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CANCER FROM INTERNAL EMITTERS

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INTRODUCTION

Irradiation from internal emitters, or internally deposited radionuclides, is an important component of radiation exposures encountered in the workplace, home, or general environment. Proper control of these sources of radiation requires a thorough understanding of the lifetime health risks of different internal emitters and factors that can influence these risks. Long-term studies of human populations exposed to various internal emitters by different routes of exposure are producing critical information for the protection of workers and members of the general public. Within the past several years, a number of interesting developments have occurred in this field. The purpose of this report is to examine these developments and discuss their potential importance for understanding lifetime cancer risks from internal emitters.

The major populations of persons being studied for lifetime health effects from internally deposited radionuclides are well known: lung cancer in underground miners who inhaled Rn progeny, liver cancer from persons injected with the Th-containing radiographic contrast medium Thorotrast, bone cancer from occupational or medical intakes of ^{226}Ra or medical injections of ^{224}Ra, and thyroid cancer from exposures to iodine radionuclides in the environment or for medical purposes. These studies, except for the thyroid studies covered elsewhere in this Symposium, form the basis for this report. The emerging data base on lung cancer in plutonium workers exposed in the early days of the MAYAK facility in Russia should also yield important information. Three recent publications provide a wealth of current information on the results and current activities in these studies. These publications are the UNSCEAR (1994) annex on radiation carcinogenesis epidemiology (1), a history of radium studies in the United States by Dr. Robert Rowland (2), and the proceedings of an international meeting on the health effects of internally deposited radionuclides held in Heidelberg in 1994 (3).

LUNG CANCER

In the 1988 BEIR IV report (4), a combined analysis was reported of four cohort studies of underground miners exposed to Rn progeny. This combined analysis involved 433,000 person-years, PY, at risk and 459 lung cancer deaths. Substantial new information on Rn progeny-exposed miners has become available recently, particularly the report on Chinese tin miners by Xuan *et al.* (5) on 135,000 PY at risk and 936 lung cancer deaths and the report on miners in W. Bohemia by Tomasek *et al.* (5) with 104,000 PY and 656 lung cancer deaths.

Lubin *et al.* (5) have conducted a joint analysis of original data from these six studies and five others representing cohort studies all currently available on miners exposed to Rn progeny (909,000 PY and 2597 lung cancers). In their analysis, Lubin *et al.* used a relative risk model in which the excess relative risk per WLM, ERR/WLM, was adjusted for the decreasing effectiveness of past exposures and attained age. It was also adjusted for the duration of exposure to compensate for frequent observation that prolonged exposures at lower exposure levels were more carcinogenic than shorter exposures at high

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levels. There was reasonably good agreement among the ERR/WLM values determined for each study with the value for the combined studies.

The availability of the large combined-study data base made it possible to examine the influence of smoking on the observed lung cancer risks. The analyses indicated that the response was sub-multiplicative but more than additive. The influence of combined exposure to arsenic was also found to be important in several studies. It is likely that there are additional confounding factors that must be identified and accounted for as these results are further refined and extrapolated to possible lower-level exposures in home environments.

LIVER CANCER

The status of studies on Thorotrast-injected patients in Germany, Denmark, and Japan has been recently updated (3). In the German study of 2326 subjects, only 85 are alive, and in the Danish study, there are 40 living subjects out of a total of 1003. The Japanese studies are smaller, and a somewhat larger percentage is still alive. In the German study, diseases that have occurred with high excesses are liver cancer, 410, liver cirrhosis, 186, myeloid leukemia, 36, and bone-marrow failure, 29. Less frequently occurring diseases that may have an excess incidence include cancers of the extrahepatic bile ducts, gallbladder and pancreas, and several other diseases.

Figure 1 illustrates several important features of liver cancer risk in the German study. These curves were computed by deleting the dose accumulated over the 10 y preceding death on the assumption that the dose was "wasted" because the cancer growth had already begun by this time. A minimal latent period of about 20 y after Thorotrast injection is apparent, as is a clear difference in the risks observed in males and females, reaching values of 680 and 400 per 10^4 PGy, respectively. A similar pattern of increasing risk with increasing time after Thorotrast injection has been observed in the Danish studies by Andersson *et al.* (3) leading to a risk coefficient for both genders combined of 510 per 10^4 PGy using 10 y for the wasted dose. When a larger amount of cumulative dose is discarded, the resulting risk coefficient will be higher. When Andersson *et al.* used 15 y, the risk coefficient became 712 liver cancers per 10^4 PGy. Obviously, it is very important to control these and other variables in making interstudy comparisons.

BONE CANCER

Studies on ^{226}Ra-exposed persons in the United States have spanned a period of about 70 years since the early studies by Martland *et al.* and somewhat later by Dr. Robley Evans (2). These various studies were eventually combined into the Center for Human Radiobiology at Argonne National Laboratory, and considerable effort was devoted to identifying and locating subjects. The most recent listing of subjects (both dial workers and other types of exposure) contained 2383 cases with measured burdens (64 bone sarcomas and 32 head carcinomas) and 4292 cases that were unmeasured (21 bone sarcomas and 5 head carcinomas). Most of these cancers occurred in female dial painters who entered the industry prior to 1950 (46 bone sarcomas and 19 head carcinomas). Rowland recently reported on a dose recalculation associated with a revision in the skeletal retention parameter used. For bone sarcomas, he obtained a satisfactory fit to the data using the relationship Incidence = Constant + $\beta D^{3.15} e^{-\gamma D}$ where D = intake; and β and γ are constants. No bone sarcomas were seen in 1339 individuals with systemic intakes of ^{226}Ra and ^{228}Ra less than a fitted value of 2900 kBq (79 μCi) (Fig. 2). After comparable dosimetric calculations for the head carcinoma cases, both linear, $I=\alpha D$, and square-

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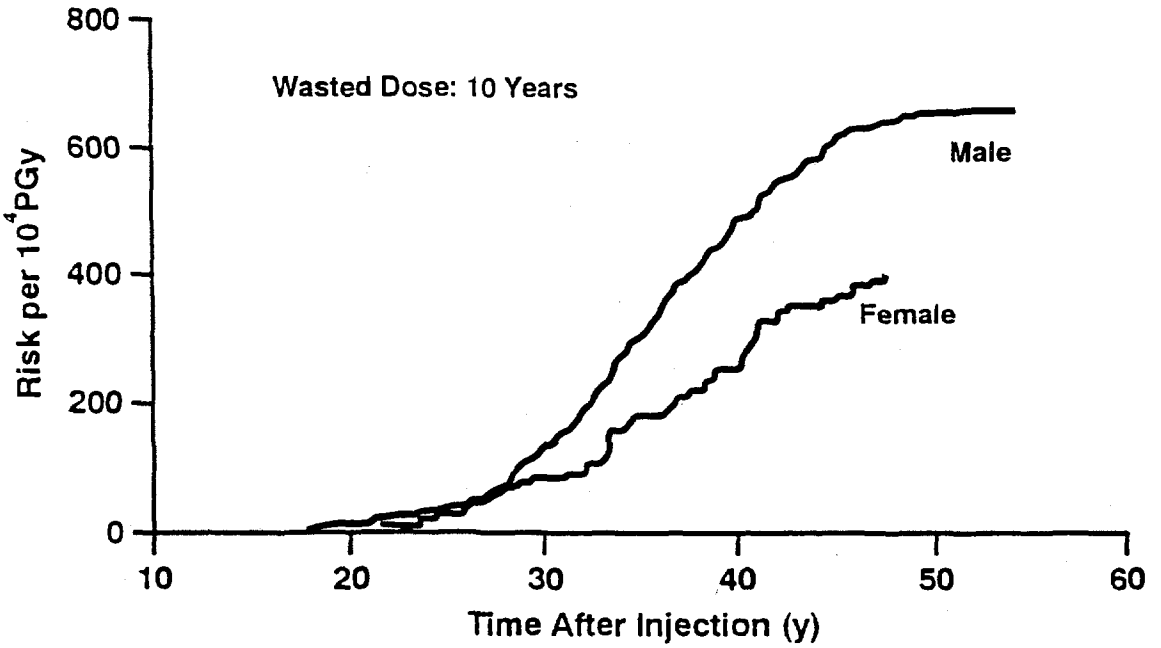

Figure 1 Risk estimates for liver cancer as a function of time after Thorotrast injection [re-drawn from van Kaick *et al.* (3)].

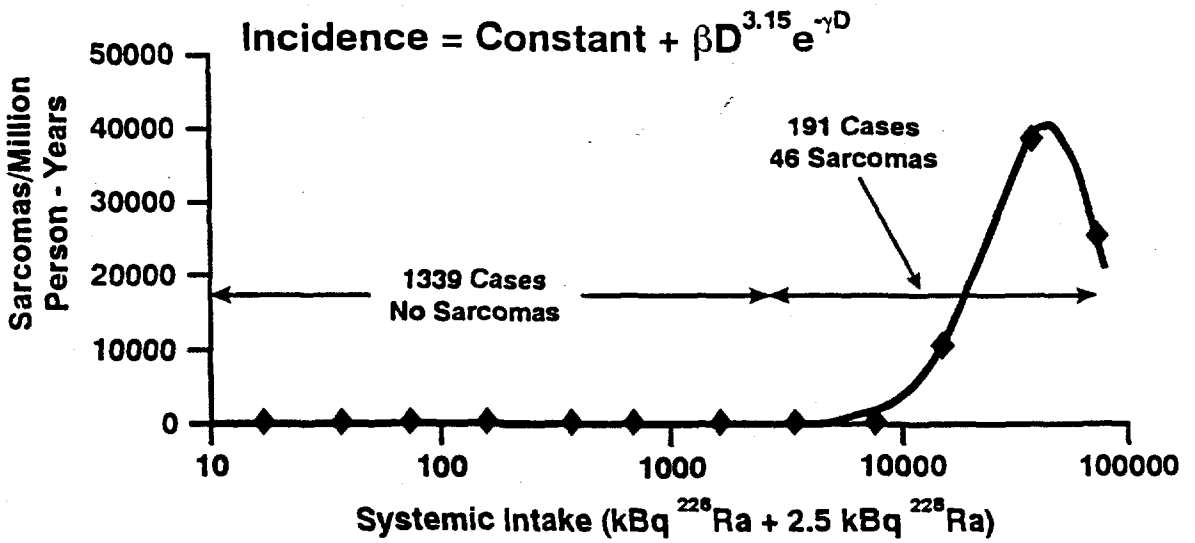

Figure 2 Incidence of bone sarcomas as a function of the intake of ^{226}Ra and ^{228}Ra in female dial workers who entered the industry before 1950 [Re-drawn from Rowland (3)].

exponential, $I=\beta D^2 e^{-\gamma D}$, functions fit the data adequately. Like the bone-sarcoma results, no head carcinomas occurred in 1395 cases with the lowest intakes but the apparent fitted threshold values were quite small and statistically insignificant. The U.S. Department of Energy terminated these studies in September 1993. Thus, it is unlikely that the database will change. Rowland's book (3) provides a very useful listing of details on each measured subject including values for intake and doses received from ^{226}Ra and ^{228}Ra.

Studies on persons injected with the short-lived isotope ^{224}Ra, $T_{1/2}$=3.62 d, conducted by Dr. H. Spiess, the late Dr. Charles Mays, and others provide additional information on bone cancer from alpha irradiation. In contrast to the continuing alpha irradiation of the skeleton for the remainder of life after injection of ^{226}Ra, the total doses from ^{224}Ra is received in less than 30 d. Because of this, many ^{224}Ra treatment protocols for ankylosing spondylitis involved multiple injections protracted over time.

In the cohort studied by Spiess and Mays, there were 900 subjects, about one-third of whom are currently alive. The most prominent finding has been bone cancers, 55, that appeared in a wave-like pattern. No new bone tumors have been seen since 1988 but breast cancers continue to occur at higher than normal rates, particularly in females who were injected with ^{224}Ra before the age of 20. At the present time, because there is no dose-response relation for these tumors, some other cause(s) may be responsible. However, breast cancer in Beagle dogs injected with ^{224}Ra tends to occur earlier than in the control dogs (B. A. Muggenburg, Personal Communication). Future attention needs to be directed to this question.

EXTRAPOLATION TO OTHER RADIONUCLIDES

From the information presented here, it is obvious that there are substantial gaps in the human data related to different routes of exposure, different radionuclides, age, health status, etc. Other approaches are necessary to fill these gaps. Life-span studies of laboratory animals have been, and are being conducted for this purpose. The importance of this approach is detailed in reference (3) and discussed in the Archive Symposium proceedings later in this volume.

ACKNOWLEDGEMENT

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