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Commentary

What are the risks of low-level exposure to α radiation from radon?

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Naturally occurring α radiation is ubiquitous in the environment, its primary source being radon gas. It has been estimated that radon, largely that in homes, constitutes more than 50% of the dose equivalent received by the general population from all sources of radiation, both naturally occurring and man-made (1). However, our knowledge of the mutagenic and carcinogenic potential of α radiation remains limited, particularly following low-level exposure such as occurs from residential radon.

The target organ for radon exposure is the epithelial lining of the lung, leading to an enhanced risk for the development of lung cancer. Epidemiologic studies of populations exposed to indoor radon have yielded conflicting results, and as a whole have not been very informative. One approach has been to utilize epidemiologic data from underground miners exposed to very high radon levels to estimate the risk associated with the very low levels present in homes (2). In their paper in the April 15 issue of the *Proceedings*, Hei *et al*. (3) present results from laboratory studies that shed new light on our understanding of the biological effects of α radiation.

There is a fundamental difference between α radiation and sparsely ionizing radiations (such as γ- or x-rays) in the way energy is distributed in irradiated cell populations or tissues. Primary ionizations will occur at intervals of 100 nm or more along a sparsely ionizing radiation track; γ- or x-rays will travel many centimeters in tissue before depositing all of their energy. This leads to a uniform distribution of energy and consequently radiation dose among the cells in the tissue, even at very low exposure levels. For α radiation, however, ionizations will occur every 0.2–0.5 nm (to put this in context, the two DNA strands in the double helix are approximately 2.5 nm apart), leading to an intense localized deposition of energy. Most α particles will travel only about 50 μm before expending all of their energy. Following low-level exposure as occurs from indoor radon, most cells in the bronchial epithelium would not be traversed by an α particle at all, and thus receive no radiation dose, while most of the others would be traversed by a single particle.

The effect on cells of traversal by a single α particle has been controversial. It has been proposed that most cells traversed by an α particle would be killed (4, 5), a phenomenon consistent with the intense deposition of energy that occurs within the cell nucleus and the clustered damage in DNA (6), as well as the evidence that DNA double-strand breaks induced by densely ionizing radiation are inefficiently repaired (7). If its primary effect was lethal, few irradiated cells in the tissue would survive to express a mutagenic event.

Hei *et al*. (3) make the important observation that in reality traversal by a single α particle has a low probability of being lethal to a cell: over 80% survive such an exposure. Moreover, the frequency of gene mutations is enhanced more than 2-fold over background in these surviving cells. The mutation frequency was further increased in cells traversed by up to four α particles, still with only a moderate cytotoxic effect.

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This research was made possible by the use of a unique microbeam radiation source, whereby individual cells can be irradiated with an exact, predetermined number of α particles.

These results are reminiscent of those of earlier studies with Auger-emitting radioisotopes, especially iodine-125 (^{125}I) (8). For each disintegration, ^{125}I releases 21 low-energy, densely ionizing Auger electrons, leading to an intense local deposition of energy. When ^{125}I is incorporated into DNA as [^{125}I]iododeoxyuridine, each disintegration leads to a DNA double-strand break (9, 10), most of these occurring within about 5 base pairs of the disintegration (11). Many earlier studies showed [^{125}I]iododeoxyuridine incorporated into DNA to be highly cytotoxic to mammalian cells. However, it is also highly mutagenic, even when normalized for the cytotoxic effect (8). These results as well as those of Hei *et al.* (3) are consistent with our current understanding that unrepaired or misrepaired DNA double-strand breaks are important mutagenic lesions, and most radiation-induced mutations are large-scale genetic events involving chromosomal deletions and rearrangements (12, 13).

What are the implications of the finding of Hei *et al*. (3) in terms of the risk of residential radon exposure? As they point out, an extremely small fraction of the epithelial cells in the human bronchial tree will be traversed each year by one or more α particles arising from residential radon exposure. Their results would indicate that this small population of cells is at significantly increased risk for the induction of mutations, presumably an early step in the induction of cancer. There is recent evidence to suggest, however, that the biological effects of α radiation in a tissue may not be restricted to those cells actually traversed by a particle. In cell cultures exposed to very low doses of α radiation, an enhanced frequency of sister chromatid exchanges (SCEs) has been observed in the chromosomes of many "bystander" cells, cells not traversed by an α particle and thus receiving no radiation exposure (14, 15). In one study, 30–50% of the cells showed an enhanced frequency of SCE after exposure to 0.3–2.5 mGy, doses leading to 1% or fewer of the cells being hit by an α particle (14). Enhanced expression of the p53 tumor suppressor gene has been shown to occur under similar conditions in bystander cells (16). In other studies, Kadhim *et al*. (17) reported the induction of genomic instability in mouse hematopoietic stem cells exposed to α radiation, leading to a persistently increased frequency of nonclonal chromosomal abnormalities arising in the progeny of the original irradiated cells after many generations of cell replication. A similar phenomenon has been reported in several other cellular systems after exposure to both densely and sparsely ionizing radiation (18–20). Evidence for these phenomena is derived largely from cell culture models, but it does suggest that biological effects of exposure to α radiation may extend beyond those cells actually traversed by an α particle, a phenomenon which could have significant impact on risk estimates.

Clearly, additional research is necessary to determine whether these factors are of consequence in the induction of lung cancer. The work of Hei *et al*. (3), however, indicates that many cells will survive traversal by one to four α particles to express a dose-dependent increase in the frequency of mutations. These findings

suggest a biologic basis for the validity of utilizing data for high-level radon exposure from the uranium miners, where most of the target cells will receive multiple hits, to estimate risks for low-level residential exposure. Epidemiologic support for this approach comes from a recent meta-analysis of eight completed case-control studies of indoor radon exposure (21). This analysis has yielded a trend of increasing risk with exposure very similar to that estimated by extrapolation from the data for those uranium miners with relatively low cumulative exposures. Overall, these results suggest that of the order of 15,000 lung cancer deaths in the United States each year may indeed result from indoor radon exposure, and that radon in homes may represent a significant public health problem (2).

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