RESIDENTIAL RADON EXPOSURE AND MULTIPLE SCLEROSIS: A PILOT STUDY

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This project was funded by the National Multiple Sclerosis Society (Grant No. PP1212).

Abstract

Environmental risk factors for Multiple Sclerosis (MS) are not clearly understood, although vitamin D and sunlight exposure are thought to be protective. MS prevalence increases with increasing latitude, in a pattern similar to that of residential radon exposure, particularly in the U.S. To further study this relationship, a pilot study was conducted of ninety-seven MS patients and 51 non-MS patient controls. Patients had been diagnosed less than five years. An interview of the 148 patients included time spent on various living levels within the home as well as demographic, medical, residential, occupational, smoking, and other information. In a subset of the group who had lived in their homes for at least five years prior to diagnosis - 25 MS and 21 control patients - radon detectors were placed for six months on different living levels in their homes. Time weighted average levels of radon exposure were calculated. Statistical methods included the t-test, odds-ratios, and logistic regression. Weekly cumulative radon values averaged 13,802.48 Bq m^{-3} h for cases and 9,369.14 Bq m^{-3} h for controls. 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 an increase in the probability of MS prevalence with each unit increase in the time-weighted average of the natural log of radon exposure was found. No statistically significant protective effect was found for either reported sunlight exposure or vitamin D use. Discussion of the strengths and weaknesses of the study is provided, as are recommendations for future research. A small sample size is a limiting factor in our conclusions.

Introduction

Multiple Sclerosis (MS) is a chronic autoimmune disease that affects the brain and spinal cord in the central nervous system. It acts by attacking the myelin sheath, a primarily fatty tissue insulating the nerve fibers (National Multiple Sclerosis Society, 2010). The myelin sheath facilitates the conduction of nerve impulses and can be damaged either directly or indirectly through autoimmune reactions or free radical attack. Demyelinization can cause scarring and hardening of the nerve fibers, resulting in numbness, weakness, pain, paralysis, and vision loss. The sheath is formed and maintained by oligodendrocytes.

The cause of MS is unknown, but is widely believed to be a T-cell mediated inflammatory process with an unidentified antigenic target (possibly a component of myelin). Disregulation of the immune system may play a major role in the development of this disease process. It is estimated that there are approximately 10,000 new (incident) cases of MS per year and approximately 350,000 to 400,000 people currently affected with MS (prevalent cases) in the U.S. The disease has a higher prevalence in northern latitudes (in the northern hemisphere), leading to the hypothesis that sunlight and/or vitamin D may be protective (Fig.1). It also has a higher prevalence among whites and women. Symptoms are most common among those aged 20 to 40.

Risk factors for the development and/or progression of this disease include female gender, Caucasian race, genetic susceptibility, and family history of MS. Hypothesized factors include reduction in solar ultraviolet radiation, multiple viruses (canine distemper, Epstein-Barr, Human Herpes 6, etc.), sex hormones, dietary fat/fatty acids, reduction in Vitamin D, environmental agents more common in cold climates, and organic solvents (Ebers and Sadovnick, 1993; Weinshenker, 1996; Hogancamp et al, 1997; Kurtzke and Page, 1997; Landtblom, 1997; McMichaael and Hall, 1997; Hernan et al, 1999; Freedman et al, 2000; Rosati, 2001; Coo and Aronson, 2004; Goldacre et al, 2004; Munger et al, 2004; Neuberger et al, 2004; Ozgocmen et al, 2005; Ascherio and Munger, 2007; Holick, 2007; Islam et al, 2007; Sloka et al, 2008; Beretich and Beretich, 2009; Westberg et al, 2009; Handel et al, 2010; Noonan et al, 2010) .

Lack of sunlight exposure is considered a strong candidate as an environmental risk factor for MS (Ascherio and Munger, 2007; Handel et al, 2010; Lucas et al, 2011) .The pronounced north - south gradient in MS prevalence in the U.S. [Figure 1] and elsewhere (Sloka et al, 2008) has long suggested a protective effect of sunlight or ultraviolet radiation (Beretich and Beretich, 2009), possibly through the mechanism of vitamin D production and/or immune suppression (McMichael and Hall, 1997) or anti-oxidant activity. Vitamin D may help maintain the immune system and help regulate cell growth and differentiation. Dairy products supply the majority of vitamin D in the diet, with nearly all milk fortified with vitamin D. In a study in Turkey, MS patients had significantly lower vitamin D levels than controls (17.3 ng/mL versus 43.1 ng/mL; $p<0.001$) (Ozgocmen et al, 2005). In a study of nurses, increased intake of dietary vitamin D in food or as a supplement was inversely associated with the risk of MS (Munger et al, 2004).

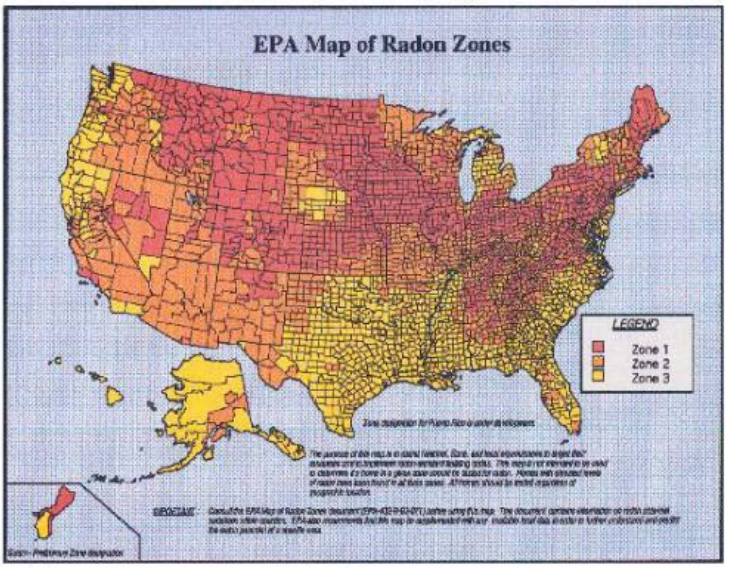

Figure 1. Geographic Distribution of Residential Radon in Homes.

Some have questioned the validity of the north-south MS gradient because different study methodologies were used. However, a recent study of three geographic areas in the U.S., which used similar MS case finding methodology, found that the north-south geographic pattern holds and remains strong after age adjustment (Noonan et al, 2010). In another study in North America childhood sun exposure significantly reduced the risk of MS in monozygotic twins (Islam et al, 2007). In the United Kingdom, skin cancer was significantly less common in people with MS than in a comparison group (Goldacre et al, 2004). The risk of mortality from MS in Sweden decreased significantly with increasing occupational exposure to ultraviolet light (Westberg et al, 2009). Sun exposure, actinic skin damage, and higher serum vitamin D levels were associated with a reduced incidence of first demyelinating events in Australia (Lucas et al, 2011). In 24 states of the U.S., mortality from MS was significantly negatively associated with residential exposure to sunlight at time of death (Freedman et al, 2000). A recent study of seasonal prevalence of MS, using MRI examinations to study the appearance of lesions found a strong seasonal pattern in subclinical MS activity, with an elevated likelihood of subclinical disease in the March-August period. Correlations were strongest for increased solar radiation and daily temperature (Meier et al, 2010).

Ionizing radiation may also be an environmental risk factor for MS (Gipps and Kidson, 1984; Axelson et al, 2001; Bolviken et al, 2003; Gilmore and Grennan, 2003; Lykken et al, 2008). In a pooled analysis of two case-control studies in Sweden, an increased risk for MS was found for those who reported exposure to radiological work (OR = 4.4, 95% CI = 1.6 to 11.6) and to X-ray examinations (OR = 1.8, 95% CI = 1.2 to 2.6). Ionizing radiation may cause free radical formation and oxidative damage (Axelson et al, 2001). In a study of 40 MS patients and 30 age and sex matched controls in Australia, MS patients exhibited significantly more cellular sensitivity to ionizing (γ) radiation than controls ($p < 0.0001$) (Gipps and Kidson, 1984).

Radon and radon progeny exposure may also be a risk factor for MS (Bolviken et al, 2003; Gilmore and Grennan, 2003; Lykken et al, 2008). Radon is lipophilic and has a similar geographic distribution to that of MS, with higher prevalence in northern latitudes (http://www.epa.gov/radon/zonemap.html). Females, who have a higher prevalence of MS than males, may also stay at home more than males and thus have higher exposure to residential radon. In Norway, the mortality rate of MS was significantly positively associated with the

content of radon in indoor air (Bolviken et al, 2003). In Northwest Ireland, MS prevalence was higher in areas with underlying radon producing granites (Gilmore and Grennan, 2003). In Grand Forks, North Dakota there was a 2.4-fold increase in ^{222}Rn levels in bedrooms of homes of 15 MS patients compared to 15 non-diseased controls. Preliminary data indicated that the whole body retention of ^{214}Bi (radon progeny) was 37 percent higher in MS patients than in the controls (Lykken et al, 2008). Thus, there are three ecological data sets (U.S., Norway, and Northwest Ireland), one case-control study (North Dakota), and one demographic data set (females with higher MS prevalence rates) that could indicate a positive association of residential radon exposure with MS prevalence.

Our purpose was to evaluate the association between MS prevalence and radon at the individual level, while controlling for other potential risk factors; the first study to do so.

Methodology

Physician confirmed definite MS cases and non-MS controls were obtained from the University of Kansas Medical Center's Neurology Department clinic. Patients were eligible if they came in for treatment during a two year period, were age 18 or greater, resided within 200 miles of the medical center (in Kansas or Missouri), were diagnosed subsequent to 12/31/99, and had their disease prevalent during the period 2000-2006. Controls were selected during the same time period as the cases and were group matched to cases on gender and age (± five years). Controls were selected randomly from patients with migraine headache, stroke, peripheral neuropathy, back pain, spinal cord injury, head trauma, and restless leg syndrome.

A questionnaire was first pilot tested on several individuals unrelated to the study and then administered to all patients in the study while they were being treated or seen at the medical center. Questions were focused on the 20 year time period prior to diagnosis and included: history of skin cancer, severe sunburn, sun exposure, outdoor jobs, sun bathing history, education, work and residential history, hobbies, sports, pets and pet illnesses, chemical exposures, smoking history, family history of MS, and time spent in different rooms and levels of the house during the week.

Permission was sought to do a radon test in their home for those patients who resided for five or more years in the same home prior to diagnosis. The test utilized long-term alpha track dosimeters (Radtrak®) placed in the subject's bedroom, basement, and living room for 5-6 months in the winter. Detectors were placed and retrieved by the Principal Investigator and were located either on furniture (taped to the furniture or to a plate) or hung from the ceiling (particularly in unfinished basements) using a standard length tape provided by the manufacturer. The investigator checked all location measurements upon retrieval of the detectors to be certain they were not moved. All detectors were immediately re-sealed in their original wrappings, sealed in plastic bags within a few days upon retrieval from the home, and sent from the investigator's office via Federal Express to the Landauer Company in Glenwood, Illinois for analysis. Ten percent of the detectors were duplicates, five percent were spiked positives (from the U.S. Environmental Protection Agency's [EPA] lab in Las Vegas, Nevada), and five percent were blanks. After obtaining a copy of the measured radon test results from Landauer, a copy was mailed to all individuals who had their home tested, along with a copy of the EPA guideline on radon for homeowners. Each radon test result report to the homeowner listed the detector number, the detector location in the house (floor, room), the measurement period (month, day, year), and the measured radon value (mean, standard deviation).

All data were double entered into the database and simple edit checks were performed. Several statistical tests were utilized, including the chi-square, Fisher's exact, and logistic regression. A multivariable logistic regression analysis was performed to adjust for all variables. A crude odds-ratio and 95% CI were calculated for the interview variables. For p values less than 0.2 an adjusted odds-ratio and 95% confidence interval was calculated for questionnaire data that was both robust (exposures reported by 10 or more cases or five or more controls) and of greatest potential relevance to the study.

Time weighted average (TWA) levels of radon exposure in the home for a typical week were calculated blind as to case or control status. To obtain the TWA, the estimated weekly time spent on different living levels in the home was multiplied by the measured radon value for that living level. Total weekly time in the home was also utilized as a variable to see if cases spent more time in the home than controls. Information concerning the individual's location in the home (including room and living level) was obtained from the interview. The t-test was utilized to determine if the mean weighted radon level and the mean time in the home differed significantly between cases and controls. An excess odds-ratio for each unit increase in the natural log (ln) of radon was computed using a logistic regression model, where the natural log transformation was used on the time weighted average radon values.

Written informed consent was obtained from all participants. The project was approved by the Human Subjects' Committee of the University of Kansas Medical Center.

Results

Interview information was obtained for 148 patients, including 97 cases (28 male, 69 female) and 51 controls (20 male, 31 female). The mean age of the male cases was 42.4, whereas for male controls the mean age was 53.4. Thus, the age match for males was not achieved. For females, the mean age of the cases was 42.3 and the mean age for controls was 44.7, less than the intended plus or minus five years [Table 1].

Mean Age (n)	**Males**	**Females**
Cases (97)	42.4 (28)	42.3 (69)
Controls (51)	53.4 (20)	44.7 (31)
Total (148)	48	100

Table 1. Age Distribution of Cases and Controls.

Cumulative weekly hours at home were 97.3 for cases and 101.4 for controls; a difference that was not statistically significant (p=0.45). However, when the data were stratified by gender, the data indicate that female controls spent a marginally significant more hours at home than cases (116.4 versus 101.1) (p=0.05); for males the corresponding figures were 87.6 for cases and 90.2 for controls (p=0.74) [Table 2].

Hours	Cases	Controls	p-value
Weekly Hours at Home (T)	97.3	101.4	0.45
(M)	87.6	90.2	0.74
(F)	101.1	116.4	0.05

Table 2. Average Weekly Hours at Home Prior to Diagnosis.
[n=148 individuals, 97 cases and 51 controls]

For the total patient population there were statistically significant increases in risk for MS for Education Level (College graduate or higher) (OR = 2.33, 95% CI = 1.10 to 4.31) and Drinks Milk (OR = 2.13, 95% CI = 1.05 to 4.32). For either yes/no or quantitative hours there was no statistically significant increased protective effect for either sunlight exposure or vitamin pill intake. There was a significant decrease in risk for skin cancer, but this was based on eight reports. Sunscreen use seemed to increase risk, but this was not statistically significant. In contrast, both sunbathing and severe sunburn seemed to increase risk. Results were the same with and without age adjustment. Milk may contain 400 International Units of vitamin D, which has been considered to be possibly protective. There were statistically significant decreases in risk for Live on Farm (OR = 0.34, 95% CI = 0.16 to 0.70), Serious Illness (OR = 0.36, 95% CI = 0.18 to 0.73), and Odors on the Job (OR = 0.49, 95% CI = 0.24 to 0.9998) [Table 3]. None of the other interview variables (e.g., smoking, occupation, chemical exposures, hobbies, pets, etc.) had any close relationship with MS prevalence.

Variable	Odds-Ratio	95% CI
Education Level	**2.33**	**1.10 to 4.31***
Drinks Milk	**2.13**	**1.05 to 4.32***
Sunscreen Use	3.46	0.74 to 16.10
Severe Sunburn	1.89	0.94 to 3.80
Sunbathed	1.57	0.71 to 3.49
Family History of MS	1.17	0.38 to 3.75
Tanning Bed Use	1.05	0.50 to 2.20
Outdoor Jobs	0.71	0.34 to 1.51
Multivitamin Pill	0.61	0.29 to 1.29
Vitamin Pill	0.57	0.29 to 1.13
Odors on the Job	**0.49**	**0.24 to 0.9998***
Serious Illness	**0.36**	**0.18 to 0.73***
Lived on Farm	**0.34**	**0.16 to 0.70***
Skin Cancer	**0.16**	**0.03 to 0.81***

*** p < 0.05**

Table 3. Interview Variables Showing Increased or Decreased Prevalence Odds-Ratios.

For either yes/no or quantitative hours, there was no statistically significant increased protective effect for either sunlight exposure or vitamin pill intake. While there was no statistically significant difference for outdoor jobs between cases and controls, there was a tendency for reduced risk. In addition, the overall population of males, which has a much reduced risk of MS in general, had significantly more years of exposure to outdoor jobs than the overall population of females (45.76 versus 6.79, $p<0.0001$) [data not shown].

Radon levels were measured in the homes of 46 patients who had lived in their current home for five or more years prior to diagnosis. These included 25 cases (seven male and 18 female) and 21 controls (12 male and nine female). Sixty radon detectors were placed in 25 case homes and forty-five radon detectors were placed in 21 control homes [Table 4]. Where feasible, each living level of the home was sampled. All but two detectors in control homes were recovered; two detectors were thrown out by the homeowners.

Category	Males	Females	Total Individuals	Total Detectors
Cases	7	18	25	60
Controls	12	9	21	25
Total	19	27	46	105

Table 4. Current Radon Measurements.

Eleven detectors were co-located, seven were blanks, and five were positively spiked. Detector comparisons showed no significant differences between what was measured and what was expected. Uncertainty estimates on the detectors ranged from two percent at the highest radon level to 20 percent at the lowest.

For 25 cases the mean radon level in the basement was 230.51 Bq m^{-3} (6.23 pCi L^{-1}), whereas for 21 controls the mean level was 211.27 Bq m^{-3} (5.71 pCi L^{-1}). In the bedroom, the corresponding mean values were 125.06 Bq m^{-3} (3.38 pCi L^{-1}) for cases and 80.29 Bq m^{-3} (2.17 pCi L^{-1}) for controls [Table 5]. Living room values were also higher for cases than controls and were intermediate between basement and second floor readings. In many cases the bedroom was on the same living level as was the living room. When data were stratified by gender, cases consistently had higher readings than controls on all living levels, including the bedroom, living room, and basement (data not shown).

Living Level	Cases (n=25)	Controls (n=21)
Basement (pCi/L)	6.23	5.71
Bedroom (pCi/L)	3.38	2.17

Table 5. Average Radon Value by Living Level in Home.

Comparing the weekly cumulative time-weighted average radon values, the cases averaged 13,802.48 Bq m^{-3} h (373.04 pCi L^{-1} h), whereas controls averaged 9,369.14 Bq m^{-3} h (253.22 pCi L^{-1} h) ($p=0.17$) [Table 6].

Hours	Cases	Controls	p-value
Cumulative TWA radon value (pCi/L-Hours)	373.04	253,22	0.17

Table 6. Average Cumulative Weekly Time Weighted Hours of Radon Exposure.

The initial logistic model that was constructed used a cutpoint determined by the median value of the time-weighted average value of radon in the homes of the controls. This was done to dichotomize the continuous variable of radon. The value chosen - 6,482.40 Bq m^{-3} h (175.20 pCi L^{-1} h) - resulted in an unadjusted odds-ratio of 1.62 (95% CI = 0.50 to 5.28), indicating both an increased prevalence of MS as radon increased and an odds-ratio that was similar to that obtained from the continuous variable analysis, which was calculated subsequently. For females, the unadjusted odds-ratio was 1.72 (95% CI = 0.49 to 12.89) [Table 7].

Analysis Type	OR	95% CI
Unadjusted (high/low)	1.62	0.50 to 5.28
Unadjusted, females (high/low)	2.50	0.49 to 12.89
Unadjusted, ln (continuous)	1.72	0.92 to 3.44
Adjusted*, ln (continuous)	1.98	0.98 to 3.98

*Adjusted for age, gender, and severe sunburn.

Table 7. Unadjusted and Adjusted Prevalence Odds-Ratios for Radon Exposure. [N=46 individuals, 25 cases and 21 controls].

Because the distribution of the radon exposure was skewed, the radon exposure levels were transformed by taking the natural log (ln) of the radon exposure. For this model, the value of ln of the weekly radon exposure was then used as a continuous variable in a logistic model, with MS as the outcome variable, to compare cases to controls. The typical model for predicting log-odds is:

$$\ln\left[\frac{\pi(x)}{1-\pi(x)}\right] = \alpha + \beta x \text{ and } \pi(x) = \frac{e^{\alpha+\beta x}}{1+e^{\alpha+\beta x}}$$

when predicting the probability that a patient has MS for a radon exposure x. The transformation changes the equations to:

$$\ln\left[\frac{\pi(\ln(x))}{1-\pi(\ln(x))}\right] = \alpha + \beta(\ln(x) \text{ for the log odds and } \pi(\ln(x)) = \frac{e^{\alpha+\beta\ln(x)}}{1+e^{\alpha+\beta\ln(x)}} = \frac{e^{\alpha} * x^{\beta}}{1+e^{\alpha}x^{\beta}}$$

for the probability. The log-odds using the transformed values are interpreted as the change in risk per unit increase in the transformed variable. When the value is increased by one unit in the transformed scale this corresponds to a change of one order of magnitude using base e in the original scale. For example, in the transformed scale a value of 4 would be equivalent to a measurement of e^4 = 54.6 Bq m^{-3} h of radon exposure in the original scale. An increase of one unit in the transformed scale would correspond to a measurement of e^5 = 148.4 Bq m^{-3} h of radon

exposure in the original scale, for an increase of 93.8 Bq m^{-3} h of radon exposure for one unit increase in the transformed scale.

This transformation resulted in an unadjusted odds-ratio for radon of 1.72 (95% CI = 0.92 to 3.44). When severe sunburn was included in the model, the adjusted odds ratio for the natural log of radon exposure was 1.80 (95% CI = 0.92 to 3.53, p = 0.09). When age, gender, and severe sunburn were included in the model the adjusted odds ratios were 3.67 (95% CI = 0.96 to 14.08, p = 0.06) for increase in severe sunburn, 4.04 (95% CI = 1.018 to 16.00, p =0.05) for female gender, and 1.98 (95% CI = 0.98 to 3.98, p = 0.06) for each increase in one unit of the ln of radon exposure [Table 7]. For each gender separately the odds ratio was 2.02 for males and 2.06 for females; results that were virtually identical and not statistically significantly different from each other. Thus, the odds-ratio for MS prevalence increased almost two-fold for each unit increase in the ln of the time-weighted average of radon exposure. It is important to stress that a unit increase in the transformed variable is actually an order of magnitude increase in the original scale.

Discussion

Specific environmental factors affecting the development and exacerbation of MS remain unclear. While there were a number of potential environmental risk factors for MS, the primary candidate for a protective effect going into this study was ultraviolet radiation and/or vitamin D use. There was also some evidence of a positive association at the ecological level with residential radon exposure as well as one case-control study that found a positive association with residential radon exposure.

Interviews with 148 individuals did not, with one exception, find any statistically significant increase in risk with either sunlight exposure or vitamin D intake. The sole exception was an increase in risk with the variable drinks milk. On the other hand, there were a number of statistically significant variables indicating a protective effect of sunlight exposure or vitamin D. These included skin cancer (based on very few cases) and lives on a farm (with presumed higher levels of sunlight exposure). A number of non-statistically significant associations pointed in the direction of a protective effect. These included vitamin pill or multivitamin pill use and outdoor jobs. Thus, there is some support for a protective effect of sunlight exposure and vitamin D on the risk of MS. The fact that education level is significantly elevated is a generally accepted finding. The presence of serious illness as a protective variable is possibly due to the selection of a control group from a neurological clinic, with possible previous medical conditions.

After measuring radon levels in 46 homes, a borderline statistically significant association was found between an increase in one unit of the ln of the time weighted average of residential radon exposure and an almost two-fold increase in the prevalence of MS. This is despite the fact that the MS cases spent somewhat less time in their homes than did the controls. Radon levels were consistently higher in case homes than control homes when stratified by living level or by gender.

Dose levels of radon and decay products actually received by the brain and the cranium (skull) have not been settled with certainty and were not measured in this study. Both radon gas and progeny can circulate in the bloodstream (National Academy Press, 1988, 1999; Harley and Robbins, 1992; Lykken and Momcilovic, 2004) and cross the blood-brain barrier into the brain and spinal cord. Radon is lipid-soluble and can concentrate more in fatty tissue, including the brain (Momcilovic et al, 2001, Lykken and Momcilovic, 2004; Momcilovic and Lykken, 2007). It accumulates in the cranium, resulting in increased ^{214}Bi gamma ray emissions and altered electroencephalographic signals (Lykken et al, 1990; Momcilovic et al, 2001). A significant

fraction of radon and decay products inhaled by cyclists was found to be stored in the body. ^{214}Bi and ^{214}Pb activities have also been detected in post exposure urine of an individual exposed to radon for 60 m (Lykken et al, 1990). Radon was flushed out of a cyclist's body after breathing radon free air for one hour (Lykken et al, 2000). Emitted alpha, beta, and gamma radiation from resulting radioactive decay could cause genetic mutations, overstimulation of the immune system, and/or damage either to DNA or DNA repair mechanisms (Calabrese and Baldwin, 1998). Numerous free radicals are produced, which could result in free radical attack either directly or indirectly on the blood-brain barrier, the myelin sheath, or on the oligodendrocytes. Free radicals can cause protein oxidation, lipid peroxidation, and DNA intercalation as well as impair signal transduction, cell membrane function, and gene expression (Momcilovic et al, 2001). Approximately 24.5 MeV of alpha and 10.1 MeV of beta energy are deposited locally as ^{222}Rn decays to ^{206}Pb, with not all occurring in the lung.

Particulate radon progeny, including both the short term decay products and the long term decay products (e.g., ^{210}Pb, with a half-life of 22 y and ^{210}Po, with a half-life of 138 d) could directly or indirectly damage the myelin sheath. Thus, radon and progeny could cause immune or oxidative reactions in the central nervous system that could lead to the development and/or the exacerbation of MS. In addition, all radon progeny are heavy metals, which are highly neurotrophic and neurotoxic. "The heavy metal radon decay products remain trapped in the brain, where they emit additional gamma radiation and alpha and beta particles over their lifetime and thus add chemical injury to the radiation injury of the brain" (Momcilovic et al, 2001).

In a recent study for every Bq of ^{222}Rn per liter volume in the ambient air there were about 21 Bq of ^{214}Bi per liter of the human body volume. Thus, "the whole body ^{214}Bi per unit volume in men and women was much higher than that of the ^{222}Rn in the home ambient air ($p<0.05$)." Whole body counter activity was measured in 385 women and 179 men and compared to the natural log activity of ^{222}Rn and ^{214}Bi in their home. A statistically significant correlation was found between ^{214}Bi concentrations and total body fat in women, but not men, possibly due to the higher fat mass in women. This study also found a seasonal pattern of radon concentration and ^{214}Bi activity in the human body (Momcilovic and Lykken, 2007).

Elevated levels of ^{210}Po and ^{210}Bi were found in the frontal and temporal lobes of Patients with Alzheimer's and Parkinson's disease (Momcilovic et al, 2001). In ongoing research on nanoparticles (< 100 nm), which could include ultrafine radon progeny, particles were translocated to the brain in monkeys and rats via the olfactory bulb, which circumvents the blood brain barrier (Oberdorster et al, 2004; Elder et al, 2006; Oberdorster et al, 2009). The authors indicate that this pathway is relevant in humans.

A study of tissues from 41 uranium miners and 11 unexposed individuals included tissues from 19 organs. Radiation values were measured in lung, kidney (cortex), brain, spinal cord, and other locations. It was determined that dose to bone may exceed in some cases the maximum permissible dose-rate of 30 rem/y. Highest concentrations of ^{210}Po and ^{210}Pb were observed in the skeleton of these miners; bone would also include the skull (cranium). Sources of ^{210}Pb which contributed to high skeletal burdens included inhalation of short-lived radon daughters, inhalation and possible ingestion of ^{210}Pb in the mine atmosphere, and inhalation of ^{222}Rn, which is stored in body fat; "upon decay, the daughters translocated via the blood stream to the skeleton." Doses measured in brain tissue were obtained from one individual, a 55 y old male. The level ranged from 1 to 50% of the dose measured in lung tissue. Levels of ^{210}Po and ^{210}Pb equaled and even exceeded dose measured in the lung and increased as the length of time on the

job increased (Blanchard and Moore, 1971). Concentration of ^{210}Pb was shown to increase with increased radon daughter exposure.

"There is no international consensus on the calculation of doses from inhaled radon decay products" (Kendall and Smith, 2002). Nonetheless the authors used the PLEIADES code and type M and type F kinetics, where F refers to fast half-time - and M to moderate time - with respect to absorption to blood. They found that the effective dose to the brain for ^{218}Po, ^{214}Pb, and ^{214}Bi (short-lived progeny) was two orders of magnitude lower for the brain than for the lung. The annual dose at 200 Bq m^{-3} to the brain was 0.15 mSv, compared to 35.8 mSv to the lung for type F aerosols. The dose for ^{222}Rn was 0.06 mSv for the brain, compared to 1.2 mSv for the lung. However, for bone surfaces the annual dose for type F decay products at 200 Bq m^{-3} was 1.48 mSv for type F aerosols. Thus, while the calculated dose to the brain tissue was relatively low, it was still present, and the skull would also have an increased dose. The gas and daughter products circulated throughout the bloodstream, as illustrated by the annual dose at 200 Bq m^{-3} of 5.20 mSv to the kidney for Type F aerosols. As mentioned above, radon is more soluble in tissues with a higher fat content; fat receives the highest dose of all tissues outside the lung. The linear no threshold model operates and low doses of radiation lead to small deleterious effects. "If radon is allowed to reach equilibrium with its decay products there will be equal activities of each. In practice, the later decay products tend to be lost by various processes, particularly deposition on surfaces, sometimes called plateout" (Kendall and Smith, 2002).

Thus, while the major known toxic effect of radon is on the lung (National Academy Press, 1999), some percentage of dose enters the brain, is absorbed by the skeleton, and may consequently cause damage to a crucial area. Such a low dose - as well as the accumulated radon progeny - could possibly act either to stimulate the immune system or damage the oligodendrocytes, even if the dose is insufficient for carcinogenesis. There is disagreement, however, as to the amount of dose received by the brain tissue and cranium. There may also be some interaction with vitamin D.

This pilot study included careful case and control definition, a detailed questionnaire, careful radon measurements, a widely dispersed patient population, and a detailed quality control procedure for all variables. The controls were selected randomly and did not have any autoimmune diseases. It is the first study to measure residential radon exposure along with other major potential risk factors for MS.

Limitations included the lack of non-neurologically diseased controls, the relatively small sample size, the shortened period for radon measurements, and the relatively small sample size, particularly for radon measurements. Because of this small sample size, the finding of a marginally significant association of residential radon exposure and the prevalence of MS could be due to chance. Separate analyses for gender and severe sunburn were considered less reliable because of low statistical power. This is the second small case-control study to find a positive association between residential radon exposure and MS prevalence (Lykken et al, 2008).

While incident cases are preferred for determining risk factors, obtaining a large enough sample of newly diagnosed patients was not feasible. Thus, prevalent cases were used. In order to partially circumvent this problem, we required that: 1) the date of diagnosis must have been within five years of the time of interview for inclusion in the study and 2) all exposure information obtained must have been prior to the time of diagnosis or severe disabling symptoms. Date of diagnosis was used because this date is firmer and less subjective than the date of symptom onset.

The time frame used for radon measurements was five to six months, shorter than the one-year time period generally preferred to allow for radon's seasonal variability. However, all measurements were done during the winter months in the same year, thus maximizing potential radon exposure in this population. Future studies should, however, use one year measurements in order to account more fully for seasonal variability. If homes were substantially remodeled (e.g., new concrete floor in basement, new air handling system, or major renovations) they were excluded from this study. While radon measurements were not obtained outdoors or at work, the predominant source of radon exposure for most individuals would occur at home. Past radon exposures in the home could not be measured; they were assumed to be approximated by the current measurements (Steck, 2009).

In conclusion, interviews with 148 individuals found some support for a protective effect from either sunlight exposure or vitamin D intake. These results were not, for the most part, statistically significant. After measuring radon exposure in 46 homes, this relatively small study found a borderline statistically significant association between radon exposure and the prevalence of MS. An increase of one unit in the natural logarithm of the time weighted average of residential radon exposure resulted in an increase in MS prevalence of almost two-fold. There was no evidence that this was due to MS patients spending more time at home. Quite the contrary, controls (particularly females) spent more time at home. A larger follow-up study, with a more rigorous study design, could shed further light on these findings.

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