Radon and Lung Cancer

Tarsheen K. Sethi, MD, Moataz N. El-Ghamry, MD, and Goetz H. Kloecker, MD, MSPH

Dr. Sethi is a Resident in the Department of Internal Medicine, Dr. El-Ghamry is an Assistant Professor in the Department of Radiation Oncology, and Dr. Kloecker is an Associate Professor in the Department of Internal Medicine, Division of Hematology/Oncology, at the University of Louisville in Louisville, Kentucky.

Address correspondence to:
Goetz Kloecker, MD, MSPH
Department of Internal Medicine
Division of Hematology/Oncology
James Graham Brown Cancer Center
529 S. Jackson St.
Louisville, KY 40202
Phone: 502-562-4358
E-mail: goetzkloecker@yahoo.com

Keywords
Radon, lung cancer, carcinogenesis, tobacco

Abstract: Lung cancer is the leading cause of cancer-related deaths worldwide. Radon exposure is the second leading cause of lung cancer, following tobacco smoke. Radon is not only an independent risk factor; it also increases the risk of lung cancer in smokers. Numerous cohort, case-control, and experimental studies have established the carcinogenic potential of radon. The possibility of radon having a causative effect on other cancers has been explored but not yet proven. One of the postulated mechanisms of carcinogenesis is DNA damage by alpha particles mediated by the production of reactive oxygen species. The latter are also thought to constitute one of the common mechanisms underlying the synergistic effect of radon and tobacco smoke. With an estimated 21,000 lung cancer deaths attributable to radon in the United States annually, the need for radon mitigation is well acknowledged. The Environmental Protection Agency (EPA) has established an indoor limit of 4 picocuries (pCi)/L, and various methods are available for indoor radon reduction when testing shows higher levels. Radon mitigation should accompany smoking cessation measures in lung cancer prevention efforts.

Background

Lung cancer is the leading cause of cancer-related deaths worldwide. The role of limiting tobacco exposure for lung cancer prevention is well recognized. Nonetheless, it is important to be aware of other risk factors implicated in its pathogenesis (Table 1). Radon exposure is the second leading cause of lung cancer following smoking, and it has caught the attention of policy makers and scientists across the globe.[1] Even in smokers, the risk of lung cancer is greater among those exposed to radon. Although the initial evidence supporting the association of radon and lung cancer came from studies involving mine workers, research in recent years has focused on indoor radon exposure and its risk to the general population.

Radon finds its place among the top 4 environmental risks to public health in the United States.[2] It is believed to cause approximately 10% of lung cancer cases in the United States each year.[3] Aside from increasing the risk of lung cancer in smokers, radon is an independent risk factor in nonsmokers. Recognition of the

Table 1. Causes of Lung Cancer[61-65]

Tobacco smokers	78% (in women) and 92% (in men) (RR, 40)
Radon	3–15% (RR, 2–10)
Environmental tobacco smoke	2–3% (RR, 1.7)
Asbestos	1–2% (RR, 1.96)
Vitamin-poor diet	1–2% (RR, 1.3)
Air pollution	1–2% (RR, 1.3–2.3)
Silicosis	0.5–1% (RR, 1.45)
Genetic	1–3% (RR, 1.3–4.0)

RR=relative risk.

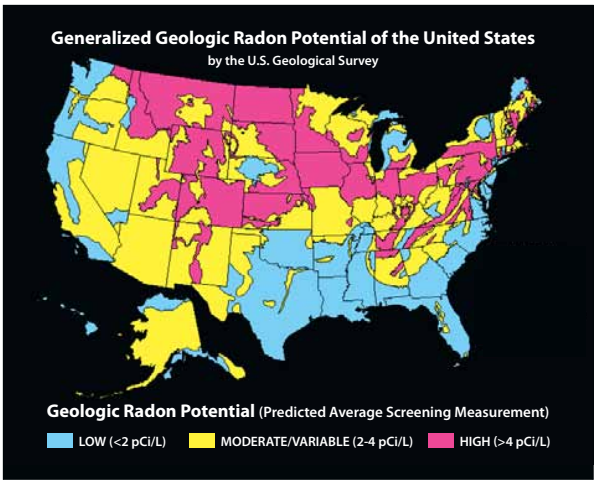

Figure 1. Radon distribution in the United States. Reprinted with permission from the US Geological Survey.[5]

carcinogenic potential of radon in studies of miners led to numerous case-control studies that evaluated the risk of indoor radon exposure. These studies have successfully demonstrated that not only is the risk of radon a very real concern, but it is a universal issue as well. This review focuses on recent advances in the understanding of the mechanisms of radon-induced injury, the epidemiologic evidence implicating indoor radon exposure in lung cancer causation, and the important preventive measures that are available.

Radon Exposure

Radon is known to accumulate in closed spaces. An increased level is seen in underground rock mines, especially those containing uranium. This concentration is mainly caused by gas entering directly from the ore, but radon can also be brought into the mine when it is dissolved in water. For indoor radon, diffusion from subsoil remains the most important source. Other additional, less significant sources include building materials and radon dissolved in water. Within the structure of a building, radon concentrations are highest in the basement, due to the proximity to the subsoil.[4] People residing near uranium mines have a higher radon exposure. Indoor radon levels vary throughout the United States, depending on local conditions (Figure 1).[5]

Pathophysiology: Mechanisms of Radon-Induced Injury

Radon-222 is a radioactive gas that forms from the decay of naturally occurring uranium-238. Uranium-238 is present throughout the earth's crust; as such, the presence of radon is also universal. As a gas, radon is relatively harmless, and only a small fraction of the inhaled gas is absorbed. In contrast, radon decay results in solid particles that readily settle within the airways. These decay products, including polonium-218 and polonium-214, mediate injury by emitting alpha radiation. Alpha radiation is classified as high linear energy transfer (LET) radiation, which means that although it has a low penetration distance, it transfers more energy to the target, thus causing a greater number of ionizing events. This process leads to more severe cell damage.[6] Becquerel (1 Bcq=1 disintegration per second) and Curie (1 Ci=3.7 x 10^{10} disintegrations per second) are the 2 commonly used measurement units of radioactivity; the former is part of the International System of Units (SI).

Alpha particles are capable of causing severe DNA damage by a direct hit on the DNA. Evidence also suggests that DNA injury may be mediated by reactive oxygen species (ROS) that are produced in the cytoplasm and subsequently reach the nucleus.[7] The effect of radon and the alpha particle is highly complex, and it is suspected that the extent of damage may exceed what has been predicted based on alpha particle physics at low doses.[8] The radiation damage by alpha particles is seen to extend beyond the directly irradiated cells. This finding is explained by the bystander effect of alpha radiation, which implies that the directly hit cell sends out signals to surrounding cells, resulting in damage and contributing to tumor genesis.[9] This effect has been observed to be more prominent at low doses.[10,11] Again, ROS are suspected to be the mediators of this effect.[12] In 2006, Breier and colleagues tested this model for the prediction of risk due to indoor radon exposure, and found it to be suitable in this setting.[13]

Experimental studies on animals have clearly demonstrated an increased risk of lung cancer with inhalation of radon.[14] In addition, nonspecific effects on the lungs have also been reported. Radon-induced cytogenetic

damage involves various mechanisms, including base mutations and chromosomal breaks. This has been supported by multiple animal and human cell line studies, including one that found gene deletion to be the most common effect at this location.[8] A recent study conducted on human lymphocytes in vitro also demonstrated the cytogenetic effect of radon.[15]

There has been a keen interest in identifying the loci for radon-induced carcinogenesis. Like most cancers, the pathogenesis of lung cancer involves many pathways and mutations. Various studies have examined the role of mutations of the p53 and p16 tumor suppressor loci, but no particular locus has thus far been proven to be predominant.[16-19] In addition, there is evidence that certain proteins mediate radon-induced inflammation, fibrosis, and carcinogenesis. Of these proteins, RAGE and S100A6 were found to be upregulated in response to radon exposure, and have been proposed as potential biomarkers of radon-induced injury.[20]

Radon and Cancer: The Epidemiologic Evidence

Radon is classified as a human carcinogen by various US agencies, including the National Toxicology Program (NTP), the International Agency for Research on Cancer (IARC), and the Agency for Toxic Substances and Disease Registry (ATSDR).[14,21,22] In addition to the scientific evidence described above, there is strong epidemiologic evidence to support the causal association between radon and lung cancer. The initial evidence emerged from the observation that many underground miners died of lung cancer. This finding led to the detailed study of various cohorts in miners across many countries, including Czechoslovakia, France, Australia, the United States, Canada, Sweden, and China.[23-25] Although most of these were in uranium mines, the studies from the last 3 countries involved other metal mines. An increased risk of lung cancer from radon exposure was demonstrated among these cohorts. The relative risk (RR) was found to be time-dependent, and decreased when more time had elapsed since last exposure. Long-term exposure yielded a greater risk than did short-term exposure, irrespective of the rate of exposure.[23] Data from these miner studies led to an interest in the risks associated with indoor radon exposure, and triggered a number of case-control studies that evaluated residential radon exposure. These studies enrolled people from the general population who had been exposed to indoor radon, and compared patients with lung cancer to lung cancer–free controls. Table 2 shows the radon exposure levels in mines and indoors, and demonstrates the risk of lung cancer attributable to radon in smokers compared with nonsmokers.

Table 2. Radon Exposure and Lung Cancer Risk[66,67]

Radon Exposure	Yearly (WLM)*	Lifetime (WLM)	Relative Risk	Smokers	Non-smokers
Mines		155†	1.49 (100 WLM)		
Indoor‡	0.2	10-20	1.3 (100 Bq/m^3)		
AR for Radon Exposure				9–11%	28–31%
Lifetime Risk (4 pCi/L)				6.2%	0.7%

*Working level is defined as the level of short-lived radon progeny per liter of air that results in the release of 1.3x10^5 MeV of potential alpha particle energy. Working level month refers to the exposure to this concentration for 170 hours.
†Average cumulative exposure from 11 cohorts of underground miners.
‡Based on an exposure level of 1pCi/L.
AR=attributable risk; WLM=working level month.

Indoor Radon Risk: The Case-Control Studies

Pooled results from case-control studies conducted in North America,[26,27] Europe,[28,29] and China[30] demonstrated increased incidence rates of lung cancer related to residential radon exposure at levels of 2.7 picocuries per liter (pCi/L) (100 Bq/m^3). One of the early indoor radon case-control studies corroborating the projected risk from miner data was based on lung cancer cases diagnosed between 1980 and 1984 in Sweden.[31] The relative risk estimates for levels 3.8–10.8 pCi/L and those above 10.8 pCi/L were 1.3 and 1.8, respectively. Another case-control study conducted in Iowa from 1993–1997 found an excess odds ratio (OR) of 0.5–0.83 with an indoor radon exposure cut-off of 4 pCi/L (148 Bq/m^3).[32] After the Biological Effects Of Ionizing Radiation (BEIR VI) report[3] in 1999, there have been 2 major meta-analyses, both published in 2006, combining 7 studies from North America and 13 studies from Europe. The North American meta-analysis[27] showed an increase in lung cancer risk by about 10% per 100 Bq/m^3 increase in radon while the European meta-analysis[28] estimated this risk to be 8.4% (16% after adjusting for uncertainties) per 100 Bq/m^3 rise in radon levels. The pooled results of 2 studies in China revealed similar outcomes,[30] with an increased risk of 13.3% per 100 Bq/m^3 of measured radon. Following these meta-analyses, there have been recent studies conducted in the United States, specifically in New Jersey and Massachusetts.[33,34] The New Jersey study revealed an increased risk for exposure greater than 75 Bq/m^3, but the results were not statistically significant.[34]

The major limitation of case-control studies is an underestimation of risk. It arises from various uncertainties,[3] and is primarily due to dosimetry errors concerning the actual estimation of exposure. The use of recent indoor radon exposure as a surrogate for past radon exposure is one such problem. Krewsky and coworkers tried to obviate this concern by using long-term alpha detectors for estimation of exposure as an inclusion criterion for study in their meta-analysis.[27] Measurement of surface activity of radon on glass objects present in the subjects' homes for the entire duration of the study period can also help estimate average past exposure.[35]

Another source of uncertainty is that risk is estimated based on the residential radon levels rather than the actual bronchial radon dose, which varies among individuals and is dependent on a number of other factors, including time spent at and away from home, exposure at other sites, and the variation of radon levels in the home. There is evidence that indoor radon concentrations vary from day-to-day and season-to-season, being more in winter and less in summer.[36] Despite the known limitations of case-control studies, direct observational data in the residential setting is of import as it has obviated the need for data extrapolation from miner studies and the errors that arise thereof.

Exposure/Response Relationship

Based on these studies, an important aspect in predicting lung cancer risk is the relationship between radon exposure and lung cancer incidence. Knowledge of this relationship is important when predicting risk at lower levels of radon exposure, such as that which occurs indoors.

The BEIR IV report constructed various theories for the possible exposure/response relationship, suggesting it can be linear, quadratic, curved, threshold, or hormetic. A linear, non–threshold curve (Figure 2, Curve A) was selected, based on data encompassing properties of alpha particle–induced carcinogenesis, extrapolation from miner data, and evidence from case-control studies available at the time.[3] Although this theory has since been corroborated by most studies, researchers agree that the existence of a threshold level—below which cancer risk is negligible—cannot be ruled out entirely.[28] Recently, much interest has been generated by the theory of hormesis (Figure 2, Curve E), which posits that low levels of radiation exposure are thought to have a protective effect. In the case of radon, this theory refers to a protective effect of low-level radon exposure against lung cancer in smokers. A possible explanation is that this low-dose exposure may eliminate the smoke-injured cells by stimulation of apoptosis and immunity.[37] Figure 2 illustrates the possible exposure/effect relationships discussed above.[38]

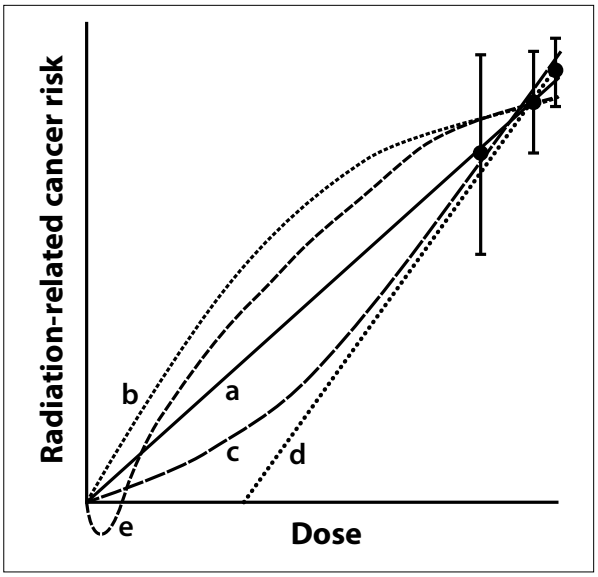

Figure 2. Possible extrapolations of radiation-induced cancer risks at very low doses of radiation. Curve a, linear; curve b, increasing slope; curve c, decreasing slope; curve d, threshold; curve e, hormetic. Reprinted with permission from Brenner DJ et al. Cancer risks attributable to low doses of ionizing radiation: assessing what we really know. *Proc Natl Acad Sci U S A*. 2003;100:13761-13766.[38]

Histopathology of Radon-Associated Lung Cancer

The histopathology of lung cancer associated with radon exposure has produced great interest among epidemiologists. Unfortunately, a prototypical histologic subtype association has not been found.[3] Various studies, including both miner and indoor radon studies, have suggested a preponderance of small cell subtypes.[27,28,39-41] One possible explanation for this association is that radon and its decay products deliver the maximum radiation dose to the central zone of the lung.[3] Nevertheless, it is important to acknowledge that all histologic subtypes have been described in association with radon, including squamous cell carcinoma and adenocarcinoma.[39,41,42]

Synergistic Effects of Radon and Smoking

More radon-related lung cancers occur in individuals who smoke. This association has been described as submultiplicative.[3] Following exposure to 4 pCi/L (148 Bq/m^3) of radon over a lifetime, 7 out of every 1,000 nonsmokers would develop lung cancer, compared with 62 out of every 1,000 smokers.[43] Moreover, this relationship may not be limited to active smokers alone, as a synergism between second-hand smoke and radon exposure is also

suspected to increase lung cancer risk.[44] This combined effect may be due to the fact that the radon dose required for injury is modified by changes in morphologic and physiologic parameters in smokers.[3] In support of this theory, a recently published study found that the effective dose of inhaled radon progeny was amplified 2 times in heavy, long-term smokers, a result of impaired mucociliary clearance and changes in ventilation.[45] In addition, particulate matter from tobacco smoke may increase the amount of attached radon progeny, impacting the dose of alpha energy delivered to the cells.

Another explanation for this synergism is that carcinogens from tobacco smoke and radioactive alpha particles may act together or at different stages in the carcinogenic pathway.[3] Although many common mechanisms may exist, inflammation is one such process, as both of these carcinogens are known to cause lung inflammation.[46] Another mechanism is ROS-mediated injury. Although it is well known that tobacco smoke produces ROS, recent evidence suggests the possibility of ROS generation by alpha particles, as discussed above. In a related study, Bonner and associates found an increased frequency in lung cancer occurrence in a population subset that lacked both genes for the GSTM1 subtype of the enzyme glutathione S-transferases (GST) and were exposed to either radon or second-hand smoke. Since GST is an important enzyme in the body's defense against oxidative stress, this finding supports oxidative injury as a common mechanism for these 2 carcinogens.[47] An important implication of the synergism between smoking and radon in the occurrence of lung cancer is that many radon-related deaths can be prevented by quitting smoking.

Risk Beyond Lung Cancer

Most clinical studies have failed to find a causal association between inhaled radon and diseases other than lung cancer; dosimetric studies have shown that the dose of radon received by the lungs far exceeds that received by any other organ. Some miner studies have suggested an association with benign lung disease, especially pulmonary fibrosis.[48] Although it was suspected that radon exposure might be linked to other malignancies (Table 3), no causal association was demonstrated in these miner studies. The discovery of higher incidences of childhood acute lymphoblastic leukemia in areas with higher indoor radon exposure has raised the possibility of a weak association (RR <2). Studies with more statistical power are needed for confirmation.[49,50]

Radon Mitigation

The EPA estimates that 21,000 lung cancer–related deaths in the United States every year are attributable to radon.[43] As a guidance tool for initiating mitigation measures, it has set an action level for homes and schools of 4 pCi/L (148 Bq/m^3), as averaged over a year. The average radon exposure in occupied living areas is 48 Bq/m^3. However, in 2005, 7 million housing units had radon levels greater than 4 pCi/L (148 Bq/m^3).[51] In addition, it has been determined that decreasing residential radon levels to below 4 pCi/L (148 Bq/m^3) would eliminate merely one-third of the lung cancer cases attributable to radon annually.[3] Thus, there has been a drive to lower the intervention level. The World Health Organization recently decreased its recommended maximum residential radon level to 2.7 pCi/L (100 Bq/m^3).[52] The most recent President's Cancer Panel report recommends decreasing the current EPA action level to below 4 pCi/L.[53]

Table 3. Radon and Potential Cancers[50,67-69]

Hematologic: leukemia, Hodgkin lymphoma
Gastrointestinal: Stomach, liver, pancreas
Kidney
Extrathoracic airways: larynx, trachea
Skin: basal cell carcinoma, squamous cell carcinoma

Radon mitigation protocols begin with the measurement of radon concentration in buildings. It is recommended that all occupied spaces below the third floor undergo radon measurement. Those areas with a radon level exceeding the cut-off (action level) warrant reduction measures. Radon testing devices include both passive tools that do not need electrical power to function and active devices. Further, the testing may be done over a short-term period within 90 days or over a long-term period greater than 90 days. Long-term detectors are recommended because they provide a value close to the annual average of radon concentration, while taking into account the day-to-day and seasonal concentration variations in indoor air. In general, radon reduction measures encompass techniques that help prevent indoor radon entry and remove any radon that has already entered indoor air.[54] These methods are further classified as passive or active, based on the use of a mechanical assist device in the latter. In order to be considered effective, a radon reduction measure should decrease levels by more than 50%. A combination of techniques may be effective in decreasing levels by up to 90%. Active soil depressurization is the most commonly used technique in the United States, and has been found to be the most effective radon reduction measure by the EPA. Furthermore, the efficacy of any measure also depends on the individual characteristics of the building to which it is applied. Table 4 compares radon reduction methods in new construction, as compiled by the EPA.[55]

Table 4. Comparison of Radon Reduction Methods Compiled by the EPA[55]

Method	Installation Cost	Operating Cost	Maximum Possible Reduction	Comments
Natural ventilation: lowest floor	Minimal	High to very high	Up to 90% or more	Useful immediate step for radon level reduction
Forced ventilation: Crawl space Lowest level/basement	 Minimal Low to moderate	 Moderate Very high	 Up to 90% or more Up to 90% or more	More controlled than natural ventilation
Heat recovery ventilation ducted units: Crawl space Lowest level/ basement	 Low to moderate Moderate to high	 Moderate Low to moderate	 Up to 90% or more 50–75%	Air intake and exhaust must be equal. Lower radon reduction is expected for houses with moderate to high air exchange rates
Wall mounted units	Low to moderate	Low to moderate	No data available	
Covering exposed earth	Moderate to high	Low	Site specific	Required to make other methods work
Sealing cracks and most openings	Minimal to high	Nominal	Site specific	Required to make other methods work
Drain-tile suction	Moderate	Low	Up to 90% or more	Best when drain suction is in a continuous unblocked loop around the house
Sub-slab	High	Low	Up to 90% or more	Best with good suction aggregate or highly permeable soil under the slab
Block wall ventilation	High	Low	Up to 90% or more	Only for houses with hollow-block basement walls. Noticeable cracks and openings should be sealed
Prevention of house depressurization	Low to moderate	Low	Site specific and depends on season	Effectiveness is time dependent
House pressurization	Moderate to high	Moderate	Up to 90%	Most effective when a tight seal is maintained

EPA=Environmental Protection Agency.

Based on their review of the existing mitigation measures in various countries, Rahman and colleagues recommended that radon reduction efforts begin with passive measures to reduce radon entry from the soil. If such methods fail, sub-slab depressurization would be effective and economical for smaller buildings. For larger buildings, increased ventilation in combination with heat exchange methods would be a viable alternative.[56]

Various studies have analyzed cost-effective detection and prevention strategies.[57,58] In a review of measures in the United Kingdom, Gray and coworkers concluded that, since even low to moderate concentrations of radon can cause lung cancer, the most cost-effective policy is to apply basic anti-radon measures in all new dwellings, instead of the 2-step strategy of detection and mitigation.[59] The cost of radon mitigation in existing dwellings clearly exceeds that of using radon-resistant construction for new dwellings. The EPA's guidelines for radon reduction include promotion of radon awareness, use of testing and mitigation measures in existing dwellings, and construction of radon-resistant new dwellings. Cessation of smoking is another important, cost-effective measure to reduce a fraction of radon-related deaths. A recent analysis by Mendez and associates revealed that quitting smoking will decrease the radon-related risk of lung cancer by a factor of 2.[60] This reduction will still leave approximately 10,000 lung cancer deaths per year that are solely attributable to radon, hence the importance of radon mitigation measures.

Guidance for Health Care Providers

Although there is overwhelming evidence that supports the carcinogenic potential of radon, lack of awareness in the general population is a major deterrent in the effective implementation of radon mitigation measures.

Education guidance for health care providers should include the following:

- Because radon is the second-leading cause of lung cancer (after tobacco exposure), it deserves a mention in cancer prevention strategies discussed during office visits.
- Most radon-related lung cancer cases occur in smokers; thus, discussions should begin with tobacco cessation advice.
- Once high levels of radon are detected, corrective measures should be implemented as soon as possible.
- Further information regarding the availability of detectors and correction measures in the United States can be found at the EPA website, at http://www.epa.gov/radon/pubs/citguide.html.[43]
- The *WHO Handbook on Indoor Radon* is a product of the WHO International Radon Project and describes residential radon exposure from a public health perspective.[52] It can be downloaded at http://whqlibdoc.who.int/publications/2009/9789241547673_eng.pdf.
- In the absence of a clear association between radon and other malignancies, protection standards continue to be based on lung cancer risk.

Conclusion

Radon is a naturally occurring carcinogen associated with lung cancer. An estimated 21,000 lung cancer deaths per year in the United States are attributable to radon. Initially, radon was thought to be a hazard only to miners, but the risk to the general population due to indoor radon exposure is now well recognized. There is strong experimental and epidemiologic evidence to support this risk. However, predictive measures for risk at low levels of exposure, such as that associated with indoor radon, are still based on a presumed exposure/response relationship. There is some scientific and epidemiologic evidence supporting a linear non-threshold exposure/response relationship, but it remains to be proven beyond doubt. Much advancement has been made in the understanding of the mechanisms of radon-induced injury over the years, and it will continue to be an area of future research. US public policy for radon control as recommended by the EPA encompasses measures to improve radon awareness, detection, and mitigation. A systematic approach toward radon mitigation using existing measures can be strengthened by continued research for more cost-effective measures that would ensure a more universal application. Furthermore, ongoing analysis of the existing methods for efficacy, longevity, and cost will help improve and sustain the quality of life measures in the future. Given that lung cancer continues to be the leading cause of cancer-related deaths globally, efforts for radon mitigation should go hand-in-hand with implementation of smoking cessation strategies.

References

1. US Department of Health and Human Services. Surgeon General releases national health advisory on radon. Washington, DC: US Department of Health and Human Services; 2005. http://www.surgeongeneral.gov/pressreleases/sg01132005.html. Accessed January 7, 2011.
2. Reuben SH. Reducing environmental cancer risk: what we can do now. In: 2008-2009 Annual Report: President's Cancer Panel, US Department Of Health and Human Services; 2010. http://deainfo.nci.nih.gov/advisory/pcp/annualReports/pcp08-09rpt/PCP_Report_08-09_508.pdf. Accessed January 7, 2011.
3. *Health Effects of Exposure to Radon: BEIR VI*. Washington, D.C.: National Academy Press; 1999.
4. Marcinowski F LR, Yeager WM. National and regional distribution of airborne radon concentrations in US homes. *Health Phys*. 1994;66:699-707.
5. Generalised radon potential of United States: United States Geological Survey; 995. [updated October 13, 1995; cited June 8, 2011]; Available at: http://energy.cr.usgs.gov/radon/rnus.html.
6. Huda W. *Review of Radiologic Physics*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2010:104-105.
7. Narayanan PK, Goodwin EH, Lehnert BE. Alpha particles initiate biological production of superoxide anions and hydrogen peroxide in human cells. *Cancer Res.* 1997;57:3963-3971.
8. Jostes RF. Genetic, cytogenetic, and carcinogenic effects of radon: a review. *Mutat Res*. 1996;340:125-139.
9. Sawant SG, Randers-Pehrson G, Geard CR, Brenner DJ, Hall EJ. The bystander effect in radiation oncogenesis: I. Transformation in C3H 10T1/2 cells in vitro can be initiated in the unirradiated neighbors of irradiated cells. *Radiat Res*. 2001;155:397-401.
10.Brenner DJ, Little JB, Sachs RK. The bystander effect in radiation oncogenesis: II. A quantitative model. *Radiat Res*. 2001;155:402-408.
11. Brenner DJ, Sachs RK. Do low dose-rate bystander effects influence domestic radon risks? *Int J Radiat Biol*. 2002;78:593-604.
12. Azzam EI, De Toledo SM, Spitz DR, Little JB. Oxidative metabolism modulates signal transduction and micronucleus formation in bystander cells from alpha-particle-irradiated normal human fibroblast cultures. *Cancer Res*. 2002;62:5436-5442.
13. Breier R, Bohm R, Kopani M. Simulation of radiation damage to lung cells after exposure to radon decay products. *Neuro Endocrinol Lett*. 2006;27:86-90.
14. *International Agency for Research on Cancer Monographs on the Evaluation of Carcinogenic Risks to Humans: Man-Made Mineral Fibres and Radon*. Vol. 43. Lyon, France: IARC Press; 1988:33-171.
15. Hamza VZ, Mohankumar MN. Cytogenetic damage in human blood lymphocytes exposed in vitro to radon. *Mutat Res*. 2009;661:1-9.
16. Taylor JA, Watson MA, Devereux TR, Michels RY, Saccomanno G, Anderson M. p53 mutation hotspot in radon-associated lung cancer. *Lancet*. 1994;343:86-87.
17. Ruano-Ravina A, Faraldo-Valles MJ, Barros-Dios JM. Is there a specific mutation of p53 gene due to radon exposure? A systematic review. *Int J Radiat Biol*. 2009;85:614-621.
18. Ruano-Ravina A, Perez-Becerra R, Fraga M, Kelsey KT, Barros-Dios JM. Analysis of the relationship between p53 immunohistochemical expression and risk factors for lung cancer, with special emphasis on residential radon exposure. *Ann Oncol*. 2008;19:109-114.
19. Bastide K, Guilly MN, Bernaudin JF, et al. Molecular analysis of the Ink4a/Rb1-Arf/Tp53 pathways in radon-induced rat lung tumors. *Lung Cancer*. 2009;63:348-353.
20. Xu NY, Zhang SP, Nie JH, Li JX, Tong J. Radon-induced proteomic profile of lung tissue in rats. *J Toxicol Environ Health A*. 2008;71:361-366.
21. US Department of Health and Human Services. Public Health Service, National Toxicology Program. Report on Carcinogens, 11th Edition. 2005. http://ntp.niehs.nih.gov/ntp/roc/eleventh/profiles/s097zird.pdf. Accessed January 7, 2011.
22. Agency for Toxic Substances and Disease Registry (ATSDR). *Toxicological Profile for Radon*. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service; 1990.
23. Lubin JH, Boice JD Jr, Edling C, et al. Lung cancer in radon-exposed estimation of risk from indoor miners and exposure. *J Natl Cancer Inst*. 1995;87:817-827.
24. Lubin JH, Boice JD Jr, Edling C, et al. *Lung Cancer and Radon: a Joint Analysis of 11 Underground Miner Studies.* Bethesda, MD: National Cancer Institute; 1994. DHS Publ No. (NIH)94-3644.
25. Hornung R. Health effects in underground uranium miners. *Occup Med*. 2001;16:331-344.

26. Krewski D, Lubin JH, Zielinski JM, et al. Residential radon and risk of lung cancer: a combined analysis of 7 North American case-control studies. *Epidemiology*. 2005;16:137-145.
27. Krewski D, Lubin JH, Zielinski JM, et al. A combined analysis of North American case-control studies of residential radon and lung cancer. *J Toxicol Environ Health A*. 2006;69:533-597.
28. Darby S, Hill D, Auvinen A, et al. Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case-control studies. *BMJ*. 2005;330:223.
29. Darby S, Hill D, Auvinen A, et al. Residential radon and lung cancer: detailed results of a collaborative analysis of individual data on 7,148 subjects with lung cancer and 14,208 subjects without lung cancer from 13 epidemiological studies in Europe. *Scand J Work Environ Health*. 2006;32:1-83.
30. Lubin JH, Wang ZY, Boice JD Jr, et al. Risk of lung cancer and residential radon in China: pooled results of two studies. *Int J Cancer*. 2004;109:132-137.
31. Pershagen G, Akerblom G, Axelson O, et al. Residential radon exposure and lung cancer in Sweden. *N Engl J Med*. 1994;330:159-164.
32. Field RW, Steck DJ, Smith BJ, et al. Residential radon gas exposure and lung cancer: the Iowa Radon Lung Cancer Study. *Am J Epidemiol*. 2000;151:1091-1102.
33. Thompson RE, Nelson DF, Popkin JH, Popkin Z. Case-control study of lung cancer risk from residential radon exposure in Worcester county, Massachusetts. *Health Phys*. 2008;94:228-241.
34. Wilcox HB, Al-Zoughool M, Garner MJ, et al. Case-control study of radon and lung cancer in New Jersey. *Radiat Prot Dosimetry*. 2008;128:169-179.
35. Mahaffey JA, Parkhurst MA, James AC, et al. Estimating past exposure to indoor radon from household glass. *Health Phys*. 1993;64:381-391.
36. Baysson H, Billon S, Laurier D, et al. Seasonal correction factors for estimating radon exposure in dwellings in France. *Radiat Prot Dosimetry*. 2003;104:245-252.
37. Sanders CL, Scott BR. Smoking and hormesis as confounding factors in radiation pulmonary carcinogenesis. *Dose Response*. 2008;6:53-79.
38. Brenner DJ, Doll R, Goodhead DT, et al. Cancer risks attributable to low doses of ionizing radiation: assessing what we really know. *Proc Natl Acad Sci U S A*. 2003;100:13761-13766.
39. Kreuzer M, Muller KM, Brachner A, et al. Histopathologic findings of lung carcinoma in German uranium miners. *Cancer*. 2000;89:2613-2621.
40. Land CE, Shimosato Y, Saccomanno G, et al. Radiation-associated lung cancer: a comparison of the histology of lung cancers in uranium miners and survivors of the atomic bombings of Hiroshima and Nagasaki. *Radiat Res*. 1993;134:234-243.
41. Saccomanno G, Auerbach O, Kuschner M, et al. A comparison between the localization of lung tumors in uranium miners and in nonminers from 1947 to 1991. *Cancer*. 1996;77:1278-1283.
42. Yao SX, Lubin JH, Qiao YL, et al. Exposure to radon progeny, tobacco use and lung cancer in a case-control study in southern China. *Radiat Res*. 1994;138:326-336.
43. Environmental Protection Agency. *A Citizen's Guide to Radon. The Guide to Protecting Yourself and Your Family From Radon*. Washington, DC; Environmental Protection Agency. http://www.epa.gov/radon/pubs/citguide.html. Accessed January 11, 2011.
44. Lagarde F, Axelsson G, Damber L, Mellander H, Nyberg F, Pershagen G. Residential radon and lung cancer among never-smokers in Sweden. *Epidemiology*. 2001;12:396-404.
45. Baias PF, Hofmann W, Winkler-Heil R, Cosma C, Duliu OG. Lung dosimetry for inhaled radon progeny in smokers. *Radiat Prot Dosimetry*. 2010;138:111-118.
46. Streffer C. The ICRP 2007 recommendations. *Radiat Prot Dosimetry*. 2007;127:2-7.
47. Bonner MR, Bennett WP, Xiong W, et al. Radon, secondhand smoke, glutathione-S-transferase M1 and lung cancer among women. *Int J Cancer*. 2006;119:1462-1467.
48. Archer VE, Renzetti AD, Doggett RS, Jarvis JQ, Colby TV. Chronic diffuse interstitial fibrosis of the lung in uranium miners. *J Occup Environ Med*. 1998;40:460-474.
49. Lubin JH, Linet MS, Boice JD, Jr, et al. Case-control study of childhood acute lymphoblastic leukemia and residential radon exposure. *J Natl Cancer Inst*. 1998;90:294-300.
50. Raaschou-Nielsen O. Indoor radon and childhood leukaemia. *Radiat Prot Dosimetry*. 2008;132:175-181.
51. Angell WJ. The US radon problem, policy, program and industry: achievements, challenges and strategies. *Radiat Prot Dosimetry*. 2008;130:8-13.
52. Zeeb H, Shannoun F. *WHO Handbook on Indoor Radon: A Public Health Perspective*. Geneva, Switzerland: World Health Organization; 2009. Accessed June 8, 2011.
53. Field RW. Environmental factors in cancer: radon. *Rev Environ Health*. 2010;25:23-31.
54. Henschel DB. Analysis of radon mitigation techniques used in existing US houses. *Radiat Prot Dosimetry*. 1994;56:21-27.
55. Environmental Protection Agency, State of Iowa, Department of Public Health. Radon Reduction Methods - A Homeowners Guide. 1995; http://www3.abe.iastate.edu/human_house/pm1350.asp. Accessed June 8, 2011.
56. Rahman NM, Tracy BL. Radon control systems in existing and new construction: a review. *Radiat Prot Dosimetry*. 2009;135:243-255.
57. Stigum H, Strand T, Magnus P. Should radon be reduced in homes? A cost-effect analysis. *Health Phys*. 2003;84:227-235.
58. Coskeran T, Denman A, Phillips P, Tornberg R. A cost-effectiveness analysis of radon protection methods in domestic properties: a comparative case study in Brixworth, Northamptonshire, UK. *J Environ Radioact*. 2006;91:73-89.
59. Gray A, Read S, McGale P, Darby S. Lung cancer deaths from indoor radon and the cost effectiveness and potential of policies to reduce them. *BMJ*. 2009;338:a3110.
60. Mendez D, Alshanqeety O, Warner KE, Lantz PM, Courant PN. The impact of declining smoking on radon-related lung cancer in the United States. *Am J Public Health*. 2011;101:310-314.
61. Pass HI, Carbone DP, Johnson DH, et al. *Principles & Practice of Lung cancer: the Official Reference Text of the IASLC*. 4th ed. Philadelphia, PA: Wolters Kluver, Lipincott Williams & Wilkins; 2010.
62. Gonzalez CA, Riboli E. Diet and cancer prevention: contributions from the European Prospective Investigation into Cancer and Nutrition (EPIC) study. *Eur J Cancer.* 2010;46:2555-2562.
63. Hein MJ, Stayner LT, Lehman E, Dement JM. Follow-up study of chrysotile textile workers: cohort mortality and exposure-response. *Occup Environ Med*. 2007;64:616-625.
64. Hung RJ, McKay JD, Gaborieau V, et al. A susceptibility locus for lung cancer maps to nicotinic acetylcholine receptor subunit genes on 15q25. *Nature*. 2008;452:633-637.
65. Raaschou-Nielsen O, Andersen ZJ, Hvidberg M, et al. Lung cancer incidence and long-term exposure to air pollution from traffic. *Environ Health Perspect*. 2011;119:860-865.
66. Lubin JH, Boice JD Jr, Edling C, et al. Lung cancer in radon-exposed miners and estimation of risk from indoor exposure. *J Natl Cancer Inst*. 1995;87:817-827.
67. Darby SC, Whitley E, Howe GR, et al. Radon and cancers other than lung cancer in underground miners: a collaborative analysis of 11 studies. *J Natl Cancer Inst*. 1995;87:378-384.
68. Kreuzer M, Grosche B, Schnelzer M, Tschense A, Dufey F, Walsh L. Radon and risk of death from cancer and cardiovascular diseases in the German uranium miners cohort study: follow-up 1946-2003. *Radiat Environ Biophys*. 2010;49:177-185.
69. Wheeler BW, Allen J, Depledge MH, Curnow A. Radon and skin cancer in southwest England: an ecologic study. *Epidemiology*. 2012;23:44-52.