Environmental Factors in Cancer: Radon
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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 updated the review and conducted a new pooling of data from 11 cohort studies (8) to develop new risk models for exposure (1). 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 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 Bq/m^3=1 pCi/L). Under standard conditions, 25y 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 pooled 11 studies (Table 1) with nearly 1.2M person-years of follow-up and nearly 2,800 lung cancer deaths. The table shows that every study reported a 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 fluorspar 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 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 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-tract 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/m^3 (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/m^3 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/m^3 (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/m^3 (0.67 pCi/L), geometric standard deviation 3.11 and arithmetic mean 47.2 Bq/m^3 (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 16,200-22,700 (95 percent uncertainty range, 3,200-39,000) lung cancer deaths, about 9,100-12,700 males and 7,100-9,900 females.

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 occur 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/m^3 (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/m^3 (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. Radiobiological 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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