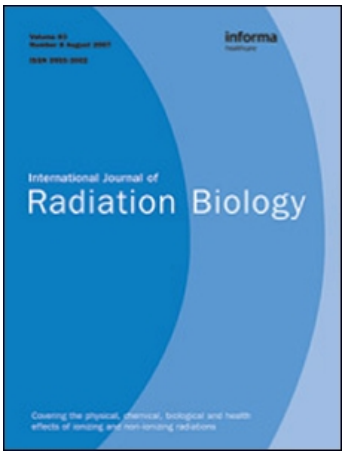

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Health effects of radon: A review of the literature

Mustafa Al-Zoughool [a]; Daniel Krewski [a]
[a] McLaughlin Center for Population Health Risk Assessment, University of Ottawa, Ottawa, Canada

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Health effects of radon: A review of the literature

MUSTAFA AL-ZOUGHOOL & DANIEL KREWSKI

McLaughlin Center for Population Health Risk Assessment, University of Ottawa, Ottawa, Canada

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Abstract

Purpose: Radon is natural radioactive noble gas that can be found in soil, water, outdoor and indoor air. Exposure to radon accounts for more that 50% of the annual effective dose of natural radioactivity. The purpose of the current review is to summarize recent literature and evaluate the weight of evidence on the adverse health effects of radon.

Conclusions: Radon is an established human lung carcinogen based on human epidemiological data supported by experimental evidence of mutagenesis studies in cell culture and laboratory animals. Extrapolation from cohort studies on miners suggested that radon is the second leading cause of lung cancer death after tobacco smoke. The majority of studies on the relationship between radon and other types of cancers showed weak or no association. Low levels of radon can be found in drinking water; however, radon released during water usage adds small quantities to indoor radon concentration. Studies showed that the risk of stomach cancer and other gastrointestinal malignancies from radon in drinking water is small. Studies of the genetic and cytogenetic effects of indoor radon yielded equivocal results; while radon exposure in miners induces gene mutations and chromosomal aberrations. Numerous *in vitro* cytogenetic studies demonstrated that radon induces different types of genetic and cytogenetic damage that is likely to play a role in radon lung carcinogenesis.

Keywords: *Radon, lung cancer, leukemia, genetic damage*

Background: Radon sources, movement in the environment, accumulation in buildings

Radon (Rn-222) is a natural radioactive noble gas that originates from the decay series of uranium-238, a naturally occurring radioactive mineral found in the earth crust with a half-life 4.5×10^9 years. Uranium levels vary on earth since certain types of rocks and soils (like granite, uranium-enriched phosphatic rocks, and shales) contain more uranium than others (Muikku et al. 2007). Radon has a half-life of 3.82 days and decays within hours to form short-lived radionuclides and other radioactive progeny with the release of alpha and beta emissions (Appleton 2007). Although radon itself is inert gas, its short-lived progeny are electrically charged particles that can attach to natural aerosol and dust, and if inhaled, tend to deposit into the lungs thus exposing the sensitive bronchial epithelial cells to alpha radiation. Exposure to radon progeny accounts for more than 50% of the annual effective dose of natural radioactivity (United Nations Scientific Committee on the Effects of Atomic Radiation 2000, Åkerblom 2005).

Radon can also be found in building materials albeit in low concentrations (de Jong et al. 2006). Building materials such as concrete, wallboard, brick and tile typically have concentrations similar to those of major rock types used for their manufacture (Mustonen 1984, Ackers et al. 1985). Although building materials generally contribute only a very small percentage of the indoor air radon concentrations, in a few areas concrete, blocks, or wallboard made by using radioactive shale or waste products from uranium mining will make a large contribution to the indoor radon (Åkerblom 2005, Man and Yeung 1998).

Radon can be released into ground water through continuous diffusion from rocks of the terrestrial crust (National Research Council [NRC] 1999b). Since radon has one of the highest water solubility among noble gases, high concentration of radon can

Correspondence: Mustafa Al-Zoughool, McLaughlin Center for Population Health Risk Assessment, University of Ottawa, Ottawa, Canada.
E-mail: malzough@uottawa.ca

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be found in ground water, which may represent a potential health risk for people using ground water as a drinking water source.

Outdoor air concentration of radon is higher over large continents than over sea. During temperature inversions (a reversal of the normal atmospheric temperature gradient), levels may reach hundreds of Bq/m^3 over regions with enhanced concentrations of uranium and radium in the ground (Segovia et al. 2007). In an extreme example, in the village of Villar de la Yegua in Spain, radon concentrations as high as 15,000 Bq/m^3 were found, and the geometric mean of radon concentration the surrounding areas was 818 Bq/m^3 (Sainz et al. 2007). Radon concentration outdoors are generally low (annual average about 10 Bq/m^3) whereas indoor radon are much higher and more variable (can range from 20 Bq/m^3 to 110,000 Bq/m^3) (Appleton 2007). Country averages of indoor radon range from 9 Bq/m^3 in Egypt, 20 Bq/m^3 in the UK, 46 Bq/m^3 in the US, 108 Bq/m^3 in Sweden, and 140 Bq/m^3 in the Czech Republic (United Nations Scientific Committee on the Effects of Atomic Radiation 2000). Air concentration of radon varies seasonally and diurnally and it is also affected by the meteorological variables such as temperature, humidity, and wind speed (Momcilovic and Lykken 2007, Seftelis et al. 2007).

Driven by lower air pressure inside buildings, radon and its decay products accumulate indoors after diffusing into pores and cracks and released into the atmosphere. Radon in soil air can be transported into a home through structural defects in the basement including: cracks in solid floors and walls below construction level; gaps in suspended concrete and timber floors and around service pipes; crawl spaces, cavities in walls, construction joints, and small cracks or pores in hollow-block walls (Appleton 2007). The flow of radon into buildings depends on building construction and permeability of the ground material (Iakovleva and Karataev 2005). Other factors that determine radon levels indoors include building type (whether urban or rural); season of the year, floor level, porosity and permeability of the bedrock; the nature of the carrier fluids (including carbon dioxide gas, surface water, and groundwater); weather; permeability of soil; and lifestyle of house occupants (Bossew and Lettner 2007). Indoor radon concentrations are on average about 1000 times lower than radon in the soil underlying the house (Iakovleva and Karataev 2001, Mnich et al. 2004).

Health risks of radon

Lung cancer

Radon is an established human lung carcinogen based on experimental evidence of mutagenesis studies in cell culture and laboratory animals (Hussain et al. 1997, Weaver et al. 1997, Collier et al. 2005), and epidemiologic cohort studies on uranium miners and case-control studies on the general public (NRC 1999a). The International Agency for Research on Cancer considered that there is sufficient evidence of the carcinogenicity of radon and its decay products to humans (International Agency for Research on Cancer, 2001; Baan and Grosse 2004).

Numerous epidemiological cohort and case-control studies were conducted to assess the risk of lung cancer due to occupational and residential radon exposure. Table I shows types of epidemiological studies to investigate the association between radon and lung cancer.

The first line of evidence of radon lung carcinogenicity came from occupational studies on miners, especially uranium miners, exposed to high levels of radon along with other radioactive chemicals and dust particles. Numerous cohort studies on miners have been completed (Radford and Renard 1984, Howe et al. 1986, 1987, Hornung and Meinhardt 1987, Morrison et al. 1988, Samet et al. 1991, Woodward et al. 1991, Kusiak et al. 1993, Tirmarche et al. 1993, Tomasek et al. 1994, Xuan et al. 1993, Tomasek 2002, Laurier et al. 2004b, Grosche et al. 2006, Villeneuve et al. 2007) with the main purpose of evaluating the risk of lung cancer due to occupational exposure to radon progeny. Most of the included studies have been conducted in uranium miners (Table II). Other types of mines were fluorspar (Morrison et al. 1988, Villeneuve et al. 2007), tin (Xuan et al. 1993), and iron (Radford and Renard 1984). All these cohort studies showed a statistically significant positive association between exposure to radon in mines and the risk of lung cancer (Table II). The excess relative risk per working level month (ERR/WLM) ranged from 0.0016–0.0506 (Table II). The ERR/WLM from the combined analysis of 11 cohort studies (Lubin et al. 1995) was 0.0049 (95% CI 0.002, 0.010), which corresponds to odds ratio (OR) of 1.49 at exposure level of 100 WLM. The ERR in the combined analysis was linear over the range of miner exposures.

Using various modeling approaches, results of lung cancer risk in miners were used to project lung cancer risk for the general population exposed to residential radon. The results suggested that 10–15% of the total lung cancer deaths in the US could be attributed to radon exposure in homes, making radon the second leading cause of lung cancer death after tobacco smoke (NRC 1999a). Such direct extrapolation of miner data to estimate lung cancer risk of residential radon raises several complications regarding differences between mine and home

Table I. Types of epidemiological studies used to evaluate the risk of lung cancer due to radon exposure.

Study type	Target population	Main purpose of the study	Method of radon dosimetry	Major findings/conclusions
Cohort studies	Miners/occupational exposure.	Determine the risk of lung cancer mortality in exposed miners	Radiation exposure was estimated using job-exposure matrix (JEM) which provides exposure values for potential alpha energy from radon and its progeny in working level months (WLM).	High levels of radon m exposure were associated with increased cancer risk.
Case-control studies	The general public/ residential exposure.	Determine the risk of lung cancer in residential settings.	Year-long residential radon levels were measured by α-track detectors and were used to estimate exposure in the 25 years prior to the index date.	Most studies reported small insignificant association between residential radon exposure and lung cancer, some studies found negative association.
Pooled analysis of the cohort studies on miners	Miners/occupational exposures.	Obtain summary estimates of the risk of lung cancer in radon-exposed miners using large sample size.	A summary of the WLM exposure was obtained for the total subjects using reported exposure levels in the individual studies.	A consistent linear relationship for cumulative radon progeny and lung cancer was observed in the range of miner exposures
Combined analysis of case-control studies	The general public/ residential exposure in Europe and North America.	Obtain accurate estimates of lung cancer risk from residential radon exposure by reducing uncertainty in radon dosimetry.	Available radon measurements form individual studies were used to estimate radon exposure for the total individuals in all homes occupied over the past 5–30 years.	A significant increase in risk of lung cancer was associated with increased radon exposures with seemingly linear dose-response relationship.

Table II. Summary of the main characteristics and risk estimates of cohort studies.

Study region (Ref number)	Type of mine	Person-years		Lung cancer deaths		Mean cumulative radon exposure in working level months†	ERR/WLM† (95% confidence interval)‡
		Exposed	Non-exposed	Exposed	Non-exposed		
Newfoundland, Canada: Extended study (Villeneuve et al. 2007)	Fluorspar	88,842	NA*	191	62	378	0.0043 (0.0023, 0.0062)
Germany (Grosche et al. 2006)	Uranium	1 565 070	236 560	2201	187	241.1	0.0021 (0.0018, 0.0024)
Czech Republic: Extended cohort (Tomasek 2002)	Uranium	127 397	NA*	495	165	NA	0.026 (0.012, 0.041)
France: Extended cohort (Laurier et al. 2004b)	Uranium	50 034	6 338	85	45	71.3	0.006 (0.001, 0.012)
France (Tirmarche et al. 1993)	Uranium	39 487	4556	45	0	70.4	0.0036 (0.001, 0.013)
Yunnan Province, China (Xuan et al. 1993)	Tin	135 357	39,985	936	44	277.4	0.0016 (0.001, 0.002)
W. Bohemia, Czech Republic (Tomasek et al. 1994)	Uranium	10 3652	4,216	656	5	198.7	0.0031 (0.002, 0.006)
Colorado Plateau (Hornung and Meinhardt 1987)	Uranium	73 509	7403	292	2	595.7	0.004 (0.003, 0.007)
Ontario, Canada (Kusiak et al. 1993)	Uranium	319 701	61 017	282	2	30.8	0.0089 (0.005, 0.015)
Newfoundland, Canada (Morrison et al. 1988)	Fluorspar	35 029	13 713	112	6	367.3	0.0076 (0.004, 0.013)
Malmberg, Sweden (Radford and Renard 1984)	Iron	32 452	841	79	0	80.6	0.0095 (0.001, 0.041)
Grants, New Mexico (Samet et al. 1991)	Uranium	46 797	12 152	68	1	110.3	0.0172 (0.006, 0.067)
Port Radium, Canada (Howe et al. 1987)	Uranium	30 454	22 222	39	18	242.8	0.0019 (0.001, 0.006)
Beaverlodge, Canada (Howe et al. 1986)	Uranium	68 040	50 345	56	9	17.2	0.0221 (0.009, 0.056)
Radium Hill, Australia (Woodward et al. 1991)	Uranium	25 549	26 301	32	22	7.6	0.0506 (0.010, 0.122)
Pooled analysis of 11 cohort studies: References 18–28 (Lubin et al. 1995)		907 459	242 332	2597	109	158.0	0.0049 (0.002, 0.010)

*Non-exposed cohort was the general male population in the same region of the study; †Among radon-exposed miners; ‡ERR/WLM, excess relative risk/working level month. Excess relative risk expresses how much increase in the risk of the disease is due to exposure to a given agent. The ERR can be obtained by subtracting one from the relative risk. Working level month is a time-integrated exposure measurement, is the product of time in working months (170 hours) and working-level (WL). One WL equals any combination of radon progeny in 1 l of air that gives the ultimate emission of 130 000 MeV of energy of alpha particles. Consequently, 1 WLM corresponds to 2.08×10^{-5} J/m^3 $\times$ 170 hours or 3.5×10^{-3} J-hours/m^3.

environments. For example; miners are all males and generally smokers while the general population consists of men, women, and children. Mean exposure levels in mines are at least one magnitude higher than in homes, and mines may contain other pollutants such as arsenic, silica, and diesel exhaust. Furthermore, physical factors such as breathing rates, size distribution of aerosol particles carrying radon and its daughters, and fraction of unattached radon differ in the two exposure groups at least one order of magnitude.

To overcome these uncertainties, many studies have been conducted to estimate the risk of residential radon in the general population. To date, about 20 case-control studies of residential radon and lung cancer have been completed (Blot et al. 1990, Pershagen et al. 1992, 1994, Schoenberg 1992, Letourneau et al. 1994, Auvinen et al. 1996, Ruosteenoja et al. 1996, Darby et al. 1998, Alavanja et al. 1999, Field et al. 2000, Lagarde et al. 2001, Tomasek et al. 2001, Barros-Dios et al. 2002, Oberaigner 2002, Wang et al. 2002, Baysson et al. 2004, Bochicchio et al. 2005, Wichmann et al. 2005, Sandler et al. 2006, Wilcox et al. 2007) . The results of these individual studies have been inconsistent mainly due to small sample size and the substantial uncertainties in radon exposure measurements. The major characteristics and findings of those studies are summarized in Table III.

The excess odds ratio (EOR) per 100 Bq/m^3 for all but three studies were positive, most of these studies failed to show a statistically significant effect of radon on lung cancer. The EOR for individual studies ranged from -0.05 to 0.56. The 95% CI included zero for all studies but the Iowa (Field et al. 2000), Swedish nationwide (Pershagen et al. 1994), Czech Republic (Tomasek et al. 2001) and Gansu, China (Wang et al. 2002) studies. Combined analysis of eight of these studies in North America (Krewski et al. 2005) and 13 studies in Europe (Darby et al. 2005) showed that the EOR and 95% CI were 0.11 (0.00, 0.28) and 0.08 (0.03–0.15), respectively. This

Table III. Major characteristics and findings of case-controls studies of residential radon and lung cancer.

Study (reference)	Cases/Controls	Estimated radon concentration* Bq/m^3	Excess odds ratio† (95% confidence interval)
North America			
New Jersey – I (Schoenberg JB 1992)	480/442	26	0.56 (-0.22, 2.97)
New Jersey – II (Wilcox et al. 2007)	561/740	32	0.05 (-0.14, 0.56)
Winnipeg (Letourneau et al. 1994)	738/738	142	0.02 (-0.05, 0.25)
Missouri (Alavanja et al. 1999)	512/553	56	0.27 (-0.20, 1.53)
Iowa (Field et al. 2000)	413/614	127	0.44 (0.05, 1.59)
Connecticut (Sandler et al. 2006)	963/949	33	0.02 (-0.21, 0.51)
Utah-South Idaho (Sandler et al. 2006)	511/862	57	0.03 (-0.20, 0.55)
Combined analysis of the above studies (Krewski et al. 2005)	*3662/4966*	*70*	0.11 (0.00, 0.28) *0.21 (0.03–0.51)*‡
Europe			
Austria (Oberaigner W 2002)	183/188	198	0.46 (<-0.046, >5.00)
Czech Republic (Tomasek et al. 2001)	171/713	500	0.09 (0.02, 0.21)
Finland nationwide(Auvinen et al. 1996)	881/1435	103	0.11 (-0.06, 0.31)
Finland southern (Ruosteenoja et al. 1996)	160/328	215	0.28 (-0.21, 0.78)
France (Baysson et al. 2004)	571/1209	133	0.05 (-0.01, 0.12)
Germany eastern (Wichmann et al. 2005)	945/1516	76	0.08 (-0.03, 0.20)
Germany western (Wichmann et al. 2005)	1323/2146	50	-0.02 (<-0.18, 0.17)
Italy (Bochicchio et al. 2005)	384/405	108	0.14 (-0.11, 0.46)
Spain (Barros-Dios et al. 2002)	156/235	131	<-0.11 (<-0.11, 0.59)
Sweden nationwide (Pershagen et al. 1994)	960/2045	96	0.10 (0.01, 0.22)
Sweden never-Smokers (Lagarde et al. 2001)	258/487	74	0.28 (-0.05, 1.05)
Sweden Stockholm (Pershagen et al. 1992)	196/375	134	0.16 (-0.14, 0.92)
United Kingdom (Darby et al. 1998)	960/3126	55	0.08 (-0.03, 0.20)
Combined analysis of the studies in Europe (Darby et al. 2005)	*7148/14208*	*105*	0.08 (0.03, 0.15) *0.16 (0.05–0.31)*‡
China			
Shenyang (Blot et al. 1990)	308/356	85	-0.05 (<0.00, 0.08)
Gansu (Wang et al. 2002)	768/1659	223	0.19 (0.05, 0.47)

*Estimated average residential radon concentration in the 5–30 exposure time window; †The excess relative risk of lung cancer per 100 Bq/m^3 increase in the time-weighted radon concentration; ‡After correction for random uncertainties in radon measurements.

was compatible with an OR of 1.12 (95% CI 1.02–1.25) per 100 Bq/m^3 predicted by downward extrapolation of miner data (NRC 1999a). Krewski et al. (2005) corrected for random uncertainties in radon measurement (discussed below) by limiting the analysis to subjects residing in one or two residences during the 5- to 30-year exposure time window and at least 20 years' coverage with [alpha]-track monitors. This adjustment increased the summary EOR from 0.11 to 0.21 (95% CI 0.03–0.51). Similarly, in the collaborative analysis of 13 European studies correction for the measurement error caused by random variability in measured radon concentrations resulted in EOR of 0.16 (95% CI 0.05–0.31) compared to 0.08 for the uncorrected radon concentration (Darby et al. 2005, Krewski et al. 2005) (Table III).

Case-control design provided a direct method to assess the risks of exposure to residential radon. Although results from most of the case-control studies generally supported the evidence of small excess of lung cancer risk associated with exposure to residential radon, the risk estimates were not statistically significant in the majority of the studies and thus were inconclusive. Small sample size and the inherent uncertainties in radon measurements most likely contributed to the inability of cases-control studies to show consistent results of increased cancer risk. In addition, since exposure levels to radon in homes are usually low compared to miners' exposure levels, the expected increase in risk of lung cancer would be small and difficult to detect with a small dataset. The BEIR VI report (NRC 1999a) suggested that the apparent inconsistency in findings among residential case-control studies was largely a consequence of exposure misclassification and random variability in radon levels. Radon studies usually estimate historical radon exposure in the 25-year period of the exposure time window by a yearlong alpha-track detector measurement of radon concentration in the current residences. Lung cancer risk may exist from exposures that occurred outside the 25-year exposure window, which is not generally included in exposure assessments; this represents a possible source of uncertainty. In addition, Changes to homes due to structure aging, remolding, and other changes introduce systematic bias in radon estimation (Alavanja et al. 1999). Other important source of exposure misclassification is subject's mobility which increases the difficulty of monitoring multiple residences and necessitates imputing data for missing homes (Krewski et al. 2005). Adjustment for random errors in radon measurements increased risk estimates as discussed before.

In contrast to the findings of case-control and cohort studies, some investigators discussed the possibility of protective effect of low levels of radiation (Matanoski et al. 1987, Loken and Feinendegen 1993). Earlier evidence of this phenomenon (called hormesis) came from a study by Cohen (1990) which showed a negative correlation between radon levels and lung cancer. However, the study was based on 'ecological' design and had many limitations, including the absence of county-specific data on smoking. Therefore, potential confounding by smoking could not be verified. Indeed, by analyzing the same data, Puskin (2003) found strong negative correlations for cancers strongly linked to cigarette smoking, weaker negative correlations for cancers moderately increased by smoking, and no correlation for cancers not linked to smoking. This indicates that the observed negative trend of radon and lung cancer found earlier was confounded by the negative correlation between smoking and radon levels. This negative correlation between radon and smoking are related to rural/urban differences, for example higher tobacco use and lower radon in urban areas (Darby et al. 2005).

Smoking is probably the most important modifying variable in radon-lung cancer association. Data from cohort studies suggested an additive, submultiplicative, and multiplicative effects of radon-tobacco smoke interaction. Applying both the additive and the multiplicative models provided best fit of the available data on interaction between smoking and radon (Lubin et al. 1995). In contrast, results from most individual and combined case-control studies did not show significant interaction between smoking and radon exposure. It has been postulated that interaction between chemicals is a phenomenon evident only at high doses (Zielinski et al. 2001); therefore, it was difficult to detect any radon-tobacco smoking interaction with low level of radon exposure encountered in most case-control studies. Both cohort and case-control studies repeatedly showed that radon lung cancer risk is higher for non-smokers than for smokers. However, the absolute risk of lung cancer in people exposed to radon is expected to be higher for smokers than for non-smokers because lung cancer rate is higher in smokers.

Cancer sites other than the lungs in miners

The few epidemiological studies that investigated effects of radon on health outcomes not related to lung cancer in miners focused mainly on the risk of leukemia. Case-control studies (Lubin et al. 1998, Law et al. 2000) and cohort studies (Darby et al. 1995) did not consistently demonstrate increased risks of mortality for hematopoietic malignancies due to occupational radon exposure in uranium mines. Most of those studies on the risk of leukemia and other cancer sites used cancer mortality as a

surrogate for incidence rates. This is likely to underestimate the true risk since a significant number of cancer cases are likely to be missed for cancers with low fatality rates. A recent case-control study of Czech uranium miners (Rericha et al. 2006) showed that the incidence of all leukemia combined and chronic lymphocytic leukemia alone was positively associated with cumulative radon exposure, while Myeloid leukemia and Hodgkin lymphoma were also associated with radon, but risk ratios (RR) were not statistically significant. There was no apparent association of radon with either non-Hodgkin lymphoma or multiple myeloma. A case-control study of former uranium miners was conducted in East Germany to examine the risk of leukemia among miners (Mohner et al. 2006). The results suggested that an elevated risk for leukemia is restricted to employees with a very long occupational career in underground uranium mining or uranium processing. Another study did not find an increased risk of leukemia among uranium miners in West Bohemia (Tomasek et al. 1993) based on 25 years of follow-up, although there was a statistically significant increase of deaths from cancers of the liver, gallbladder and extrahepatic bile ducts. In this study, it was impossible to establish that the relationship was causal since mortality did not increase with duration of employment underground or with cumulative radon exposure. In the Newfoundland fluorspar miners (Morrison et al. 1988), there was a significant excess of the observed numbers of cancers of the lungs, buccal cavity, pharynx and of the salivary glands. However, the small numbers of salivary gland ($n = 2$) and buccal cavity and pharynx ($n = 6$) cancers did not allow for detailed analysis of the dose-response and complicated interpretation of the results for those cancer types.

The most informative analysis of cancers other than lung cancer was based on pooling of data from 11 studies of underground miners (Darby et al. 1995). For each cohort, the expected number of deaths was calculated based on external national or regional age- and calendar year-specific rates. The association for specific cancers with cumulative exposure to radon progeny was evaluated both for the combined total time since employment and separately for time since first employment categories of less than 10 years and equal to or greater than 10 years. Overall, there was no excess of deaths from cancers other than lung-cancer (observed/expected O/E, 1.01; 95% CI, 0.95, 1.07). Of the 28 individual cancer categories evaluated, there were significant excesses of mortality for stomach cancer (O/E, 1.33; 95% CI, 1.16, 1.52) and primary liver cancer (O/E, 1.73; 95% CI, 1.29, 2.28). Risk of mortality for leukemia increased in the period less than 10 years since starting working (O/E, 1.93; 95% CI, 1.19–2.95). However, since none of the mortalities of these cancers were significantly related to cumulative radon exposure, they are unlikely to be related to exposure to radon and radon progeny. This pooled analysis provided strong evidence that exposure to high levels of radon is not likely to increase mortality from cancers other than the lung.

Epidemiological studies investigating the risk of leukemia in miners rely on cumulative radon progeny exposure in WLM; yet it is uncertain how much of this radon progeny exposure measurement corresponds to the actual dose delivered to different target tissues, including the red bone marrow (RBM) (Eatough 2004) .The transfer rate of radon decay products across the lung-blood boundary determines the dose to a wide range of body tissues including the RBM (Kendall and Smith 2002). Therefore, before drawing conclusions regarding the risk of leukemia and other non-lung cancers from radon exposure in miners, it is necessary to re-evaluate the existing data on leukemia mortality in underground metal-ore miners based on the available models for radon dosimetry that accounted for not only lung deposition of radon and its progeny, but also for distribution to and absorption in other organs. It is equally important to apply those dosimetric considerations for any future studies looking into other health effects of radon (Laurier et al. 2004a).

Cancer sites other than the lungs in the general population

Several ecological studies and surveys suggested a positive correlation between exposure to indoor radon and the risk of adult acute leukemia (especially myeloid leukemia) and childhood leukemia (Lucie 1989, Henshaw et al. 1990, Haque and Kirk 1992, Evrard et al. 2006). Other studies suggested that a number of cancers might also be weakly correlated with indoor radon, especially kidney cancer, prostate cancer, malignant melanoma, and some childhood cancers (Butland et al. 1990, Henshaw et al. 1990, Axelson 1995). These studies were based on ecological design in which radon levels were regressed against incidence of several cancer sites. Average radon concentrations were obtained from national or county surveys and recorded as population-averaged arithmetic mean. In some cases, crude geographical or geological features of the inhabited areas were used to derive estimates of levels of radiation emission and subsequently used as surrogates for exposure assessment (Forastiere et al. 1992). This type of study design has many limitations, including lack of measurement of individual exposure to indoor radiation, lack of control population, the difficulty in separating radon effect from that of indoor gamma radiation, and the absence of

multiple regression analyses of potential confounders (Eatough and Henshaw 1994). In addition, ecologic studies were based on the assumption that national mean radon concentrations apply to areas where cancer registries have been compiled.

To overcome some of the above limitations, a study was conducted in Iowa for joint prediction of county-average radon levels and estimation of the associated leukemia risk (Smith et al. 2007). The study used Bayesian hierarchical risk model, and although the model is applied to population-level incidence rates, the approach can be generalized to individual-level risk models for which spatial dependencies and measurement error were based on considerations in the prediction of an exposure covariate. The results suggested a slight non-significant association with chronic lymphocytic leukemia and chronic meyloctyic leukemia. However, there was a marginal negative association between acute lymphocytic leukemia and county radon levels. Other ecologic studies found a non-significant negative association between radon exposure and acute lymphocytic leukemia or childhood leukemia (Viel 1993, Richardson et al. 1991, Thorne et al. 1996, Collman et al. 1988). In another ecologic study (Boice et al. 2007), the authors evaluated the possible impact of mining and milling of uranium in Montrose County on the Western Slope of Colorado on health of communities living near the same county. Mortality rates between 1950 and 2000 among Montrose County residents were compared to rates among residents in five similar counties in Colorado. The results showed no significant excesses for any causes of death of cancers of the breast, kidney, liver, bone, or childhood cancer, leukemia, non-Hodgkin lymphoma, renal disease or non-malignant respiratory disease.

More elegant case-control studies that included individual measurements of radon exposures have been conducted and showed no association between radon exposure and leukemia (Forastiere et al. 1998, Lubin et al. 1998, Kaletsch et al. 1999, Steinbuch et al. 1999, Law et al. 2000). Using a Bayesian hierarchical model to analyze data from a case-control study, Toti et al. (2005) conducted case-control study and found no association between adult myeloid leukemia and indoor radon concentration. A recent review paper concluded that current evidence from the literature argues against the causality of association between exposure to radon progeny and the risk of lung cancer (Charles 2007).

In summary, the majority of studies investigating the risk of cancers other than the lung due to occupational and residential radon exposure provided weak or no evidence of an association.

Radon in drinking water and health risks

Radon concentration in surface water is usually low (less than 4,000 Bq/m^3), while its levels in ground water are relatively higher since ground water passes through rock and soils rich in uranium that release radon into water (NRC 1999b). Levels as high as 10,000,000 Bq/m^3 were found in some drinking ground water supplies in the US. At this level, water usage can be a significant source of indoor radon. Radon gas may be released into the air when the water is boiled, used in showers, or agitated (Becker III 1984). Considering the relatively small volume of water used in homes, the large volume of indoor air into which radon is emitted and the exchange of indoor air with the ambient atmosphere, radon released during water usage adds relatively small quantities to the indoor radon. More specifically, the use of water containing 10,000 Bq/m^3 would increase indoor air concentration by an estimate average of Bq/m^3 (NRC 1999b). The risk associated with radon in drinking water depends on number of underlying factors including the amount of ingested water, the effective exposure duration, and the overall water-to-air transfer factor. The US National Research Council (NRC) in their report (NRC 1999b) used age- and gender-averaged tap water usage of 0.6 l/day and assumed that all radon remained dissolved in water during the transfer process. Cancer risk of ingested radon dissolved in drinking water is derived from the fraction of dose absorbed by the tissues at risk. Subsequently, the stomach as port of entry represents a particular concern with an estimated 90% of the ingested radon dose is delivered to the stomach (Kendall and Smith 2002). The dose delivered to the sensitive cells in the stomach, namely in the stomach wall, depends on the diffusion rate of radon into the wall (International Commission on Radiological Protection 1994). The diffusion of radon within the stomach was modeled to determine the expected time-integrated concentration of radon at the depth of the cells at risk (Sharma et al. 1997). Based on a diffusion coefficient of $5 \times 10^{-6}\,cm^2\ S^{-1}$, the integrated concentration in the sensitive cells of the stomach wall was about 30% of that in the stomach content.

A few studies have been conducted on the association of radon in drinking water and gastrointestinal malignancies (Wilkinson 1985, Kjellberg and Wiseman 1995, Ye et al. 1998, Auvinen et al. 2005). The studies have shown mixed results: Two studies (Ye et al. 1998, Auvinen et al. 2005) found no association between radon levels in water and stomach cancer, while in the study by Kjellberg and Wiseman (1995), a positive correlation was found between radon levels and the incidence of stomach

cancer in females, and the mortality of stomach cancer for male, female, and total population. In the other ecologic study (Wilkinson 1985), occurrence of stomach cancer has been correlated with water uranium deposits in New Mexico. The major limitation of these studies is that they did not include individual exposures. Furthermore, effects of confounding factors such as smoking, diet ... etc. were not determined. The NRC committee (NRC 1999b) estimated that overall age-and gender-averaged cancer death risk from lifetime ingestion of radon dissolved in drinking water at concentration of 1 Bq/m^3 is 0.2×10^{-8} which corresponds to an estimated annual mortality of 20, about 80% of them are stomach cancer. The contribution of radon to the overall risk is relatively small value when compared with an estimated 13,000 annual deaths of stomach cancer from other causes. The committee also estimated that the lifetime risk of lung cancer for the total US population resulting from air exposure to radon from a waterborne radon concentration of 1 Bq/m^3 is 1.6×10^{-8}.

It seems reasonable to conclude, then, that cancer risk posed by radon in household public water supply is small and can be attributed to the transfer of radon into air and the subsequent inhalation of radon decay products, and not from ingestion of water. The risk could be higher for people private wells for water supply where radon levels could be high and variable (Mose et al. 2001, Pachocki et al. 2002, Villalba et al. 2005).

Genetic and cytogenetic effects

The mechanism of lung cancer induction by radon is unclear but may involve both genetic and epigenetic pathways, both are necessary in the neoplastic conversion (Jostes 1996). The evidence of genotoxicity of radon came from *in vitro* mutagencitiy studies which showed that radon can induce alterations in genes important for cancer cell proliferation and differentiation (O'Neill et al. 2005, Li et al. 2007). Occupational studies on uranium miners showed that about 31% of lung cancers contained the same mutation at codon 249 of the p53 gene (Vahakangas et al. 1992, Taylor et al. 1994). Other types of genetic damage induced by radon include chromosomal aberrations and micronuclei formation. These cytogenetic changes are generally considered lethal events, but if they persist after cell division and become stable, they might also contribute to cancer formation (Ghosh et al. 2007). Studying genetic and cytogenetic events is necessary for complete understanding of the molecular mechanisms of radon lung carcinogenesis and may help determine the risk at low exposure levels typically encountered in residential settings.

Genetic analysis of samples of lung adenocarcinoma from highly exposed uranium miners showed the presence of mutations in p53 and k-ras genes (McDonald et al. 1995). In addition, a pilot study involving a cohort of former East German uranium miners found an increased frequency of chromosomal aberrations in blood lymphocytes (Popp et al. 2000). Another study on uranium miners showed that the incidence of cytogenetic damage (chromosomal aberrations and micronuclei formation) was higher and persisted for a long time in uranium miners compared to the general public (Meszaros et al. 2004)

Several studies on the association of indoor radon and mutations, chromosomal aberrations and micronuclei formation have been conducted. Bridges et al. (1991) reported a correlation between frequency of a mutation of the hypoxanthine guanine phosphoribosyl transferase gene (hprt) and indoor radon exposure. In this study, the investigators selected 20 persons, mostly never-smokers, from homes that had been monitored for radon. Mutation frequency was significantly associated with radon concentration in the homes. In a larger follow-up study by the same group (Cole et al. 1996), no significant correlation between the frequency of mutants or translocations in circulating lymphocytes and exposure to radon gas in homes. Also, Lindhom et al. (1999) did not observe an increase in the rate of stable or unstable chromosomal aberrations in peripheral blood lymphocytes in people chronically exposed to high concentrations of domestic radon. Another study that was conducted in Germany (Bauchinger et al. 1994) performed conventional chromosomal analyses in blood lymphocytes of 25 persons living continuously in houses with indoor radon concentrations exceeding the average in German houses of 50 B/qm^3 by a factor of 5–60. The mean frequencies of dicentrics and rings per cell ($1.5 \pm 0.4 \times 10^{-3}$) were significantly higher than control levels ($0.54 \pm 0.11 \times 10^{-3}$). Grouping the persons by estimated cumulative exposure showed a tendency for an exposure-effect relationship. Estimated radon exposures ranged from 700–6300 Bq/m^3. In a follow up study, painting of three chromosomes by fluorescence in situ hybridization (FISH) techniques was carried out on the same lymphocyte samples (Bauchinger et al. 1996). The mean frequency of symmetrical translocations was slightly (1- to 5-fold), but not significantly ($p < 0.1$), raised in the radon group compared to the controls.

In comparison to the equivocal results from studies on people exposed to indoor radon, numerous in vitro cytogenetic studies demonstrated that radon induces micronuclei formation, chromosomal aberrations, and cell proliferation (Jostes 1996, Lutze et al. 1992). In addition, exposure to radon and

alpha particles in vitro induces *hprt* gene mutations that ranged from complete deletion of the gene, partial deletions, and gene rearrangements (Lutze et al. 1992). In general, these genetic and cytogenetic changes induced by radon were linear and dose-dependent.

The apparent discrepancy between results of in vitro studies and those conducted in the general population regarding genetic and cytogenetic effects could be attributed to the low radon exposure doses in the household settings. Indeed, experimental animals and cells in culture are typically exposed to higher radon doses than in homes. Since miner studies showed that radon exposure causes mutations in cancer-relevant genes (McDonald et al. 1995, Jostes 1996), it seems reasonable that residential radon exposure might add to the genetic load of lung cancer risk.

Conclusions

Information from epidemiological cohort and case-control studies as well as experiments on laboratory animals and cell culture has clearly demonstrated that radon is a lung carcinogen. Extrapolation from cohort studies on miners suggested that radon is the second leading cause of lung cancer death after tobacco smoke. Results on the risk of other types of malignancies were less consistent and much more uncertain than for radon and lung cancer and therefore indicated that radon and its progeny are not a significant cause of other cancers. Induction of genetic and cytogenetic damage seems to play important role in radon lung carcinogenesis. Any future studies looking into other health effects of radon should consider dosimeteric models that estimate the actual dose delivered to target tissues.

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