ radon\right)$ and the corresponding figure for urinary bladder is $1.02\ (0.68 - 1.54)$.

A French cohort study showed an excess mortality from kidney cancer in uranium miners[63], and the risk for mortality is not apparently associated with cumulative radon exposure. It has been found in a case-cohort study on Czech uranium miners[94] that the relative risk (RR) is 1.13 for kidney cancer (95% CI: 0.62-2.04) and 0.84 for bladder cancer (95% CI: 0.43-1.65), when compared to 180 WLM (90th percentile) of cumulative lifetime radon exposure to 3 WLM (10th percentile) This indicates kidney cancer is associated with cumulative radon exposure. But, studies on the Swedish uranium miners[111] and Ontario uranium miners[153] have not observed the significant trend or association for cancer of kidney with increasing cumulative radon exposure among the miners. A research team presented the ratio of observed to expected (O/E) deaths of 0.85 (95% CI: 0.31-1.85) for kidney cancer in relation to cumulative radon exposure[111].

An association between childhood kidney cancer and county levels radon exposure has been found in North Carolina[136]. The RR of mortality from childhood kidney cancer found in this study is slightly increased with county levels radon exposure; the RR = 0.96 (95% CI: 0.65-1.41) for radon exposure of $229 - 1375\ pCi.l^{-1}$ and also RR = 1.13 (95% CI: 0.74-1.70) for high radon exposure of $1376 - 10,692\ pCi.l^{-1}$, compared to low radon level of $0 - 228\ pCi.l^{-1}$. A few studies have indicated the significant association between the exposure to indoor radon and the risk of kidney cancer incidence[96,154]. The correlation coefficient (r) of 0.86 ($p < 0.001$) for the incidence of kidney cancer with the radon exposure of 20 to 50 $Bq.m^{-3}$ has been found as highly significant in Canada[96]. A study[95] observed an increased odd ratio between 2 and 3 in the higher exposure categories for kidney cancer. A systematic review and meta-analysis of observational epidemiological studies on radon exposure and kidney cancer has been carried out by a research group[155]. Their subgroup analysis revealed that the association between radon exposure and risks of kidney cancer among studies in Europe is marginally positive and significant, but none evidence for the increased risk of kidney cancer has been provided in two population-based studies. It has also been mentioned in this study that association between radon exposure and kidney cancer cannot be excluded because of its biological plausibility. In a cohort study in Finland[152], authors have not found the substantially increased risk of bladder or kidney cancers with ingested radionuclides in the well water. So, it is found that the link between radon exposure and kidney cancer is controversial, but in correlation type studies suggested that radon is a risk factor for inducing kidney cancer.

### 4.11 Prostate cancer and diseases

Prostate cancer is the most common type of cancer diagnosed and the second most common cancer in men worldwide.

Using population-averaged radon values from fourteen countries, a study has shown a positive correlation between radon level in houses and the incidence of prostate cancer[156]. A Swedish study on iron miners' cohort found that the ratio of observed to expected (O/E) deaths for mortality from prostate cancer is 1.20 (95% CI: 0.81-1.73), but this study does not indicates the mortality from prostate cancer is correlated to cumulative radon exposure[111]. On the basis of data from American Cancer Society CPS-II, a large-scale cohort study has not seen the association between residential radon exposure and prostate cancer incidence[88]. Hazard ratio (HR) of mortality from prostate cancer per each 100 $Bq.m^{-3}$ has been found as 0.99 (95% CI: 0.79-1.23) in this study. The studies relevant to both correlation and case-control have indicated that prostate cancer risk is correlated with exposure to indoor radon, but few studies are not quite consistent with each other[154]. However, it is observed that evidence regarding prostate cancer risk from radon exposure and its progeny is scarce.

### 4.12 Certain diseases of female and unborn baby

A study on the environmental radon monitoring in blood and urine samples of female patients has found a significant association of the radon concentration in blood and urine with the cancer patients[157]. This study also found that the radon concentration levels in women blood and urine samples of exposed group are higher than those of control group. It has been observed in a study[158] that females living in the vicinity (inside the crater) of Furnas volcano presented a higher risk of breast cancer, compared to females inhabiting an island without historical records of volcanic activity. According to the authors of this study, the higher risk of breast cancer may partially be explained by the presence of high levels of radon ($> 200\ Bq.m^{-3}$) in indoor air of houses in Furnas. A census based cohort study in Iceland has showed a significant excess risk of breast cancer among the women residents of high-temperature geothermal areas where exposure through water can include radon[(100)]. Hazard risk (HR) for breast cancer among women has been found as 1.46 (95% CI 1.02 to 2.09) and 1.62 (95% CI 1.12 to 2.36) for the warm reference area and the cold reference area, respectively. On the basis of hormone receptor status in the Western US women, a research co-workers suggests a positive association between county levels of radon exposure and certain invasive breast cancer[(159)]. They have observed that the risk of invasive breast cancer among the women is increased by 47% (95% CI: 1.10, 1.97) for highest radon exposure of $\geq 57.4\ Bq.m^{-3}$ and that increased by 19% (95% CI: 0.95, 1.49) for radon exposure between $\geq 33.3$ to $57.4\ Bq.m^{-3}$, when compared to women exposed by lowest ($< 33.3\ Bq.m^{-3}$); but in the Northeast, Midwest, or South of the US, the radon exposure is not associated with increased risk of invasive breast cancer.

The alpha-radiation emitted by the decay of radon can damage the reproductive systems and aggravates the infertility of women[(160)]. Fetuses are more susceptible to radon-induced cancer from their rapidly dividing cells and faster respiration. Radon exposure and pregnancy is dangerous because fetuses exposed to radon in the womb have an increased risk of lung cancer later in life. Other than lung cancer, some harmful radon effects can occur elsewhere. The exposure to higher levels of radon in pregnant women can lead to induce risk of teratogenic birth defects in the offspring, which include the defects in the arms and legs, such as malformation or absence of fingers, toes, feet, hands or an entire limb. Based on the data on birth defects provided by Texas Birth Defects Registry, it is reported in a study that the residential radon levels exhibited the strong and consistent associations with occurrence of birth defects, particularly cleft lip with or without cleft palate, and with cystic hygroma, or lymphangioma[(161)]. Authors of this study have suggested that the associations for Down syndrome and skeletal malformations including lower limb reduction defects and inward deformities of the feet are quite inconsistent. Also, they have not found the association between the residential radon level and the total birth defects, microcephaly, or eye defects. It is found in a review report that the alpha-radiations emitted from the radon and uranium can reduce the growth of offspring at different gestation periods of women and can damage the fetal or embryo and female reproductive systems significantly[(162)]. This is because of the dissolved radon in blood of mother can pass through placenta into the developing child. If the developing child is in the fetal stages, a radon particle passing into the fetus would likely move to brain and other organs. At this stage, exposure to alpha particles may results in severe inhibition in brain development leading to mental retardation[(26)], which is a type of birth defects.

### 4.13 Other diseases or cancers

A study conducted in USA has reported that the radon concentrations in water ranged from 20 to $180,000 pCi\ .l^{-1}$ and airborne radon in homes ranged from 0.05 to $210 pCi\ .l^{-1}$ are significantly correlated with the rates for all cancers combined and rate for reproductive cancer in some counties of Maine[(69)]. High levels of radon in homes have an effect on male sterility, especially on the activity of sperm. A case study[(163)] in Iraqi Kurdistan has shown an exponential relationship between annual effective dose by inhalation of radon and the rate of male infertility. Authors of this study have observed that average values of radon concentration and annual effective dose inside the homes having a high rate of male infertility are ranged from $128.34 \pm 35.87$ to $238 \pm 76.54 Bq \cdot m^{-3}$, from $3.234 \pm 6.00 mSv \cdot y^{-1}$, respectively.

A cohort study evaluated the association between the chronic radon exposure and all-cause mortality among participants and individuals[(89)]. The authors of this study have found 4·98% increase in mortality risk (95% CI: 4·10%-5·86%, $p < 0.001$) for diabetes mellitus (DM), independent of exposure to $PM_{2 \cdot 5}$.

It is observed in a study that the population living in the vicinity of Furnas volcano presented a relatively higher risk for cancer in some group of organs, especially of lip, oral cavity, and pharynx cancer, compared to population residing an island without historical records of volcanic activity[(158)]. According to the authors of this study, the higher risk for such cancer may partially be explained by the presence of high levels of radon ($> 200\ Bq.m^{-3}$) in indoor air of houses in Furnas. In German uranium miners' cohort, there is found a constant (but not significant) increase risk of pharyngeal cancer with increasing cumulative radon exposure (ERR/WLM=0.16%; 95% CI: $-0.045$ to 0.37%) among the miners[(112)]. The laryngeal cancer risk among the German uranium miners due to exposure to radon progeny is not observed by a study, but only a slightly elevated risk is observed (OR 1.13, 95% CI: 0.75-1.70) for cumulative radon exposure of at least 1,000 WLM[(164)].

## 5 Discussions on health hazard problems

### 5.1. Lung cancer and diseases

The indoor radon concentrations in both workplaces and homes are the two main sources of exposure of lungs. Radon itself does not directly cause lung cancer. Main causative agent for inducing lung cancer is the radon's decay products [165], particularly alpha emitters of $^{218}$Po, $^{214}$Po and $^{210}$Po. These polonium radioisotopes are responsible for inducing damage in the basal cells of lungs, and hence to cause lung cancer. The risk for lung cancer incidence and mortality from lung cancer due to exposure to both radon and its decay products have been well documented in a large number of different epidemiological, cohorts, mining and ecological studies. These studies have reported that the occupational and residential radon exposures are strongly and positively associated to the lung cancer incidence and mortality. According to the IARC, the radon and its decay products are designated a carcinogenic element for inducing lung cancer [19]. Several major health organizations like American Lung Association, Centers for Disease Control, and American Medical Association are agree with estimates that radon causes thousands of lung cancer deaths every year [54]. It is found that the lung cancer caused by radon exposure during 1999 – 2016 is increased by a factor of 1.4 in US. So, it is clear that the high level of radon exposure is a risk factor for inducing lung cancer. A positive linear trend may be observed between radon concentrations and lung cancer mortality.

Cigarette smoke appears to interact with radon and its progeny to potentiate their effects [32]. Combined effect of radon inhalation and tobacco smoking can lead to increase the lung cancer risk effectively. That means if a tobacco smoker breathes radon contaminated air, his/her chance of developing lung cancer will be very high. Lung cancer is the only respiratory effect that has been clearly associated with exposure to radon and its progeny depending on the duration of time spends by consumers in the radon contaminated closed spaces, and also associated with smoking habits [25,32,37]. This observations may suggest that the lung cancer risk may also linearly vary more significantly with radon inhalation and tobacco smoking combined.

It may be noted that the risk of lung cancer incidence from radon exposure is related to race. A study reported the significant trends in mortality from silicosis and pulmonary fibrosis lung diseases among white miners [127]. Lung cancer risk due to radon is also gender dependent. It has been found in two studies that the lung cancer risk associated to radon exposure is higher in females than in males [83,86]. But, the study on the association between gender and radon-induced lung cancer incidence is very sparse. It may also be noted that children have smaller lungs and faster breathing rates, compared to adults, which may result in higher radiation doses to the children lungs due to radon exposure [32]. So, an equal amount of radon exposure can induce lung cancer in children effectively than in non-smokers.

Some studies on miner cohorts have identified that mortality occurs due to lung cancer as well as non-cancer lung diseases. Few ecological studies have shown that residential radon exposure may increase the risk of chronic obstructive pulmonary disease (COPD) or mortality from COPD [87,89]. Recently, a review study reported that the relation of the COPD incidence with radon exposure is controversial [166]. However, another study [88] does not support COPD or any other cause of mortality beyond lung cancer. A research group suggests that the lung cancer mortality pattern differed between the sexes [86]. Confounding factors such as exposure to some respiratory toxicants, smoking history, and work experience are likely major contributors to mortalities from noncancer respiratory diseases [32]. However, the evidences on the radon associated health effects of the lungs other than lung cancer are limited.

Health effects other than lung cancer associated with exposure to radon progeny have been of concern for human [25].

### 5.2 Skin cancer and diseases

Results of many studies have been revealed that the radon exposure is a possible risk factor for inducing several types of skin cancer in general population. Relevant studies for miners are very limited, only two studies have examined the radon related skin cancer among uranium miners and reported that the MGM and BCC skin cancers are positively associated to radon in the mines [93,94]. So, the evidences of the radon-related skin cancers among miners are scanty. Further studies on miners are needed to confirm such association.

On the other hand, a large number of ecological and cohort studies have reported the association between high levels of environmental radon exposure and some skin cancers, particularly BCC, NMSC and MGM of the skin. The NMSC and SCC are significantly associated to high levels of environmental radon exposure, mentioned in three ecological studies conducted in England [72,101,102]. It is found that the long-term residential radon exposure is strongly contributed to develop BCC [103], but a study does not agree with this association [101]. However, the theoretical models and evidences from ecological studies suggest that environmental or domestic radon exposure may be a risk factor for inducing skin cancer. Interestingly, the BCC of skin is significantly associated with both occupational and residential radon exposures among both miners and general population. So, present study demands BCC disease of skin should be consider as a radon-induced disease for man.

Many studies suggested that the UV radiation and air pollutants are also relevant risk factors for inducing many types of skin cancer. More recently, the Environmental Perspectives 125(06)-June 2017 explored the dependence between the skin cancer and the effects of both radon and UV exposure in different population[167]. More research on the epidemiological evidences is needed to confirm the relationship between radon exposure and skin cancer.

### 5.3 Stomach or gastric cancer and diseases

Evidences show that the high levels of radon and its decay progeny can pose a considerable radiation dose to the stomach. Radon exposure by swallowed air or from pulmonary secretions can also induce stomach cancer. Few miners' studies reported that the risks for incidence of stomach cancer and mortality from stomach cancer are significantly related to the cumulative radon exposure[111–113]. Results from some epidemiology studies provide the corroborate evidences regarding the positive and strong association between the groundwater radon exposure and the increased risk of stomach cancer[70,109], which supports the National Research Council[168] that radon in groundwater is a significant risk for stomach cancer. But, a study[116] does not support such association, even for radon concentrations above 300 $Bq.l^{-1}$; this study found an indication of stomach cancer risk as a result of the effect of uranium, radium, or other radionuclides in drinking water. However, many studies including ecological and cohort have found a significant link between the stomach cancer and the radon exposure, and also for mortality from stomach cancer caused by radon.

Few studies reported the stomach cancer incidence and/or mortality due to radon exposure is higher in females than in males[86,115], this indicates the risk of stomach cancer incidence or mortality due to radon exposure is gender dependent. It may think that this association may biological plausible. The correlation of the cancers of esophageal, and rectum, or colorectal with the alpha exposure by radon has also been reported in some studies[113,119].

The NAS Committee assessed that dissolved radon in drinking water causes about 20 deaths per year in the USA[169]. It is observed in most of the studies that the relative risk factor or hazard ratio for stomach cancer is greater than 1, even greater than 2 found in some cases[113]. This indicates the high level of radon exposure is a risk factor for stomach cancer incidence. Further, epidemiological and case-cohort studies are needed to confirm the relationship of the radon levels with the stomach cancer.

Moreover, after leaving the stomach, the ingested water is absorbed mostly in the small intestine. The radon from small intestine is transferred to bloodstream within 5 minutes, because a study showed that ingested water appears in plasma and blood cells as soon as 5 minutes after ingestion[170]. The radon along with water molecules is then transported rapidly through blood circulation, and they are distributed to all over the body, to the interstitial fluids and to cells. After absorbed into the bloodstream, the radon and its decay progeny delivered alpha radiations dose to the sensitive cells in some organs[106]. It may be noted that inhaled radon and its progeny may also be distributed to different parts of the body via blood circulation. During this processes different organs including large and small intestines, pancreas, kidney, liver, ureter, or urinary bladder may also be absorbed relatively small amount of alpha radiation doses from the radon and its decay progeny in blood and excess water, when compared to lungs.

### 5.4 Cardiovascular diseases

A number of studies have seen that a risk of mortality from coronary heart disease (CHD) among the fluorspar miners due to high level radon exposure[84,121,122], but few studies did not support such risk amongst uranium miners. So, it may assume that some confounding risk factors for CHD may exist largely in the fluorspar mines than the uranium mines. It has been observed in a study that the incidence of cardiovascular disease (CVD) exceeds the average value in residential areas with high radon levels[71]. The radiation dose to blood and walls of coronary arteries due to the radon and its decay progeny indicate that exposure to radon can increase the incidence of CVDs. Tobacco smoking can significantly enhance the risk of CHD mortality[84], while few studies observed tobacco smoking does not change in CHD mortality risk[121,122]. So, the effects of smoking on the CHD mortality risk are controversial.

A group of research team has not found a trend evident regarding the association of cumulative radon exposure with the relative risks for deaths from CHD as well as from the circulatory system disease and acute myocardial infarction. It is observed that congestive heart failure (CHF) related to radon exposure is independent of effect of $PM_{2.5}$[89]. In a study, authors have concluded that radon exposure may indeed increase the incidence of CVDs; they have also suggested that the radiation may be considered as one of many risk factors for cardiovascular diseases[171]. So, it is difficult to establish a link between these malignancies in cardiovascular system and radon exposures, however, it may assume that the CVD is partially, but not significantly, associated to radon exposure.

More systematic studies on miners, cohort and epidemiological and also additional data from the general population are needed to confirm the real relationship between radon exposure and cardiovascular system disease.

### 5.5 Blood cancer and diseases

It is observed that risks of diseases and cancers in blood, including of all leukaemias, associated to radon exposure have been addressed well in several studies. Results of several miner and ecological studies and survey reports have indicate a positive correlation of the exposure to radon with the risks of incidence of certain adult acute leukaemia and childhood leukaemia. Many of them have reported that the risks of leukaemia incidence and of increased leukaemia mortality among the radon-exposed miners are not likely to have been caused by radon, as the analysis in these studies give no strong evidences for considerable risk for leukaemia from cumulative radon exposure. This observation agrees well with two epidemiological studies[96,172], but a study[125] reported that the leukaemia incidence is associated to radon exposure. The risk of leukaemia incidence is also depending upon the exposure to dust particles or gamma rays and the duration of employment in mines[124,127,128]. However, more studies are needed to know whether leukaemia incidence is associated to the miners exposed to the radon and its daughters, or not.

Some evidences of association (non-significant) of inducing non-CLL and HL have been seen among the highly radon-exposed miners, but, the strong and positive relationships have been found for CLL incidence with cumulative radon exposure. Surprisingly, the risk of MTM related to radon is seen only in miners, so many reliable and suitable research is thought to be essential to find the exact reason for inducing the MTM among the miners; and if found, the multiple myeloma (MTM) should be considered an occupational disease in miners.

Many studies reported that the risks of inducing AML, CML, ALL and CLL are positively and significantly correlated with residential radon exposures. Of these, the CLL incidence is strongly and positively associated to residential radon exposure. The mechanisms of radon-induced CLL may be similar to those by which radon causes lung cancer[133]. A study has found that women are at more risk of inducing hematologic cancer caused by the exposure to radon at county level[134]. Remarkably, the non-NHL is seen in residents living in geothermal areas only, so it may consider the NHL is a disease in residents of such geothermal areas. To confirm this consideration, many reliable and suitable studies on NHL incidence in such areas are thought to be necessary.

Results in many ecological studies have revealed that the risk of incidence of leukaemia, particularly AML and ALL, among children is positively associated to the high levels of indoor or domestic radon exposures. The association of domestic radon exposure with ALL is stronger and significant among the children, particularly during their childhood period, but such association is weaker for adults[129]. The childhood leukaemia in areas with different radon levels has also been observed by a research team[138]. This research team reported that the association between childhood ALL and continued residence at normal or high radon levels areas has been showed a similar trend.

It is more surprisingly observed that the risk of CLL incidence among both miners (uranium) and residents is strongly and positively related to radon exposure. So, the present study demands CLL disease should be consider as a radon-induced disease for both workers and general population.

### 5.6 Diseases and cancer in cerebrovascular and central nervous system

Evidences regarding the association of the risk of brain and nervous system cancer with the cumulative radon exposure are sparse in miners study. Only two studies on the French cohort uranium miners' have found that this association is significant[143,144], but such association has not been found in a German uranium miners' cohort[112]. A census-based cohort study[142] does not support the evidence for the association between the domestic radon exposure and the central nervous system (CNS) tumors, despite relative high radon levels have been present in the areas.

On the other hand, cancer or diseases of brain, nervous system and spinal cord due to residential or indoor radon exposure has been documented in several ecological and cohort studies. In case of child, it is observed that high levels of radon at home can increase the risk of mortality from childhood cancer such as brain and CNS cancers[136]. A stronger and significant association between the high levels of residential radon exposure and the risks of cancers in brain and spinal cord has been found in adults[86,145–147], but two studies have not found such association[69,88]. Of these, only a study[86] observed that the association is high for women rather than men. Data of this study revealed that risk factor for brain cancer mortality related to radon exposure among women can also be increased as a result of the effects of sociodemographic variables, arsenic topsoil levels, and altitude. All the above observations indicate the risk of brain cancer incidence is gender dependent and may be sensitive to soft tissues of child. So, it may realize that high levels or long-term radon exposure may possibly associate to brain cancer risk among man, and the association is strong for children and women only. A research team hypothesised that presence of particulate matter in ambient air can modify the association between residential radon and risk of brain tumour, in fact they have observed that the association is stronger even at outdoor NOx concentrations [145].

In case of cerebrovascular diseases (CeVD), a number of French cohort studies on uranium miners have shown a significant positive association between CeVD incidence or mortality and cumulative radon exposure, together with a significant excess relative risk (ERR) per 100 $WLM$ [64,65,148]; but, a study on Newfoundland fluorspar miners does not found such association [121]. A nationwide cross-section study [149] reported that the high level or long-term indoor radon exposure is strongly correlated with stroke even after adjusting potential confounding factors, and most strong correlation has been found among participants of age over 76 years. Hard physical activity is identified as a potential modifying factor of the exposure-risk relation [148]. The exact mechanism of indoor radon causes stroke is not identified, a group of research workers assumed that radon may have directly affected the blood vessels [149]. Once radon enters the body, it can dissolve into bloodstream. The dissolved radon in blood entering the gas exchange compartment is then transported to any tissue through the blood circulation. Since the radiation from radon is strong enough to cause cell damage [20], so it is plausible that radon within the blood stream and vascular tissue causes vascular damage resulting in thromboembolic diseases such as stroke [173].

Interestingly, the diseases in the brain, nervous system, or in cerebrovascular are observed only among the French uranium miners, but not observed among the miners of German uranium and Newfoundland fluorspar. So, the present study suggests these diseases are not only associated to radon exposure in uranium mines, but also associated to some confounding factors those are mostly present in French uranium mines. However, more epidemiological miners study for CNS and ecological study for CeVD are needed to confirm the relationship of the radon levels with the diseases or cancers in both cerebrovascular and central nervous system.

### 5.7 Pancreatic cancer

Some studies, particularly studies on miners, on the investigation of the association between radon exposure and pancreatic cancer are very limited. Few studies suggest environmental radon may be a significant risk factor for inducing pancreatic cancer [150,151]. These studies reported that the relationship between radon exposure and incidence of pancreatic cancer may vary with the racial disparities. The overall risk of pancreatic cancer due to changes in DNA is thought to be the same for most racial groups. But, the racial disparities in pancreatic cancer may be due to the different DNA methylation levels between Blacks and Whites [174]. However, it is observed that the radon exposure may induce pancreatic cancer. More studies are needed to confirm the relationship between the incidence of pancreatic cancer and the radon exposure.

### 5.8 Liver cancer and diseases

Evidences on the correlation between radon exposure and liver cancer are sparse in literatures. Two mining studies reported the possible increased risks of liver cancer caused by radon [111,112], whereas two others decline this association [110,124]. The mining studies on the liver cancer related to radon exposure are limited. Not a single ecological study has been found regarding this association. It is observed that alcohol consumption and radon exposure together can enhance the risk of liver cancer significantly [112]. However, further studies, particularly epidemiological, case-control and ecological types, are needed to know the exact risk factors for liver cancer incidence among the miners.

### 5.9 Gallbladder and extrahepatic bile ducts cancer and diseases

Evidences regarding the correlation between the radon exposure and the cancers of both gallbladder and extrahepatic bile ducts in literatures are sparse. Several miners study reported the positive and significant relationship between the radon exposure and the risks for gallbladder and extrahepatic bile ducts incidence or mortality among different categories of mining workers [94,111,124]. Studies on the evidences regarding the residential or indoor radon related gallbladder and extrahepatic bile ducts cancer incidence have not found. So, it may think that this cancer is a mining disease. Epidemiological, case-control and ecological types studies are needed to clarify the role of radon in the development of this cancer.

### 5.10 Kidney cancer and diseases

The results of some miners' studies have been revealed that the kidney cancer incidence or mortality is not associated to the cumulative radon exposure. Only a case-cohort study [94] has shown that kidney cancer is associated with high levels of radon exposure. The results and reports given in several correlation type ecological studies have revealed that the risk for kidney cancer incidence is significantly correlated with the exposure to the residential or indoor radon and radon daughters [95,96,154], but, such correlation is found as weakly in other studies [136,155]. A research team have claimed that the environmental radon exposure is a causative risk factor for inducing kidney cancer [96], and they have also found that the correlation for radon and kidney cancer is significantly greater than that for gamma-radiation. Based on the toxicological data, the UNSCEAR suggests that exposure to uranium may be related to urological cancers, especially to the kidney cancer, because of the potential of uranium to cause both adverse radiological and metal effects upon that organ [175]. So, link between radon exposure and kidney cancer is controversial. But, this link cannot be ruled out; because, second only to the lungs, the kidney receives the highest dose compared to other organs after entry of the radon and its decay products into the human body from the lungs [58,96]. Additionally, kidney filters the dissolved radon and its daughters in blood and excess water, and filtering of radon and its daughters through the kidneys is suggested to explain the correlation seen for kidney cancer [95]. More epidemiological studies are needed to confirm this association.

### 5.11 Prostate cancer and diseases

Studies that investigated the association between prostate cancer risk and radon exposure are very sparse. Most of the studies indicate that prostate cancer risk is not associated with radon exposure, but only a study found positive association [156]. Mechanism involved on this association is not clear. To examine the mechanism involved in prostate cancer incidence caused by radon exposure, a group of research workers suggested that mutation in the p53 gene is likely to be a late event in the malignant transformation process of human benign prostate epithelial (HBPE) cells by radon [176]. On the other hand, relating to the mortality risk for prostate cancer in connection with the underground work, a research team have indicated in the population-based case–control and literature review study that the underground mining act as a protective factor against the prostate cancer [177]. This indication has been explored and supported further in a study [178] by analysing prostate cancer mortality in the German 'Wismut' uranium miner cohort. So, the relationship between the prostate cancer risk and the radon exposure is controversial.

### 5.12 Diseases of female and unborn baby

Radon exposure can significantly affects the reproductive system and fertility of women [160]. It is observed that the association of the radon alpha activity with the blood and urine combined may persist in the females with cancer problems [157]. The risk of induced breast cancer significantly varies with the county-level radon exposure [159]. It is found that the risk for radiation-induced breast cancer in men is negligible, but it is induced significantly in female [162]. Evidences of the effects of radon exposure on breast and reproductive system combined among female are lacking.

Radon may affects the unborn child, and its alpha radiation activity can reduce the growth of offspring at different gestation periods of pregnant women. Fetuses exposed to radon in the womb have an increased risk of lung cancer later in life. Exposure to radon may results in severe inhibition in brain development at the fetal stages and this can lead to develop mental retardation [26]. The radon decay products are assumed to be associated to develop severe mental retardation in developing child, as they are more concentrated in developing brain. Other than lung cancer and mental retardation, the pregnant women exposed to higher levels of residential radon is in risk of inducing some teratogenic birth defects in the offspring effectively as well as other types of birth defects, particularly cleft lip with or without cleft palate and with cystic hygroma [161], but this radon exposure cannot induce risk of microcephaly, or eye defects in the offspring.

### 5.13 Other diseases or cancer

To find the evidences regarding some other diseases or cancers related to radon exposure, few studies have observed that the high levels of radon exposure are correlated to the risks of reproductive cancer or diseases [69,163], cancers in lip, oral cavity, and also pharynx cancer [112,158], and also for diabetes [89]. A slightly elevated risk of laryngeal cancer is observed for cumulative radon exposure of at least 1,000 WLM [164]. On the other hand, thyroid gland is sensitive to ionizing radiation, but no studies have been found to show the correlation between elevated radon exposure and thyroid cancer incidence, for instance, there are no association have been found between county-level radon exposure and incidence of female thyroid cancer in Iowa, New Jersey, and Wisconsin in USA [179]. No information is located regarding immunological and neurological effects after inhalation exposure to radon at concentrations considered relevant to human health [32].

However, from the above discussions, it is observed that the high levels of radon and its decay progenies can pose a considerable radiation dose to several organs of the body, especially to lungs, skin, kidney, blood, unborn child, stomach, or even to pregnant women. The high levels of prolonged radon exposures are able to develop many health hazards problems to the human body. The health hazards associated to the radon exposure are mainly due to the short-lived daughter products, particularly alpha emitters $^{218}Po$, $^{214}Po$ and $^{210}Po$, of radon.

In case of evidences regarding the health effects related to the thoron and it decay products, there is no sufficient and comparable amount of surveys, data sets and maps exist in most of the published literatures. It may assumed that the effective dose from indoor $^{220}$Rn (thoron) and its short-lived decay progeny is usually much lower than that from indoor $^{222}$Rn (radon) and its progeny. This is due to the short half-life of $^{220}$Rn (55 *s*), compared to 3.825 *d* half-life of $^{222}$Rn, so that in most cases the $^{220}$Rn infiltrates from the rocks, soils and waters to a much lesser degree than the $^{222}$Rn. Therefore it is believed that geogenic contribution to the activity level of thoron, and consequently its decay progeny is small[85]. Also, while the ratio of mean concentration of $^{222}$Rn progenies to $^{222}$Rn, called equilibrium factor, is quite homogeneous within a room, such ratio is not homogeneous for thoron due to its steep gradient from the source, especially within few tenths centimeters from walls[27,180,181], and hence thoron concentration strongly decreases with the distance from walls of the room. However, as it is evident that an elevated level of indoor radon has the potential to induce several health risks to the consumers. So, identification of the sources of radon, its entry into the indoor spaces and also its remediation are essential for protecting the human lives.

It may important to mention that the ionizing radiation is not constantly harmful, but it is sometimes hormetic. The hypothesis of radiation hormesis is that the small amount of dose due to exposure to ionizing radiation, comparable to and just above the natural background levels, is not harmful but sometimes shows beneficial effects in living organisms, while it is accepting that the large amount of radiation dose is always harmful. In the radiation hormesis hypothesis, it is assumed that the low doses and dose-rates of ionizing radiation stimulate the activation of DNA repair mechanisms, apoptosis and immune functions and eliminate the radiation-induced transformed cells, and hence protect against diseases. The radiation hormetic effects have been observed in atomic-bomb survivors for leukemia[182] and solid cancers[183], as well as in common people for lung cancer[184]. It is observed that the radiation hormesis effect appears to protect against spontaneous lung cancer incidence, while at higher lung doses the effect of radiation hormesis will disappear and the lung cancer risk reaches the expected spontaneous incidence[185]. Some studies into the effects of ionizing radiation have not reported the hormetic effects for some diseases including cancer[61,186,187], rather these studies found the linear dose-response relationship and the highly mutagenic effects in the mammalian cell's nuclei. More commonly accepted model of dose-response relation in radiobiology is the linear-no-threshold (LNT) model and it is generally used by regulatory agencies for policy making purposes of human radiation exposure. The LNT model states that the relationship between the radiation dose and the risk of radiation-induced adverse health effects is linear across all doses, so that small doses are still damaging although that less than higher doses. The BEIR VII report and the ICRP continue to support the LNT hypothesis[188,189]; because the LNT hypothesis is very well established, and provided the current understanding of mechanisms and quantitative data on dose and time–dose relationship. According to the BEIR VII report, the current scientific evidence is consistent with the hypothesis that at the low doses there is a linear dose-response relationship between the exposure to ionizing radiation and the development of solid cancers in humans. There is no a threshold dose limit below which cancers are not induced, although at the low radiation doses the number of induced cancers will be small[189]. Other health effects such as heart disease and stroke occur at higher radiation doses[189]. The BEIR VII reported that the adaptation, low-dose hypersensitivity, bystander effect, hormesis, and genomic instability are based only on phenomenological data with little mechanistic information. Many strong radiation protection organizations are in place, the scientists and government officials are very reluctant to seriously consider the implications of the radiation hormesis phenomenon[190]. The medical and radiation committees also refuse to consider valid evidence of radiation hormesis in cancer, other diseases, and health[191]. The hormetic dose response model has been rejected principally because of its early and close historical association with the controversial medical practice of homeopathy[192]. In a study it has been mentioned that the low doses activate or stimulate the exposed living organs, while both moderate and high doses inhibit this response[185] . Recently, a review article introduces various studies that have reported the beneficial and harmful effects of low-dose radiation[193]. According to authors of this study, the LNT theory may be out of date and the low-dose radiation may have beneficial effects (radiation hormesis) depending on the specific conditions; otherwise, the low-dose radiation may have no effects. More recently, a study reported that if the smallest dose of radiation hits the DNA of a cell then it induces a potential carcinogenic effect and causes a genetic mutation[82]. So, it is evident that the concept of radiation hormesis in humans is still controversial.

Generally, lack of knowledge and perceptions about radon is very common to almost all general population. For example, various studies[194,195] regarding the public's understanding and perceptions about radon have showed that majority of individuals do not know the crucial information about the background of radon and radon causes health effects. It is therefore very important to consider seriously how health risks associated to radon is understood by residents residing in a radon-prone area, or, by households living in a house where the radon in indoor spaces and domestic water reach elevated levels. According to WHO's recommendation, the reference levels for radon should not to be exceeded 300 $Bq.m^{-3}$ for indoor air[41] and 100 $Bq.l^{-1}$ for drinking water[169]. For the safety of general population, the local authority should initiate the radon awareness programs for public in certain geographic areas where both the residential and domestic radon activity levels in air and water have been present above the recommended reference levels. The program organizers must be described simply the strategies for reducing the radon exposure, effective remedial measures of radon, and public health risks caused by radon as given by different international commissions and organizers. From such programs, the local people must be benefited to gain the knowledge and perceptions of the health risks associated with exposure to the radon and its decay progeny.

If the levels of indoor radon and water radon in a house have been found above the WHO's recommended reference levels, then the households should be taken preventive actions to resist radon exposure by incorporating scientific techniques through engineering means so that they will be able to get advantage from a significant radon reduction in their health risks. In a radon contaminated area, public should be asked to drink water after boiling or stirring well and they should try to increase the ventilation of their houses in order to minimize radiological hazards from radon.

## 6 Conclusions

The health hazard effects due to inhaled or ingested radon from air and water have been studied well by a lot of researchers. Under normal circumstances, the alpha radiation dose to human's organ is mostly due to intake of indoor radon. Major part of the dose is delivered by solid decay products of radon, especially $^{218}$Po, $^{214}$Po and $^{210}$Po, rather than radon gas itself.

The main danger from high radon exposure is an increased positive risk for lung cancer incidence. Radon exposure is also significantly associated to induce some non-cancer lung diseases. Tobacco smoking habits and radon exposure combined can enhance the lung cancer risk.

Environmental or domestic radon exposure may be a risk factor for inducing skin cancer, particularly for BCC, NMSC and MGM of the skin. The BCC is significantly associated with occupational and residential radon exposures, and hence present study demands BCC disease should be consider as a radon-induced disease for man. The UV radiation and air pollutants are also relevant risk factors for inducing many types of skin cancer.

Radon in ingested water or from pulmonary secretions can induce stomach cancer. Some epidemiology studies suggest positive and strong association between the high levels of groundwater radon exposure and the increased risk of stomach cancer, which supports the National Research Council [168]. Stomach cancer risk may also be attributed to uranium, radium, or other elements present in drinking water.

Link between malignancies in cardiovascular system and radon exposures is controversial; however, the cardiovascular disease is partially associated to radon exposure, and other confounding factors cannot be ruled out.

Risks of diseases and cancers in blood, including of all leukaemias, associated to radon exposure have been documented well in several studies. The risk of leukaemia incidence or increased mortality from leukaemia among radon-exposed miners is not caused by radon exposure, but the risk depends on exposure to dust particles or gamma rays in mines. The chronic lymphocytic leukaemia (CLL) incidence is strong and positively associated with the occupational and residential radon exposures among both miners and general population. Present study demands CLL disease should be consider as a radon-induced disease for man. Surprisingly, the risk of multiple myeloma related to radon is seen only in miners. The association of domestic radon exposure with ALL is stronger and significant among the children, particularly during their childhood period, but such association is weaker for adults. So, radon exposure is a risk factor for inducing many leukaemias.

The risks of cancer in brain, nervous system, cerebrovascular diseases, and also stroke are associated significantly with the high levels and long-term mining or residential radon exposures. The brain cancer risk due to radon is strong only for the children and women. The sociodemographic variables, particulate matter in air, arsenic topsoil levels and altitude can modify the brain cancer incidence.

There are no sufficient evidences found in the literatures regarding the cancers in pancreas, liver, gallbladder and extrahepatic bile ducts caused by the radionuclides of radon decay chain. Environmental radon may be a possible significant risk factor for inducing pancreatic cancer. Not a single study has been found regarding the association between residential radon exposure and the cancers in liver, gallbladder, and extrahepatic bile ducts.

Several correlation type ecological studies have suggested the risk of kidney cancer is significantly correlated with the exposure to the residential or indoor radon and radon daughters. Exposure to uranium may be related to the kidney cancer incidence because uranium has the potential to induce both adverse radiological and metal effects upon that organ. So, link between radon exposure and kidney cancer is controversial. But, this link cannot be ruled out, because, the organ kidney filters the dissolved radon and its daughters in blood and excess water, and filtering of radon and its daughters through the kidneys is suggested to explain the correlation seen for kidney cancer [95].

Evidences mentioned in most of the studies indicated that prostate cancer risk is not associated with radon exposure.

Radon alpha activity has a significant effect on the reproductive system and fertility, and can reduce the growth of offspring. Evidences of the effects of radon exposure on breast and reproductive system combined among female are lacking. The pregnant women exposed to high levels of radon can induce severe mental retardation, teratogenic birth defects as well as occurrence of some defects, particularly cleft lip with or without cleft palate and with cystic hygroma, in the offspring.

Radon exposure may also be relevant for inducing cancers in lip, oral cavity, and also pharynx and laryngeal cancers. Other than cancer, the radon exposure may be associated to risks of COPD in lungs, esophageal, and rectum, or colorectal of digestive system, and risk of reproductive system.

Radon induced diseases including cancer are susceptible to race, gender, or children, particularly cancers or diseases in lungs, stomach, brain, pancreas, female breast, and fetus.

Other than cancers in lungs, skin, blood and stomach, more study is required for finding the evidences of the correlation of radon exposure with other chronic diseases. Such studies are also required to focus on how the radon and its decay products are interacting with the targeted tissues or cells of an organ of the human body and on the level of damages in the exposed organs.

In radon-prone areas, public should be asked to drink water after boiling or stirring well and they should try to increase the ventilation of their houses in order to minimize radiological hazards from radon.

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### Conflict of interest

There are no conflicts of interest.

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