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SPECIAL ISSUE ON ENVIRONMENTAL FACTORS IN CANCER: PART 2

Selected papers from the President's Cancer Panel 2008-2009 Meeting Series

Guest Editor: R. William Field

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Preface

The role of the President's Cancer Panel, which reports directly to the President of the United States of America (U.S.), is to "monitor the development and execution of the activities of the U.S. National Cancer Program". This is the second, of a two part, special issue of *Reviews on Environmental Health* (Part 1 was published in December 2009 - Volume 24, No. 4) highlighting selected papers presented during 2008 and 2009 by prominent public health scientists, health advocates, and governmental representatives at four President's Cancer Panel meetings on *Environmental Factors in Cancer*, which were organized by the U.S. National Cancer Institute. The 2008-2009 meeting series explored the evidence regarding causal associations between environmental exposures and cancer, as well as the evidence assessing the magnitude of the cancer burden attributed to environmental exposures. The meeting series addressed a wide range of questions, including evaluating the adequacy of current governmental regulation and policies to protect workers and the public from exposure to carcinogens, the adequacy of research resources to evaluate the relations between environmental exposures and cancer, identifying workers and populations that are disproportionately affected by cancer, the health impact of agriculturally related chemicals on cancer, the contribution of foreign sources of carcinogens to the U.S cancer burden, and the increased cancer risk posed by medically related ionizing radiation exposure, former nuclear weapons testing, and radiation emitted from consumer goods.

The two-part special issue includes an introduction by Dr. LaSalle D. Leffall, Jr., who serves as chair of the President's Cancer Panel, and Dr. Margaret L. Kripke, a member of the President's Cancer panel, followed by a selection of the papers presented within the four topical areas—Part 1 - (1) Industrial and Manufacturing Exposures; (2) Agricultural Exposures; and Part 2 - (3) Indoor/Outdoor Air Pollution and Water Contamination; and (4) Nuclear Fallout, Electromagnetic Fields, and Radiation Exposure. The authors of the selected papers were provided an opportunity to perform minor editorial changes, but otherwise the papers remain relatively unchanged from those originally presented to the President's Cancer Panel as a "White Paper".

Although all papers presented to the President's Cancer Panel will be available as a U.S. government document, the importance of further global dissemination of the papers cannot not be overstated. As the special issue will be indexed in *PubMed* and other indexing/abstracting services, the special issue allows a greater identification and availability of these cutting-edge papers to a broader spectrum of researchers, public health professionals, health care experts, students, and scientific organizations. Enhanced communication between researchers, public health practitioners, government agencies, nonprofit organizations, and other stakeholders is critical to the goal of reducing the burden of environmentally-induced cancers.

We thank the President's Cancer Panel for providing this important forum to discuss environmental causes of cancer and look forward to their upcoming report to the President.

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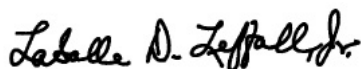
Introduction

The President's Cancer Panel (PCP, The Panel) is a Presidentially appointed Federal advisory committee established under the National Cancer Act of 1971. The Panel is charged with monitoring the development and execution of the activities of the National Cancer Program (NCP). To do so, the Panel holds at least four public meetings a year on a preselected aspect of the NCP to solicit input from a variety of stakeholders. The Panel summarizes findings from these meetings and makes recommendations focused on improving the NCP in an annual report to the President of the United States. For more information on the charter and mission of the President's Cancer Panel, please visit the PCP website at <http://deainfo.nci.nih.gov/advisory/pcp/pcp.htm>.

Because of issues raised in recent series' concerning the potential for increased cancer risk associated with various environmental contaminants and the growing body of research on such risks, the Panel concluded that an exploration of the current understanding and emerging science regarding environmental cancer risk would be both informative and timely for their 2008-2009 series. During this series, the Panel convened four meetings focused on industrial and occupational exposures, agricultural exposures, air and water contaminants, and ionizing and non-ionizing radiation exposures in relation to cancer risk. Through the course of these meetings, the Panel received testimony from 45 experts from academia, government, industry, and the environmental and cancer advocacy communities, as well as from the public. Many of the white papers published in this special edition of *Reviews on Environmental Health* are actual submissions from speakers who presented testimony during the 2008-2009 President's Cancer Panel meeting series. More information on the 2008-2009 meeting series including meeting statements and summaries are posted on the PCP website.

The Panel found that the percentage of cancers that develop as a result of environmental exposures is not known. Furthermore, it is believed that existing estimates are based on outdated science and significantly underestimate the actual influence of environment on cancer. Additionally, infants, children, and adolescents are especially vulnerable to environmental contaminants. Prevention efforts in environmental cancer are impeded by insufficient research and ineffective regulations. Research on environmental links to cancer and alternative green chemistry approaches been hindered by inadequate funding and workforce issues. The current regulatory approach in the U.S. is reactionary rather than precautionary and is impaired by inadequate funding and staffing, weak laws, decentralized and uneven enforcement, complex requirements, and industry influence. The Panel is summarizing its findings from the 2008-2009 meeting series and developing policy recommendations to the President for its upcoming report entitled, *Reducing Environmental Cancer Risk: What We Can Do Now*. The report will be released in January 2010 and will be available in PDF format on the PCP website. Hard copies of the report will be available in late winter 2010 and can be requested by contacting the Panel at pcp-r@mail.nih.gov.

Sincerely,



LaSalle D. Leffall Jr., M.D.
Chair, President's Cancer Panel



Margaret L. Kripke, Ph.D.
Member, President's Cancer Panel

Environmental Factors in Cancer: Radon

President's Cancer Panel - December 4, 2008

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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/m³ (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/m³ (2.7 pCi/L) (Table 1). It is worth noting that these direct risk estimates mirror the 12% increased-risk estimate at 100 Bq/m³ 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/m³ 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/m³ (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.

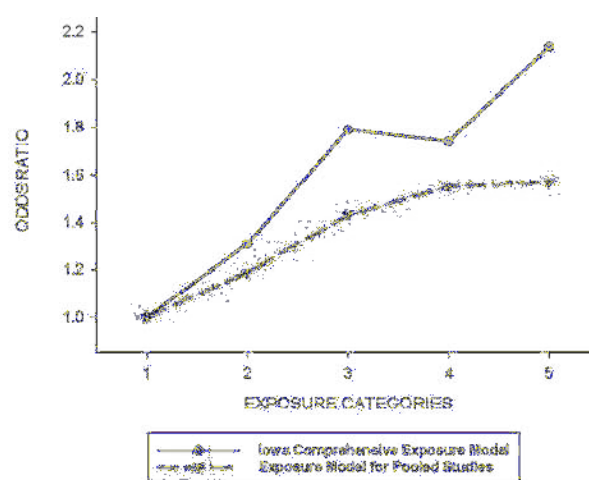


Fig. 1: Iowa radon lung cancer study

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.

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/m³ (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

Table 2. All cause estimated 2008 U.S. cancer 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 Duct5	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)

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 later 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 et 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

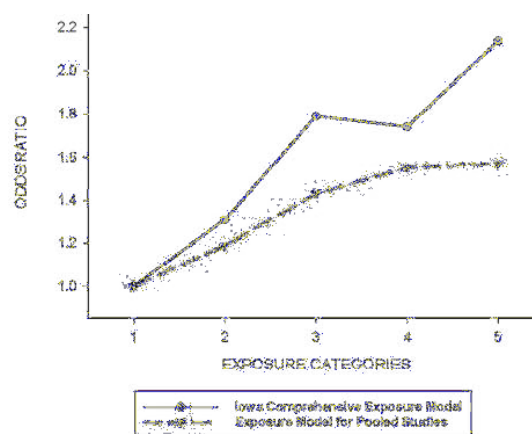


Fig. 2: Number of single U.S. family homes and number with radon-reduction features. Source: EPA 2008 Office of Inspector General Report

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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Environmental Factors in Cancer: Radon

President's Cancer Panel - December 4, 2008

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INTRODUCTION

Radioactive radon (more precisely radon-222) results from the decay of radium-226, which is the fifth decay product of uranium-238 and ubiquitous in soils and rocks /1/. Radon is an inert gas that can migrate along rock fissures and accumulate in enclosed areas, such as mine tunnels and houses. Radon dissipates rapidly in air and outdoor levels are typically low; however, in a few areas outdoor radon levels may exceed indoor guidelines /2,3/. Radon and its short-lived decay products polonium-218 and polonium-214 can be inhaled into the lung where alpha decay occurs. These alpha particles can interact with cells and directly or indirectly damage DNA. Radon represents about half of the population radiation dose from natural sources /4/. In vitro studies, experimental animal studies, radiobiological analyses, 15 cohort studies of radon-exposed underground miners and 22 case-control studies of residential radon exposure conclusively demonstrate that radon is a human lung carcinogen /1,5,6/.

These findings raise concerns about lung cancer risk to the general population exposed to relatively low concentrations of airborne radon in their homes. In 1988, the National Research Council's Committee on the Biological Effects of Ionizing Radiation (BEIR IV) reviewed all available science and pooled data from four cohort studies of miners to develop a lung cancer risk model for exposure to radon and its decay products /7/. In 1999, the BEIR

VI Report /1/ updated the review and conducted a new pooling of data from 11 cohort studies /8/ to develop new risk models for exposure. Governments and others have used these models to estimate radon-attributable lung cancers from residential radon exposure /1/. Estimates of the proportion of lung cancers attributable to residential radon include eight percent in Canada /9/, nine percent in Europe /10/, 2-12 percent in France /11/, seven percent in Germany /12/, four percent in the Netherlands /13/, 20 percent in Sweden /13/, and 10-15 percent in the United States (U.S.) /1,14,15/

In a few areas of the U.S., high concentrations of radon gas may occur in well water, which can add to indoor air concentrations when it is released during showering, washing clothes, flushing toilets, etc. /16/ Radon in water can also be ingested, potentially exposing internal organs. Dosimetric analyses identified a potential radiation dose from radon to the stomach and bone marrow; however, estimated doses are extremely low, and there is little epidemiologic evidence supporting an association between radon and cancers other than lung cancer /1,16/.

MEASURES OF EXPOSURE

Measures of exposure used in miner and residential radon studies have differed. Studies of miners use Working Level Months, which is a cumulative metric and a product of duration of exposure and Working Level, a measure of total

potential alpha energy from short-lived decay products per liter of air. In contrast, residential studies base cumulative exposure on the product of years of residential exposure and the number of alpha disintegrations per unit volume, measured in Becquerels per second per cubic meter, the preferred International Units, or pico-Curies per liter, an historical unit still commonly used (with $37 \text{ Bq/m}^3 = 1 \text{ pCi/L}$). Under standard conditions, 25 y in a home at 37, 100 and 148 Bq/m^3 (or 1.0, 2.7 and 4.0 pCi/L) results in approximately 3, 10, and 15 WLM of exposure to radon and its decay products, respectively /17/.

EPIDEMIOLOGIC STUDIES OF RADON-EXPOSED MINERS

The primary source of data for studying exposure to radon and its decay products and lung cancer has been epidemiologic studies of underground miners. The BEIR VI Committee /1/ pooled 11 studies with nearly 1.2M person-years of follow-up and nearly 2,800 lung cancer deaths. Every study reported significantly increased lung cancer mortality with exposure to radon and its progeny. Since 1999, this body of material has continued to grow. Several cohorts have been updated and additional cohorts reported /18/. There are now at least 15 studies with individualized radon exposure estimates, and the number of lung cancer deaths has more than doubled. Results continue to support the BEIR VI models. Although most cohorts enrolled uranium miners, populations were very diverse, involving workers at tin, iron ore and fluor spar mines. This diversity enhances validity, since concomitant mine exposures, such as diesel exhaust and airborne arsenic, would not be uniformly present.

Mean exposure in the miners was 164 WLM, about 10-fold the exposure from long-term residence at the U.S. EPA action level. However, the BEIR VI Report also presented results for

miners < 50 WLM, including 242K person-years and 110 lung cancer deaths in non-exposed miners and 450,000 person-years and 353 lung cancer deaths in exposed miners /1/. Mean exposure was 14.8 WLM, which is comparable to long-term residence in a home at the EPA action level. Risk estimates from this subgroup were nearly identical to the miner-based risk model, from the complete data, which further validated the risk model, as well as to residential studies (see below).

EPIDEMIOLOGIC STUDIES OF RADON EXPOSURE IN HOMES

Recognition that residential radon may represent the second leading cause of lung cancer raised concerns among scientists that differences between mine and home environments may effect validity of risk estimates from miner-based models. The application of miner-based risk models to exposures in homes are subject to multiple uncertainties, including: (i) differences in exposure rate and duration and in breathing patterns between working miners and home residents; (ii) differences between mines and homes in the proportions of radon and its decay products (equilibrium level) and in the presence of concomitant exposures; and (iii) the absence of data on the effects in females and in children /1/.

The BEIR VI Committee /1/ opined that the most direct way to assess the lung cancer risk with long-term residential radon exposure was with case-control studies of residentially exposed individuals. However, the ability to detect a dose-response relationship in residential studies is hampered by difficulties in reconstructing past exposures, the relatively low radon concentrations in most homes, and the low expected radon-associated lung cancer risk /19,20/. Consequently, large numbers of subjects are needed.

Investigators recognized that the pooling of original data from multiple studies offered the best

approach to address sample size limitations, in particular, to evaluate radon effects with increased precision, identify adjustment factors and test study homogeneity. In 1989, the U.S. Department of Energy and the Commission on European Communities sponsored a workshop that brought together investigators who had ongoing or planned studies of lung cancer and residential radon to establish a framework for data pooling /21/. In 1991 and 1995, additional workshops continued the harmonization process, including comparable radon measurement protocols that utilized long-term alpha-track detectors /22,23/.

Three distinct data pooling efforts emerged, including two studies in China /24/, 13 studies in Europe /10,25/ and seven studies in North America /17,26/. A world pooling of all studies is currently underway. Figure 1 is a forest plot of odds ratios /OR/ and 95 percent confidence intervals for the 22 studies. While results for individual studies varied, only three studies, Shenyang, Spain and Germany (western), had fitted ORs at 100 Bq/m³ (2.7 pCi/L) which were less than one. Note that if radon had no effect on lung cancer, the probability of 19 of 22 ORs being greater than one by chance is $p < 0.01$. The pooled ORs at 100 Bq/m³ for the China, Europe and North America studies were 1.13 (1.01,1.36), 1.08 (1.03,1.16) and 1.11 (1.00,1.28), respectively, and statistically significant. These ORs were remarkably similar to the estimate of 1.12 (1.02, 1.25) extrapolated from miner-based models /26/.

RADON-ATTRIBUTABLE LUNG CANCER

The BEIR VI Report provided estimates of attributable risk (AR) of lung cancer from radon for the U.S. population, defined as the proportion of all lung cancers attributable to lifetime exposure to radon /27/. The Report lists assumptions required for the calculations. These include: (i) linearity of the exposure-response at the lowest range of cumulative exposures for the general

population; (ii) comparable radon risks for durations of residential exposure in excess of 40+ years and at very low concentrations, e.g., <50 Bq/m³ (1.4 pCi/L); (iii) validity of risk models for females, since miner cohorts included only males; (iv) equivalent radon effects for all ages at exposure, e.g., analyses found no evidence that children are especially affected by radon just because of their age; (v) the effect of smoking on radon risks in miners applies to residential radon exposures, i.e., radon exposure has twice the effect on lung cancer risk in never-smokers compared to ever-smokers; (vi) the K-factor is one, i.e., the dosimetric analysis was correct in determining that one unit of cumulative radon exposure in mines and one unit in homes have equal effectiveness; and (vii) other differences between miners and those exposed in homes do not modify the risk model for radon exposure.

AR calculations combine miner-based risk models with the estimate of radon in U.S. homes, which was derived from a national survey /28/. The distribution of radon concentrations in U.S. homes is approximately log-normally distributed with geometric mean 24.8 Bq/m³ (0.67 pCi/L), geometric standard deviation 3.11 and arithmetic mean 47.2 Bq/m³ (1.28 pCi/L).

Calculations of the AR for lung cancer in U.S. males from lifetime residential radon exposure yielded an estimate range of 10-14 percent, with 95 percent uncertainty limits of 2-24 percent /1,15/. Assumption (iii), equivalent risks in females, implies that models are used without adjustment for females, resulting in a similar AR range for females. An estimated 162,000 new deaths (91,000 males and 71,000 females) from lung cancer are expected in 2008 (http://seer.cancer.gov/csr/1975_2005/results_single/sect_01_table.01.pdf).

Residential radon exposure is estimated responsible for 16,200 to 22,700 (95 percent uncertainty range, 3,200 to 39,000) lung cancer deaths, about 9,100 to 12,700 males and 7,100 to 9,900 females.

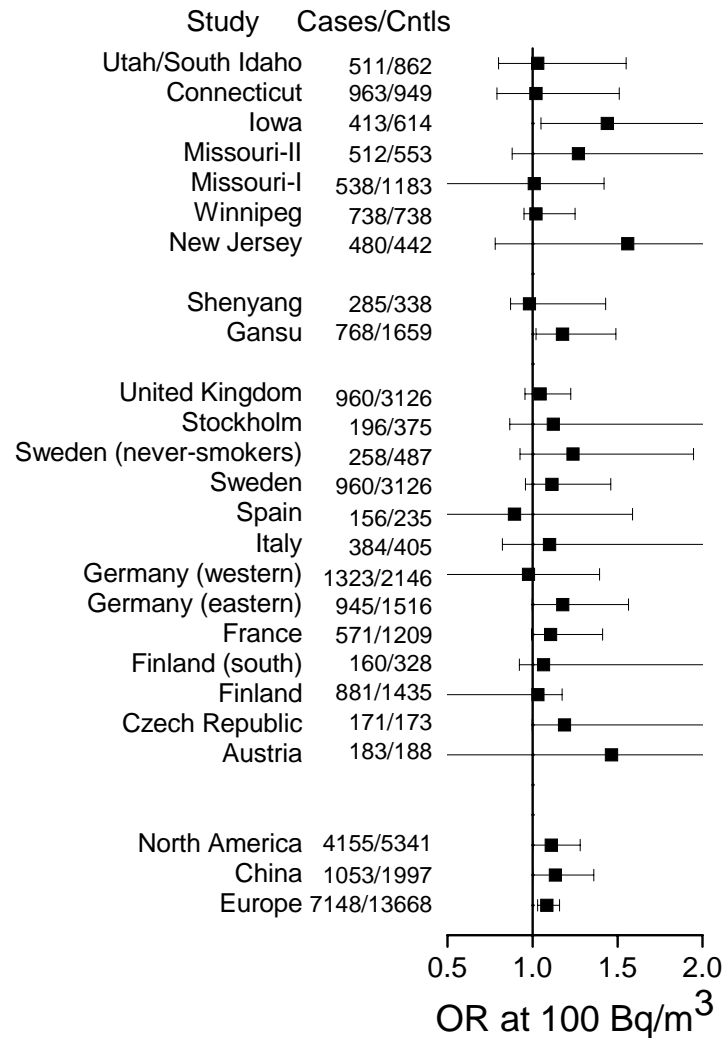


Fig. 1: Odds ratios (OR) at 100 Becquerels per cubic-meter (2.7 picoCuries per liter) and numbers of cases and controls in lung cancer case-control studies of residential radon exposure and summary OR estimates for pooled data for European, Chinese and North American studies.

The analysis of miners suggested enhanced effects of radon in never-smokers compared to ever-smokers, i.e., a sub-multiplicative association for radon and smoking. ARs for lung cancer from residential radon exposure were 9-13 percent among ever-smokers and 19-26 percent among never-smokers. Smoking is responsible for about 90 percent and 80 percent of lung cancers in males and females, respectively /29/. Thus, the estimated

radon-attributable lung cancer deaths number 4,400-6,100 in never-smokers and 12,500-18,000 in ever-smokers. Thus, although the AR for residential radon is greater in never-smokers, about three times the number of radon-attributable deaths occurs in ever-smokers.

Radioactive radon gas occurs naturally and exposure cannot be entirely eliminated. "Effective" AR indicates the proportion of lung cancer deaths

that would be eliminated if home radon concentrations were lower, but not reduced to ambient outdoor levels. Since the distribution of radon concentrations in U.S. homes is approximately log-normal, the bulk of homes have very low concentrations. About 4-6 percent of U.S. homes exceed the EPA action level for mitigation of 148 Bq/m³ (4 pCi/L). If homes above the current action level were mitigated to lower concentrations, then about one-third of the 16,200-22,700 radon-attributable lung cancer deaths could be prevented /1/. If homes above 74 Bq/m³ (2 pCi/L) were mitigated, then about half of radon-attributable lung cancer deaths could be prevented.

FINAL COMMENTS

Radon is one of the most extensively investigated human lung carcinogens /1,6/. Laboratory studies have demonstrated that cellular traversal of a single alpha particle can cause DNA damage, including double strand breaks, thus providing direct evidence of low dose effects /1/. In addition, alpha particles have other indirect genotoxic and non-genotoxic effects on traversed and neighboring non-traversed cells. Radiobio-logical analyses have described energy mechanics and cellular effects, including inverse dose-rate effects and the diminution of inverse dose-rate effects, both of which have been observed in data from cohort studies of miners /30/. Every epidemiologic study of exposed miners found that radon exposure increased lung cancer risk across the entire ranges of the observed radon exposure, a range that often includes cumulative exposures from long-term residence in homes at the EPA action level. Multiple case-control studies of residential radon exposure and lung cancer and the pooling of those studies confirmed the excess risk, which, moreover, was nearly identical to the extrapolation of risks based on the miners studies. The diversity and consistency of the information indicates that the

weight of evidence for radon carcinogenicity is overwhelming.

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