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Perspective Article

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Radionuclide-induced skeletal cancers

S.C. Miller

Division of Radiobiology, University of Utah School of Medicine, Salt Lake City, UT, USA

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Internally incorporated alpha particle-emitting bone-seeking radionuclides are potent carcinogens[1]. Plutonium, for example, is one of the most feared compounds known and these are exacerbated by recent terrorism concerns. The transuranium elements neptunium, plutonium, americium, curium, californium and einsteinium are produced in significant amounts in nuclear reactors and constitute long-lived components of nuclear waste. These nuclides are also used in thermoelectric power sources, cardiac pacemakers, smoke detectors, etc. Scientific studies are needed to add clarity to the risk and use of these materials, in addition to furthering our understanding of disease mechanisms associated with human exposures. This information may have substantial influence on public policy decisions (e.g. energy policy) and protection of workers and the public.

Toxicity of internally deposited alpha-emitting bone-seeking radionuclides

The consequences of human exposures to bone-seeking, alpha-emitting nuclides date to the early part of the 1900s. Radium salts were used in industrial applications and biological effects were first observed in watch-dial painters. These were mostly young women who had substantial internal ingestion of radium salts. The skeletal effects, described as "radium jaw" were first observed by a New York dentist in 1924[2]. Later reports showed radiographic changes in skeletal tissues after ingested radium and mesothorium from watch dial painting and patients injected with 226Ra to treat schizophrenia[3,4] or 224Ra for ankylosing spondylitis and tuberculosis[5]. Radium-induced malignancies have been documented in this population and include both a sharp excess of skeletal and breast cancers[5,6]. The human radium experience continues to serve as the basis for estimating health risks and the setting of population and occupational exposure limits.

Internal deposition of the transuranium elements is characterized by their firm fixation in and slow release from body organs. This and their high biological effectiveness for tumor induction from their alpha-radiation constitutes a major portion of the risk associated with accidental or environmental exposures. The potential for induction of various neoplasms resulting from internal deposition to plutonium, other actinide elements or radium is now well recognized[1].

Relative risk of bone cancers from different nuclides in experimental studies

Lifespan carcinogenesis studies conducted in beagle dogs were started in the 1950s and analyses continue to the present[7]. These studies provided substantial information on the relative toxicity of bone-seeking nuclides in an animal model that approximated the human. The relative toxicity or "toxicity ratio" defined as the relative effectiveness per gray of average skeletal radiation dose compared to 226Ra was estimated in animals exposed to various nuclides as young adults. These are summarized in Table 1.

Differential deposition and retention patterns of nuclides in skeletal tissues - implications for carcinogenicity

Bone cancer risk per unit of average skeletal radiation dose varies among the nuclides (Table 1). This is likely due to differences in their localization and distribution within the skeletal tissues. Recent work has focused on the local microdistribution of nuclides and the cell populations at risk for exposure to alpha emissions[9]. For example, 239Pu initially deposits on bone surfaces where it may expose cells at or near the bone surface. With bone remodeling, the initial 239Pu deposits are buried in bone where fewer cells would be at risk for alpha radiation. By contrast, radium tends to deposit in the bone volume, perhaps following pathways of calcium or bone fluids. Thus, the larger numbers of osteogenic cells on the bone surface would be less likely to

Corresponding author: Scott C. Miller, Ph.D., University of Utah School of Medicine, Division of Radiobiology, 729 Arapeen Drive, Suite 2334, Salt Lake City, UT 84108-1218, USA
E-mail: scott.miller@hsc.utah.edu

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Table 1. The toxicity for skeletal cancer induction per Gy of average skeletal dose relative to 226Ra[8].

Nuclide	Exposure	Toxicity Ratio ± SD
226Ra	Single exposure	1.00
239Pu	Single exposure	16 ± 5
239Pu	Continuous exposure	32 ± 10
224Ra	Chronic exposure	16 ± 5
224Ra	Single exposure	6 ± 2
228Th	Single exposure	8.5 ± 2.3
241Am	Single exposure	6 ± 0.8
249Cf	Single exposure	6 ± 3
252Cf	Single exposure	4 ± 2

be exposed to an alpha emission from 226Ra vs. 239Pu. This likely accounts for the much greater carcinogenicity of 239Pu than for 226Ra[10].

Tissue properties of skeletal sites prone to develop tumors with bone volume- or bone surface-seeking radionuclides.

The distribution and skeletal characteristics of sites of primary tumor occurrence observed in dogs exposed to bone surface-seeking 239Pu compared with bone volume-seeking 90Sr, 241Am, 228Th, 249,252Cf, 224Ra and 226Ra has been compared[11]. In the 239Pu vs. 226Ra exposed animals, there were significantly more 239Pu tumors in the vertebra but less in the calvarium, maxilla, and most of the long bones. In humans, a large percentage of suspected radium-induced bone cancers were observed in the appendicular skeleton[12]. In experimental studies, 239Pu but not 226Ra tumors were statistically more likely to occur in tissue sites that had red bone marrow (vs. fatty marrow) and sites with greater relative bone turnover rates[11,13]. Radium tumors have a greater likelihood of occurring in cortical bone whereas plutonium tumors tend to occur in red bone marrow, higher turnover cancellous bone sites.

Premalignant changes in skeletal tissues with radium vs. plutonium

Radium-226 causes substantial histopathological damage to the skeleton that includes microvascular damage, local bone necrosis and osteopenia, and a proliferative fibrous response, similar to osteitis fibrosis. At dose levels where these tissue reactions are observed, there is a strong probability of tumor induction. While some endosteal "damage" has been reported following 239Pu exposures, extensive tissue changes prior to malignant transformation are generally not observed.

Plutonium-induced skeletal cancers in humans

In spite of common beliefs, there are no statistically confirmed occurrences of plutonium-induced skeletal cancers in the United States, except for possibly one tumor that developed in a former Los Alamos worker. However, in Russia, exposures to plutonium were common and also more severe when they occurred. Recently, we have reported a greater bone cancer occurrence among Russians who worked in plutonium production facilities[14]. Similar to what was observed in experimental studies, the majority of the skeletal tumors occurred in the axial skeleton (73%).

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