Environmental Factors in Cancer: Radon

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INTRODUCTION

Over 50% of the average individual's radiation dose comes from exposure to radon decay products. Two of the radon decay products, Polonium-218 and Polonium-214, account for the majority of the radiation exposure to the lungs. Because we are building homes without radon resistant features faster than we are mitigating homes to reduce radon concentrations, more people are exposed to radon than ever before. Furthermore, the increased use of medical procedures and tests that utilize radiation has increased substantially. The consequence of this mounting radiation exposure for an individual is genomic instability and an increased potential for cancer. In the following paper, the generic term radon will be used to refer to radon and its decay products.

CURRENT UNDERSTANDING

Radon Causes Lung Cancer Even Below the United States Environmental Protection Agency's (U.S. EPA's) Radon Action Level of 150 Bq/m^3 (4 pCi/L)

Exposure to radon is the second leading cause of lung cancer in the United States, and primary cause of lung cancer for individuals who have never smoked. The North American (Krewski et al. 2006, Krewski et al. 2005), European (Darby et al. 2006, Darby et al. 2005), and Chinese (Lubin et al. 2004) pooled residential radon studies all have reported statistically significant increases (ranging from 8% to 18% depending on the method of analyses) in lung cancer risk at 100 Bq/m^3 (2.7 pCi/L) (Table 1). It is worth noting that these direct risk estimates mirror the 12% increased-risk estimate at 100 Bq/m^3 that was predicted by the downward extrapolation of findings from the radon-exposed underground miners (National Research Council 1999).

Pooled Risk Estimates Likely Underestimate the True Risk Posed by Protracted Radon Exposure

There is substantial evidence to conclude that radon exposure may carry a higher risk for lung cancer than prior epidemiologic studies have reported. If the level of individual radon exposure is misclassified in a study, this generally causes the study to underestimate the risk. Nondifferential misclassification of exposure generally results in a bias toward the null when assessing the relationship between exposure and disease (Kelsey et al. 1986, Pierce et al. 1990). Misclassification of residential radon exposure can occur from: (1) errors in radon detector measurement; (2) the failure to consider temporal and spatial radon variations within a home; (3) missing information

Table 1. *Summary risk estimates from the Pooled Residential Radon Studies*

Residential Epidemiologic Study	# of Studies Pooled	# of lung cancer cases/controls	Increased risk per 100 Bqm^3	Increased risk per 100 Bqm^3 Adjusted for temporal radon variation	Increased risk at 100 Bqm^3 Analyses based on improved radon concentration data*
North American Pooled Analysis	7	3,662/4,966	11% (95% CI: 0% - 28%)	Pending**	18% (95% CI: 2% - 43%)
European Pooled Analysis	13	7,148/14,208	8% (95% CI: 3% - 16%)	16% (95% CI: 5% - 31%)	-
Chinese Pooled Analysis	2	1,050/1,995	13% (95% CI: 1% - 36%)	-	-

* Analysis restricted to individuals who resided in either one or two homes for the period 5 to 30 years prior to recruitment with at least 20 years covered by a year-long radon measurement.

** Smith B, Field RW, Zielinski J, Alavanja M, Klotz JB, Krewski D, Létourneau EG, Lubin JH, Lynch CF, Lyon JL, Sandler DP, Schoenberg JB, Steck DJ, Stolwijk JA, Weinberg C, Wilcox HB. A combined analysis of North American case-control studies of residential radon and lung cancer: Adjustment for variation in radon measurements. In preparation.

on radon exposure from other sites, such as prior homes; (4) the failure to properly link radon concentrations with subject mobility; and (5) measuring radon gas as a surrogate for radon progeny exposure (Field et al. 1996). Studies that are performed with methods that minimize exposure misclassification often report higher levels of risk for radon exposure. For example, in the North American pooled analysis (Table 1), lung cancer risk increased from 11% to 18% at 100 Bq/m^3 when the analysis was restricted to individuals who resided in either one or two homes for the period 5 to 30 years prior to recruitment and also had at least 20 years covered by a year-long radon measurement. The European Pooled Residential Radon Study performed an additional analysis, which attempted to adjust for some of the uncertainty in the temporal variation of radon. As shown in Table 1, this one adjustment, a regression calibration, doubled the lung cancer risk from 8% to 16% at 100 Bq/m^3 (2.7 pCi/L). A regression calibration for the North American Study is in progress (Smith et al. 2008). While the individual methods noted above help improve exposure assessment and decrease misclassification, most studies address only a few of the potential sources of exposure misclassification (Field et al. 1996). One particular residential radon case control study, the Iowa Radon Lung Cancer Study (IRLCS), incorporated methods to reduce the five sources of exposure misclassification (Field et al. 2000, Fisher et al 1998, Steck et al. 1999, Field et al. 1996). The National Research Council's Biological Effects of Ionizing Radiation (BEIR) VI Committee (NRC 1999) concluded that the power of a residential radon study to detect an excess lung cancer risk could be greatly enhanced by targeting populations that have both high radon exposures and low residential mobility. Iowa has the highest average radon concentration in the United States and very low population mobility. The IRLCS targeted women because they historically spent more time in the home and had less occupational exposure to lung carcinogens. Moreover, the IRLCS included only women who lived in their current home for at least 20 years. The IRLCS study design consisted of four strategic components to reduce exposure misclassification.

These were: 1) rapid reporting of cases; 2) mailed questionnaires followed by face-to-face interviews; 3) comprehensive radon exposure assessments; and 4) independent histopathologic review of lung cancer tissues. Through rapid case reporting, personal interviews were conducted with 69% of cases. The interview of live cases provided more accurate information than that obtained by interviewing relatives. The IRLCS incorporated the most advanced radon exposure assessment techniques ever performed in a residential radon study. Historical information of participant mobility within the home, time spent outside the home, and time spent in other buildings was ascertained. The mobility assessment accounted for the time the participant moved into their current home until study enrollment (Field et al. 1998). Numerous yearlong radon measurements were performed on each level of the participant's home. Outdoor radon measurements were also conducted in addition to workplace radon exposure assessments. All these spatially diverse measurements were linked to where the participant spent time, for at least the proceeding 20 years, in order to obtain a cumulative radon exposure for the individual.

The methodology used to calculate radon exposure in an epidemiologic investigation is particularly critical to assessing risk. As seen in Figure 1, the application of the more stringent, *a priori*-defined, IRLCS method to model radon exposure produced higher risk estimates (solid line) compared to the application of a less-stringent method (dashed lines). The later less-stringent method averaged the living area and basement radon measurement without linkage to participant mobility (Field et al. 1996) and is representative of the radon-exposure model used in both the North American and European pooled analyses. Importantly, Figure 1 illustrates how risk estimates may be underestimated in pooled analyses. Even when included in the pooling, well designed case-control studies may not benefit pooled analyses if the pooled analyses are performed using less rigorous methods than the original study to calculate radon exposure.

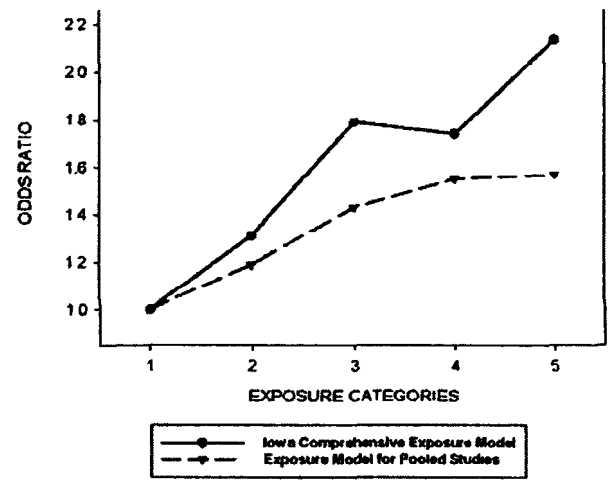

Fig. 1: Iowa radon lung cancer study

Most Radon-Induced Lung Cancers Occur Below the U.S. EPA's Radon Action Level

Because of the log normal distribution of radon, the vast majority of homes in the United States exhibit radon concentrations under the United States (U.S.) EPA's radon action level. However, in some states like Iowa, over half of the homes can exceed the radon action level. The National Research Council's (NRC 1999) BEIR VI committee has estimated that approximately one-third of radon-related cancers could be averted by reducing residential radon concentrations below 150 Bq/m^3 (4 pCi/L) nationwide. In order to reduce the overall number of radon attributable lung cancer deaths in the United States by 50%, radon concentrations in all homes in the United States could not exceed 74 Bq/m^3 (2 pCi/L).

Protracted Radon Exposure Increases the Risk of All Types of Lung Cancer

The Iowa Radon Lung Cancer Study found that large cell carcinoma exhibited a statistically

significant positive trend with increasing radon exposure. A suggestive trend was also noted for squamous cell carcinoma. However, all the histological types appeared to be elevated with protracted radon exposure and differences in the linear excess risks between histologic types was not significantly different (Field et al 2000). The European pooled analysis detected a significantly increased dose-response relationship for small cell lung cancer (Darby 2006, Darby 2005). However, similar to the Iowa Study, the variation between the dose-response relationships for the major histological subtypes did not differ. The investigators from the North American Pooling (Krewski et al. 2006, 2005) also reported that the largest risk was observed for small-cell carcinoma, but as noted in both the IRLCs and European Pooled Studies, the confidence limits overlapped the risk estimates for the other histologic types of lung cancer.

Table 2. *All cause estimated 2008 U.S. canxcer mortality by selected cancer types as compared to estimated radon-induced lung cancer mortality*

CANCER TYPE	ESTIMATED DEATHS*
1. Lung and Bronchus	161,840
2. Colon and Rectum	49,960
3. Breast Cancer	40,930
4. Pancreas	34,290
5. Prostate	28,660
6. Leukemia	21,710
Radon-Induced Lung Cancer	21,000
7. Non-Hodgkins Lymphoma	19,160
8. Liver and Bile Dudt5	18,410
9. Ovary	15,520
10. Esophagus	14,280
11. Urinary Bladder	14,000
12. Kidney and Renal Pelvis	13,010
13. Stomach	10,880
14. Myeloma	10,690
15. Melanoma	8,420

*Adapted from Jemal, A et al. (2008)

Radon is One of Our Major Environmental Toxicants in the United States

Radon is a potent environmental carcinogen. The National Research Council's BEIRVI Committee report (NRC 1999) provided the foundation for the U.S. EPA's (2003) most recent assessment of risks from radon in homes. Guided by the BEIR VI report, the U.S. EPA estimated that approximately 21,100 (14.4%) of the 146,400 lung cancer deaths that occurred nationally in 1995 were related to radon exposure. Among individuals who never smoked, 26% of lung cancer deaths were radon-related. The report also estimated that the lung cancer risk from a lifetime radon exposure at the U.S. EPA's action level of 150 Bq/m^3 (4 pCi/L) was 2.3% for the entire population, 4.1% for individuals who ever smoked, and 0.73% for individuals who never smoked.

Table 2 ranks the estimated 2008 mortality for radon-induced lung cancer in comparison to some other common types of cancer. While the risk of lung cancer from radon exposure pales to the risk of lung cancer posed by smoking, the number of radon-induced lung cancer deaths exceed the number of deaths for many other types of cancers (e.g., non-Hodgkin's lymphoma, liver, ovarian, kidney, melanoma, etc.) from all causes. In fact, comparative human health-based risk assessments performed by the U.S. EPA and numerous state agencies have consistently ranked radon among the most important environmental health risks facing the nation (Johnson 2000). Moreover, a 1998 Harvard Center for Risk Analysis study judged radon the number one health risk in the home (HCRA 1998). One can question whether the U.S. EPA's radon action level is sufficiently geared towards disease prevention, given the number of radon-induced lung cancer deaths and the fact that the radon-related risk of lung cancer can be lowered by minimizing radon exposure.

Mitigation and Radon Resistant New Construction (RRNC) Methods Are Available to Reduce the Risk

Well-established methods are available to reduce radon concentrations in homes to well below 150 Bq/m^3 (4 pCi/L) for existing homes that currently exhibit elevated radon concentrations (WHO 2008, Brodhead 1995, Brodhead et al. 1993, U.S. EPA 1992). For example, in a recent evaluation of the effectiveness of radon mitigation systems in Minnesota, Steck (2008) examined the pre and post mitigation radon test results for 166 homes. The median age of the mitigation systems was 2 years with a range from 0.5 to 7 years. Pre-mitigation radon concentrations averaged 380 Bq/m^3 (10.3 pCi/L), while post mitigation radon concentrations averaged 44 Bq/m^3 (1.2 pCi/L). In addition, cost-effective radon-resistant new construction (RRNC) methods that effectively impede radon entry into a home are available (U.S. EPA 2008, WHO 2008).

Individual Susceptibility to Radon-Induced Lung Cancer

Individuals who smoke have an increased susceptibility to radon-induced lung cancer, because of the sub-multiplicative association between radon and smoking (Krewski et al. 2006, Krewski et al 2005, Darby et al. 2006, Darby et al. 2005). While the data are generally lacking, it is likely that individuals who are exposed to other lung carcinogens (e.g., ETS, nickel, radiation from medical procedures, etc) as well as to mixtures of toxicants may also have increased susceptibility to radon-induced lung cancer. Furthermore, infants and children are generally considered more radiosensitive than adults. Unfortunately, studies have not been performed that directly assess whether or not elevated radon exposure in childhood infers greater risk of developing radon-induced lung cancer latter in life. Certain genotypes may predispose individuals to increased risk from protracted radon exposure. For example, it is estimated that 40% to 60% of Caucasians exhibit a null allele (i.e., homozygous deletion) for Glutathione-S-transferase M1 (GSTM1) and do not express the enzyme. Bonner et al. (2006) found that protracted radon exposure over 121 Bq/m^3 was associated with a 3-fold increase in lung cancer risk for individuals with a GSTM1 null genotype. Additional well-designed studies to examine the association between protracted radon exposure and factors contributing to individual susceptibility (e.g., genetic polymorphisms) warrant consideration.

Adverse Health Outcomes Related to Protracted Radon Exposure Other than Lung Cancer

Darby et al. (1995) have examined radon-related cancer specific mortality, other than lung cancer, in the miner populations that were included in the BEIR VI report (Darby et al. 1995). The study included over 64,000 workers who were employed in the underground mines for an average of six years. At the time of the publication, the miners were followed on average for 17 years. Statistically significant increases in risk were noted for leukemia in the period less than 10 years since starting work. Statistically significant increases in mortality were detected for both stomach and liver cancer, but the mortality findings for stomach and liver cancers were not related to cumulative exposure. Statistically significant exposure related excess relative risks were found also for pancreatic cancer, but this finding was considered a chance finding by the authors. A very recent study by Kreuzer et al. (2008) of 59,000 mine workers employed for at least 6 months from 1946 to 1989 at the former Wismut mining company in Eastern Germany detected statistically significant increases related to cumulative exposure in mortality for stomach and liver cancers. However, after the results were adjusted for potential confounders (e.g., dust, arsenic), they lost statistical significance.

The authors stated that the data "*provide some evidence of increased risk of extrapulmonary cancers associated with radon, but chance and confounding cannot be ruled out.*"

One of the limitations of both of these studies was the inability to assess cancer incidence. In addition, the miner-based studies included mostly men, which limited the generalizability of the findings. For example, studies have not been performed to assess possible associations between radon exposure and breast cancer. Another fairly recent epidemiologic study evaluated the incidence, rather than mortality, of leukemia, lymphoma, and multiple myeloma in Czech uranium miners (Řeřicha et al. 2007). The researchers reported a positive association between radon exposure and leukemia. Chronic lymphocytic leukemia (CLL) was also associated with radon exposure. This result is somewhat surprising because an increase in CLL has not previously been demonstrated to be associated with radiation exposure. Other studies, including a recent methodologically advanced study by Smith et al. (2007) found associations between indoor radon and leukemia, including CLL, at the geographic level. Over 20 ecological studies examining the relation between radon exposure and leukemia have been carried out. A review of many of these studies can be found elsewhere (Laurier et al. 2001). It should be noted that the above suggested associations have not been confirmed in either a well-designed case-control or cohort epidemiologic study performed in the general population (Laurier et al. 2001, Möhner et al. 2006).

In a recent review paper by Linet et al. (2007), the authors stated further studies are needed to assess the possible association between radiation, including radon, and CLL. In addition, because the skin, bone marrow, and kidney (in addition to the respiratory epithelium) may also receive appreciable doses in an elevated radon environment (Kendall at al 2002), well-designed analytic epidemiologic studies examining the possible association between protracted radon exposure and cancer incidence (e.g., leukemia, skin cancer, kidney cancer, etc.) are highly recommended.

RESEARCH AND POLICY NEEDS

Epidemiologic Research

Additional epidemiologic studies to assess risk factors affecting individual susceptibility (e.g., genetic polymorphisms) to protracted radon exposure as well studies investigating possible associations between radon exposure and cancer outcomes, other than lung cancer, are also recommended. These studies could, cost effectively, be included as components of on-going prospective cohort studies (e.g., National Children's Study, Agricultural Health Study, etc.) or initiated as new case control studies that include assessment of multiple toxicant exposures (e.g., planned studies of rare cancers, etc. (NCI 2008)). Fortunately, novel retrospective radon progeny detectors are now calibrated for use in large-scale epidemiologic studies. These glass-based detectors can provide reliable retrospective radon progeny assessment of exposures, including exposures that occurred decades ago, by measuring embedded radon decay products on glass surfaces (e.g., picture frames) that have been carried from house-to-house with the individual (Steck et al. 2002, Steck and Field 1999, Field et al. 1999, Steck et al. 1993).

Occupational Exposure

Workplaces have the potential for greatly elevated radon concentrations. In addition to underground miners, these occupations include: workers remediating radioactive-contaminated sites, including uranium mill sites and mill tailings; workers at underground nuclear waste repositories; radon mitigation contractors and testers; employees of natural caves; phosphate fertilizer plant workers; oil refinery workers; utility tunnel workers; subway

tunnel workers; construction excavators; power plant workers, including geothermal power and coal; employees of radon health mines; employees of radon balneotherapy spas (waterborne radon source); water plant operators (waterborne radon source); fish hatchery attendants (waterborne radon source); employees who come in contact with technologically enhanced sources of naturally occurring radioactive materials; and incidental exposure in almost any occupation from local geologic radon sources (Field 1999). In a recent survey of radon occurrence in Missouri, no significant differences were noted between the radon concentrations measured in homes versus nearby workplaces (Field et al. 2008), yet little focus has been placed on radon exposures occurring in the workplace. National strategies to reduce work-related radon exposures, as well as elevated radon in our nation's schools, are long overdue.

Policy

The U.S. EPA deserves significant credit for their tremendous leadership over the past 20 years to reduce radon exposure on many fronts. However, greater success has reportedly been impeded by the U.S. EPA's reliance on voluntary programs. The recent U.S. EPA's Office of Inspector General (OIG) Report states that "Nearly two decades after passage of the 1988 Indoor Radon Abatement Act (IRAA), exposure to indoor radon continues to grow. Efforts to reduce exposure through mitigation or building with radon-resistant new construction have not kept pace. Of 6.7 million new single family detached homes built nationwide between 2001 and 2005, only about 469,000 incorporated radon-resistant features. Of 76.1 million existing single family homes in the United States in 2005, only about 2.1 million had radon-reducing features in place" (EPA 2008).

Figure 2 from the report displays the difference between the number of single U.S. family homes

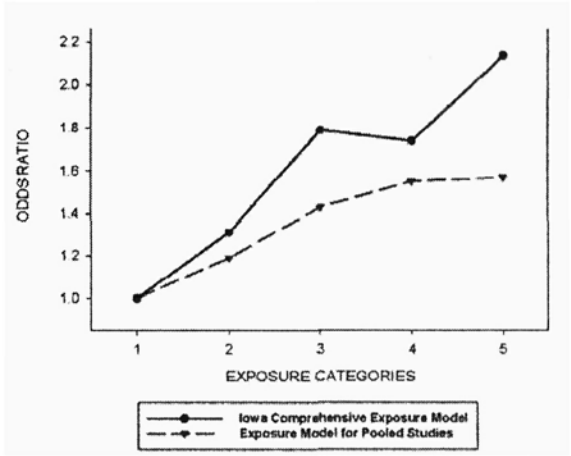

Fig. 2: Number of single U.S. family homes and number with radon-reduction features. Source: EPA 2008 Office of Inspector General Report

versus number of U.S. single family homes with radon-resistant features. Social-economically stressed individuals are particularly at risk for radon-related lung cancer. In addition to having elevated rates of smoking, they often rent homes without radon-resistant construction features, or if they own a home, they are often unable to pay the cost (~ $1,100 to mitigate an existing home) for a radon mitigation system. Among other recommendations, the U.S. EPA's Office of Inspector General strongly recommended that the U.S. EPA consider using their authority, including legislation, already provided under the 1988 Indoor Radon Abatement Act (IRAA) to reduce the risk posed by protracted radon exposure. There is precedent for legislating practices to limit exposure to toxins in construction. The prohibitive use of lead-based paint in the U.S. is an example. The requirement of radon-resistant construction methods, at an approximate cost of $500 per home, is cost-effective when one considers potential savings in health care expenditures from disease prevention. In a similar manner to smoking, where we are essentially allowing a "bioterrorist within" to attack over a million Americans each year, radon is a "dirty

bomb" within our homes that attacks millions of people each year. The adverse health effects from radon will increase as more people are exposed, with the aging of our population, and with increased medically-related radiation exposure. Numerous cost/benefit analyses have clearly indicated that both mitigation of existing homes and adopting radon resistant new construction features can be justified on a national level (WHO 2008, Steck 2008).

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