The Relationship between Multiple Sclerosis Prevalence and Density of Radon Gas in the Environment (Review)

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ABSTRACT

Introduction: Radon (Rn) is a chemically inert gas with no odor, color, and taste. It is created from the decay of uranium in the soil and can penetrate the building through the interiors. As a result, Rn can enter the human body with the release of alpha radiation along with airborne dust and cause chronic illnesses such as lung cancer and multiple sclerosis. The Multiple Sclerosis disease, as a complex multifactor disease, is the most common widespread neurotic disorder among the young people. The purpose of this study was to collect and review the past studies published in this field since 1996.

Materials and Methods: In this review, the related articles were searched and studied using key words such as "Radon, Action, Thoron, MS, MS Disseminated, and Sclerosis" using the PRISMA statement.

Results: After reviewing the studies, several effective factors in the prevalence of MS were identified. Some of these factors were a result of the exposure to high levels of radon gas. Penetrations from the building cracks of floor, soil bed, and dwelling materials as well as the water resources are among the most important sources of Rn.

Conclusion: According to the results, the amount of Rn and it’s daughters in the environment are recognized as the risk factors for the MS prevalence.

myelin nervous cells leads to disorders in the transmission of nerve signals from the brain and the spinal cord to other parts of the body, which leads to the emergence of the special MS symptoms. In fact, MS is recognized as a chronic disease of self-immunity and inflammation that is fully cost-effective. The treatment of MS includes disease symptom management. Moreover, MS is a highly debilitating chronic illness with social and economic consequences and is recognized as the second most common cause of young people's disability.

The most important symptoms of MS are having optical disorders, fingers and toes' fading, a momentum electric shock in the body, cold and warm sensation in some parts of the body, incoordination in body organs (especially feet in walking), impatience, too much sleep, body blemishes, laziness and numbness, early fatigue, general weakness of the body, muscle spasm, lack of coordination between words in the speech, headache, excessive urinary excretion, longer digestion, sensitive and early suffering, constipation, nightmare, and interest to eat the acidity foods with cold nature (such as dairy products, especially yogurt and ice cream). In the case of disease progress, MS leads to the lack of control in the urine discharge, hot/cold weather intolerance, decreased sexual desire, severe weakness in making intimate relationships with spouse, and experiencing premature ejaculation in men, depression and low self-esteem, isolation, and imbalance, as well as having muscle vibrations while moving and walking.

The MS is more common among women than men and usually strikes at the age of 24 up to 40 years. According to the International Federation of MS, the average outbreak of the disease was 30 in 100000 in 2008, which rose to 33 in 100000 in 2013. The highest prevalence rate was in the North America (140 in 100000) and Europe (108 in 100000); whereas, the lowest was in the south of African desert (1.2 in 100000) and East Asia (2.2 in 100000). In Iran, the prevalence rate of MS is 15-30 in 100000. According to the WHO classification in the Atlas of MS in 2008, Iran belongs to the medium-range regions. Based on a study of the geographical distribution of MS, Iran is located in an area with a low MS prevalence rate.

The conducted research is partly in agreement with the first category, but violates the second. However, according to recent studies, it has become clear that Iran is now located in the area with medium to high prevalence.

Although many studies have been conducted on MS, the cause of this disease is still unknown. Yet, it is reported that a set of environmental causes, infections, genetic problems, immune system, viruses, toxins, and metabolic problems as well as materials such as nitric oxide are involved in its occurrence. Rn, as an external factor, was found to be effective on MS occurrence and aggravation. Radon is a gas that is chemically inert or ineffective and does not have any odor, color, and taste. It also decays naturally from $^{238}\text{U}$, $^{235}\text{U}$, and $^{222}\text{Th}$ in many types of soil, rock, and water produced in the earth. The $^{222}\text{Rn}$ is produced from the decay of $^{238}\text{U}$, as the most important source of internal radiation. Humans are generally exposed to it throughout their lives. Three radon isotopes ($^{219}\text{Rn}$, $^{220}\text{Rn}$, $^{222}\text{Rn}$) are in the form of gas and are released from the earth, stone, construction materials, and short-lived decay products gathered in closed spaces, especially in the building. $^{219}\text{Rn}$ and $^{220}\text{Rn}$ are not as important as $^{222}\text{Rn}$ due to their short lives. The most important sources of radon are soil, construction materials (e.g. rock, cement, etc.), water resources, and natural energy sources (such as gas, coal, etc.)

Radon density in the buildings is also widely related to the geological structure, structure of the building, and the ventilation system. Therefore, radon density depends on many different factors. Although soil, rock, and foundation structure around the building is the most important source of radon, radon caused by building materials may increase it's density in the indoor environment. The half-life of $^{222}\text{Rn}$ is 3.83 days that is enough to enter the indoor space of the building. Based on the WHO report, the effects of Rn on health are divided into two categories: the lung cancer and other diseases. Radon is known to be the second leading cause of lung cancer after cigarette smoking.
smoking. Radon also causes other diseases such as leukemia, liver cancer, cardiovascular disease, and MS\textsuperscript{14, 15}. Different studies are undertaken in this regard. As an example, MS has a significant positive correlation ($p < 0.01$) with Rn contents in indoor air. Based on these data, this hypothesis is proposed that the content of Rn in inhaled air is a risk factor in MS\textsuperscript{16}. Nevertheless, to the best of our knowledge, no review study has been ever conducted in recent years aiming to do a synthesis review on the literature in this regard. Thus, this study aimed to conclude the findings by reviewing the recent studies published since 1996.

**Materials and Methods**

In this review, keywords were selected using mesh, thoron, radon, action, MS, disseminated sclerosis, and multiple sclerosis. The search was conducted among the english sources and databases such as Science Direct, Google Scholar, Pub Med, Scopus, and ISI. The PRISMA statement was employed to select the articles (See Figure 1 for the flowchart).

As Figure 1 represents, 249 articles were found from the general search results. Then, the duplicates and unrelated articles were removed, so that 235 articles remained as the final database of the study, including 6 ecological studies, 1 review, 3 pilot, 1 guidelines, and 3 case-control studies. All the articles were published from 1996 to 2019. The criteria for selecting articles included the type of study, subject relevance, and the articles availability.

**Results**

Radon gas has not only positive functional effects, but also negative harmful effects\textsuperscript{17}. In this review, the harmful effects of Rn on the development of the MS disease were addressed. Radon gas has an important role in the development of various diseases including lung cancer, leukemia, skin cancer\textsuperscript{18}, gastric cancer\textsuperscript{17}, and MS\textsuperscript{14}.

Numerous studies have been conducted on the relationship between Rn and MS in the countries with high risk of MS. These countries included the United States\textsuperscript{18-20}, England\textsuperscript{21}, Ireland\textsuperscript{22, 23}, Norway\textsuperscript{24}, and Sweden\textsuperscript{25}. The relationship between the occurrence of MS and Rn has been...
proven statistically and inferentially in the studied countries by measuring the density of Rn. In other words, if the area had a high Rn density, the rate of MS prevalence was also high. Neuberger et al. carried out a research in the city of Kansas, the United States. Their results showed that the adjusted odds-ratio for MS prevalence increased by 1.98 (95% CI = 0.98 to 3.98, p = 0.06) for each unit increase in the time-weighted average of the natural log of radon exposure. Although not statistically significant, a trend of increase was observed in the probability of MS prevalence with each unit increase in the time-weighted average of the natural log of radon exposure. Furthermore, the study carried out in Wales, England, by Groves et al. showed that although a trend of increasing MS incidence was identified with increased radon concentration, the correlation was not statistically significant.

**Effective factors in increasing radon gas**

Factors affecting the increasing indoor Rn include the type of building materials used in the building, cracks in the walls and the floor, type of the rock and soil, foundation of the building, and used water resources. These factors are the main sources through which Rn enters into the building from the existing cracks and gaps on the floor of the building, so that Rn in the soil gradually accumulates under the building and its pressure rises. Because the air pressure inside the building is usually less than the air pressure in the soil, the Rn can enter the building through the wells, drains, and cracks on the building floors. The amount of Rn in the closed environment is different in different days and seasons and depends on the seams and cracks of the floor, walls of the building, amount of ventilation, and air exchange in the building. Besides, concentration of Rn is usually more in the lower floors of the building and the underground level than in the top floors.

**Methods of measuring Rn concentration**

Generally, in some ecological studies, the density of Rn has been measured by the radiation protection organization of the country. As a result, a certain amount is mentioned for each house. In some studies, the nuclear track method, active Alpha track dosimeter, radon gas map, charcoal canisters, whole body counter steel, and responding to the questionnaire were conducted based on ionizing radiation.

**The collected data on MS patients in the examined studies**

Data on MS patients in Norway were collected based on the urban type, the mortality rate in 1951-1977, and cases of men/women disability in 1978. Data on MS patients in Ireland were collected by administering a questionnaire to 67 patients who referred to an MS center (33% of responses). The questionnaire included the heating type, building age, number of building floors, sewage drainage system, and used water source. There respondents responded to these questions in accordance with their childhood experience (before age 15).

The MS 20-65 year old patients in Sweden were selected from a large hospital in the southern and southeastern Sweden. In this case-control study, the control people were selected randomly from the Sweden Registry Office. The data were collected using questionnaires sent to individuals by email. The questionnaire covered these issues: type of occupation, specific exposures to certain agents or animals at work, treatment or examination by X ray, contact with animals, and prolonged use of medications.

In a pilot study in Kansas, the United States, the MS patients were selected from a clinic. The selected patients were treated for two years, their age was more than 68 years, and lived in the same building since five years ago. The data were collected by a questionnaire. To collect the information about MS patients in Wales, the UK, clinical research database was employed. The study population consisted of all patients who lived in Wales, UK over the last five years. Data over death rates from motor neuron disease (MND) in the countries of England and Wales in 1981-1989 were obtained from the office of population, censuses, and surveys (OPCS).
Effective factors in increasing the occurrence of MS

In the examined studies, the prevalence of MS increased in North America, which was attributed to the radiological sources emitted by a nuclear fall-out in Washington State. The original sources noted that the geographical distribution of MS incidence was affected by the potential influence of air-borne radioactive debris from atmospheric nuclear tests. Furthermore, presence of a major nuclear-material processing facility in that state was a more significant effective factor in this regard. The areas in these studies included East Washington, Northern Iowa, Norway, and the northern areas of the United States that showed the highest levels of Rn and MS 19.

Another factor affecting the prevalence of MS is the exposure to high levels of Rn and some environmental factors during childhood, before age15, especially for men 22, 23, 29. Furthermore, it was found that the prevalence rate of MS in arid regions was more than coastal areas 19. Regarding latitude, in the Norwegian and English studies, northern regions located at higher latitudes had the highest prevalence rate of MS 24, 29. The other environmental factors that cause MS include sunshine, carbon monoxide, ultraviolet radiation, temperature, latent virus, ionizing radiation, pets, and toxic chemicals 19.

Given that the MS virus is mentioned as one of the causes for developing MS, the related hypothesis is that some types of viruses may remain latent in the body organs for a long time. These viruses can be re-activated due to a variety of factors, among which the most important one is exposure to high doses of ionizing radiation 24. The reason is that Rn is in the group of ionizing radiation derived from radon decay as well as alpha and beta particles. Release of these products have a risk of irradiation in causing MS 15, 19, 24. This gas has a particular dependence on fat, so it is stored in organs rich in fat-like neural systems and narrow bones. It also can cause breast cancer or tissue cancer 20, because the pod myelin sheaths (nerve fibers), made of fatty materials, are attacked in MS patients. Thus, it can be concluded that the pod myelin fat is solved by environmental radon 18, 31. The most convincing scientific studies on MS and ionizing radiation conducted in Norway showed that radon was an effective factor in MS 24.

Table 1: Characteristics of the included studies over the relationship MS prevalence with concentration of Rn in the environment

<table>
<thead>
<tr>
<th>study</th>
<th>Year and country</th>
<th>Study Design</th>
<th>MS potions database</th>
<th>Number</th>
<th>Age</th>
<th>Domestic radon concentration database</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groves, 2016 21</td>
<td>2005-2012 in England and Wales</td>
<td>Ecological</td>
<td>The Health Improvement Network (THIN) clinical research database</td>
<td>115 case</td>
<td>15-85</td>
<td>Radon gas map and utilized data at postcode sector level</td>
<td>0.096</td>
</tr>
<tr>
<td>Neuberger, 2011 24</td>
<td>2000-2006 In Kansas, USA</td>
<td>A pilot case control study</td>
<td>The University of Kansas Medical Center’s Neurology Department clinic</td>
<td>97 MS patients and 51 non-MS controls</td>
<td>Mean age: 42.35</td>
<td>Long-term alpha track dosimeters for 5-6 months in the winter</td>
<td>0.06</td>
</tr>
<tr>
<td>Momcilovic, 2005 29</td>
<td>1988-2004 In Grand Forks, North Dakota</td>
<td>Ecological</td>
<td>Participating in community-based bioavailability studies over a period of 13 years</td>
<td>315 female and 179 male</td>
<td>-</td>
<td>Whole body counter data, steel room Bi 214 background</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Bolviken, 2003 24, 2001 31</td>
<td>1987-1989 in 6 of Norway’s 19 counties</td>
<td>Ecological</td>
<td>Based on municipal rates for the sum of deaths in the period from 1951 to 1977 and disability pension cases in 1978 for both sexes</td>
<td>195 case in rural and in urban areas</td>
<td>-</td>
<td>The nuclear track method for 6-month periods</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Study</td>
<td>Year and Country</td>
<td>Study Design</td>
<td>MS Potions Database</td>
<td>Number of Population Study Case of MS</td>
<td>Age (Year)</td>
<td>Domestic Radon Concentration Database</td>
<td>P Value</td>
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<tr>
<td>Carroll, 2005 23</td>
<td>1992 in Ireland</td>
<td>Pilot</td>
<td>Communications with General Practitioners, Neurologists, County Physicians, Hospital Coding Lists, Local MS Societies, Respite Care Facilities and Interferon Prescription Lists.</td>
<td>671 case</td>
<td>36.8</td>
<td>Radiological Protection Institute of Ireland (RPII) by sampling homes in 10-Km grid squares</td>
<td>No</td>
</tr>
<tr>
<td>Neilson, 1996 28</td>
<td>1981-1989 in England and Wales</td>
<td>Ecological</td>
<td>Data for deaths from motor neuron disease (MND) mortality were obtained from the Office of population censuses and Surveys (OPCS)</td>
<td>9220 Deaths</td>
<td>15 to 85 upper</td>
<td>The National Radiological Protection Board (NRPB) by sampling homes in 10-Km grid squares</td>
<td>&lt; 0.05  &lt; 0.01</td>
</tr>
<tr>
<td>Eidbo &amp; Prater, 2004 20</td>
<td>1993 in 92 of Iowa's 99 counties</td>
<td>Ecological</td>
<td>National Multiple Sclerosis Society (NMSS) - Iowa Chapter</td>
<td>100000 population (cases/100k)</td>
<td>All ages</td>
<td>Environmental Protection Agency (Pekmezovic et al.) 9-page questionnaire x-ray examinations, radiological work, cosmic radiation, gamma radiation and treatment with ionizing radiation</td>
<td>No</td>
</tr>
<tr>
<td>Axelson, 2001 25</td>
<td>1981-1985 in the two largest hospitals in south-central Sweden that two counties covered by these hospitals</td>
<td>Case-control</td>
<td>Cases of MS obtained in the two largest hospitals in south-central Sweden and controls were randomly drawn from this register of the population in these two counties from where the cases were obtained</td>
<td>From 83 cases (response rate 89%) and 467 controls (response rate 80%) in these two counties</td>
<td>20-65</td>
<td>No</td>
<td></td>
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<tr>
<td>Axelson, 2001 25</td>
<td>1983-1988 in two counties in southeast Sweden</td>
<td>Case-control</td>
<td>Cases of MS obtained at the main hospitals in two counties in southeast Sweden and controls were randomly drawn from this register of the population in these two counties from where the cases were obtained</td>
<td>91 Responding cases (response rate 94%) and 348 population controls (response rate 87%)</td>
<td>20-65</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Lykken, 2008 17</td>
<td>In Grand Forks, North Dakota</td>
<td>Case-control</td>
<td>The Grand Forks MS Support Group, subjects with no apparent health problems were recruited locally</td>
<td>15 MS patients and 15 non-diseased controls</td>
<td>-</td>
<td>The $^{222}$Rn was measured with charcoal canisters</td>
<td>No</td>
</tr>
<tr>
<td>Gilmore, 2003 22</td>
<td>1971-1981 in Northwest Ireland</td>
<td>Pilot</td>
<td>Membership of the MS Society in Ireland</td>
<td>67 respondents, response rate 33%</td>
<td>Before the age of 15</td>
<td>Radiological Protection Institute of Ireland (RPII)</td>
<td>No</td>
</tr>
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</table>
Discussion

Based on the findings, some of the reviewed studies over the relationship between Rn and MS were undertaken in countries where the prevalence of this disease was high. By measuring the concentration of Rn in these countries, a relationship was found between the incidence of MS and Rn. However, given that most of these studies were of ecological type, further precise case-control studies are required for finding the relationship of indoor Rn concentration and other environmental factors with development of MS.

The ecological studies seek to measure the density of in each building among the MS patients who referred to the treatment centers. The results of these studies indicated that increased density of Rn had a positive significant relationship with MS. In experimental studies, the density of Rn is measured by measuring devices. The data from MS patients were collected via questionnaires. The findings of these studies also revealed a relationship between the density of Rn and MS.

Gross et al. conducted a retrospective study on the incidence of MS and its association with Rn concentrations in the UK's Welsh area. In this study, 115 individuals were selected and the amount of Rn was calculated using a map of Rn concentration in the region, which was specified for each house. The results showed that although the prevalence of MS increased with increasing of the Rn concentration, the correlation was not significant.

Neoberger et al. examined a relationship between MS and concentration of indoor Rn in the city of Kansas, USA. In this research, 97 MS patients with with less than five years of disease diagnosis and 51 healthy controls were employed. To measure the concentration of Rn in the air, active alpha dosimeters were used for a period of six months for people who had lived in the same houses for at least five years prior to the study. The results showed that the association of MS with Rn concentration was not statistically significant, but the increasing trend of the MS outbreak probability was found to increase with each unit in the average remaining radon exposure time.

Bolviken et al. studied the association between the concentration of indoor Rn and airborne magnesium loss on MS patients in Norway. The researchers applied the alpha groove dosimeter in 7500 residential homes randomly selected in a continuous period of six months and found a significant positive correlation (p < 0.01) between MS and Rn concentration in the air.

Conclusion

As the finding revealed, Rn and its daughters, in respiratory air, are considered as serious risk factors of MS. Due to limited resources and data on MS patients, the relationship between Rn and MS cannot be definitely denied. Although the concentration of Rn was effective on MS, this finding needs further exploration.

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Conflict of interest

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References

4. Ghanati EH, Daghighi A. Economic expenditures of multiple sclerosis medications and feasibility of...
providing health insurance policies for medications. Journal of Health Administration. 2011;14(45):37-54.
27. Groves-Kirkby CJ, Denman AR, Campbell J, et al. Is environmental radon gas associated with the incidence of neurodegenerative conditions? A retrospective study of multiple sclerosis in radon.