Incidence of Plutonium-induced Bone Cancer In Neutered Mice

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ABSTRACT

The incidence of bone cancer, after a single i.p. injection of monomeric {superscript 239}Pu citrate, is significantly higher in female than in male mice. To evaluate the role of the gonads in this sex-related difference, male and female C57BL/Do (albino) mice were castrated at 40 days of age. Fifty days later, they were given injections of {superscript 239}Pu. After castration, the frequency of bone sarcomas in the two sexes was approximately equal. This resulted from an increased incidence in the castrated males and a decreased incidence in the ovariectomized females as compared to the intact plutonium-treated mice.

RESULTS AND DISCUSSION

Gonadectomy produced a marked change in the incidence of plutonium-induced bone cancer at 2 dosage levels (2.9 and 0.9 μCi/kg) in C57BL/Do (albino) mice (Table 1). Compared to the intact animals, the incidence rose appreciably in the castrated males (χ² significant at p < 0.5), and a prominent decrease occurred in the ovariectomized females (χ² significant at p < 0.05). After castration, the bone tumor incidence in the males was approximately equal or slightly higher than observed in the neutered females, indicating that the sex-related difference in the incidence of plutonium-induced bone cancer is gonad dependent. The testicle appeared to inhibit, and the ovary to promote, the formation of radiation-induced bone tumors. Bone neoplasia was not observed in the nonirradiated intact or neutered mice.

The much higher frequency of bone sarcomas in intact female mice cannot be due to a difference in radiation dose since Smith et al. (21) have demonstrated a higher retention of monomeric plutonium in intact male as compared to female mice. This sex-related metabolic difference in retention was eliminated when the males were castrated prior to injection (22). Ovariectomy did not change the retention of plutonium in the females, but plutonium retention in castrated males decreased to that in the females (22). Since the tumor incidence was highest in the intact females which have the lower retention, it is obvious that the higher bone tumor incidence in female mice was not the result of higher skeletal concentrations of the radionuclide.

The mechanisms involved in the sex-related differences in bone carcinogenesis in mice are as yet undetermined, although it has been postulated that the effect is related to the osteogenic stimulation produced by estrogens (18). In the mouse, the sex difference is clearly gonad related (25), and estrogens appear to exert a significant effect. For example, Nilsson and Rönnbäck (18) have demonstrated that long-acting estrogens given s.c. significantly increased the incidence of {superscript 90}Sr-induced bone tumors in mice. The estrogens appear to act as promoting rather than initiating agents. This is indicated by their ability to increase the bone sarcoma incidence in irradiated mice but not in their unirradiated controls.

A feature of mice that may possibly be a factor in the significantly higher osteosarcoma incidence in females is their unusual skeletal response to estrogens. In mice, endosteal disturbances...
bone growth is produced by estrogen administration in both females and males, and prolonged treatment will eventually lead to closure of the marrow cavities in some of the long bones (28). The closure of the marrow cavities occurs physiologically during the preovulatory phase of the egg-laying cycle in birds (11), but only after estrogen administration in mice. The pronounced endosteal response of the mouse to estrogens does not occur in some of the other commonly used laboratory animals such as rats, hamsters, rabbits, cats, and dogs, which are species that do not show a sex-related difference in the incidence of bone cancer (27). Mice are also unique in their prolonged estrogen retention in the skeleton (1), in their specific estrogen localization along the endosteum (4), and in their metabolism of testosterone and progesterone (1). 

Whether or not enhanced osteogenesis is a promoting factor (14) in the development of bone cancer has not been unequivocally demonstrated; however, there is evidence supporting such a hypothesis. For example, children who develop bone cancer tend to be taller than their age-matched cohorts (9); degenerative bone conditions such as Paget's disease and osteoporosis are associated with an increased incidence of bone cancer (12, 19); and the incidence of bone cancer in the various canine breeds increases with body weight (3, 26). A factor that does not support this hypothesis is the absence of bone tumors in the sites of pathological fractures in heavily irradiated dogs (24). Also, experimentally induced fractures in irradiated mice did not increase the osteosarcoma risk (10). Thus, it is possible that estrogenic promotion of bone cancer in mice is independent of osteogenesis. Such a conclusion is consistent with the observation in this study that gonadectomy produced obvious differences in the incidence of bone tumors but did not induce microscopic or radiographically apparent changes such as an increase in trabecular bone which occurs with estrogen administration. Cellular kinetic evaluations have not yet been made.

The reason for the apparent inhibitory affect of the testicle on induction of radiation-induced bone cancer in mice is not resolved. However, one possibility is inhibition of estrogen binding to skeletal receptor sites by testosterone. For example, testosterone-induced inhibition has been demonstrated at estrogen receptor sites in endothelial cells (5), and testosterone-induced inhibition of estrogens in the skeleton has been reported in the mouse by Gardner and Pfeiffer (8). However, Urist et al. (28) were not able to demonstrate any inhibitory effect in bone related to relatively high doses of testosterone.

Ovariectomy also increased the interval from radionuclide injection to death with bone tumor on or before the indicated time, divided by the number of injected mice.

<table>
<thead>
<tr>
<th>Injected dose (μCi 239Pu/kg)</th>
<th>Female</th>
<th>Male</th>
<th>Neutered</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.9</td>
<td>2/12 = 17% (596 ± 16)</td>
<td>13/28 = 46% (491 ± 103)</td>
<td>14/28 = 50% (515 ± 101)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.9</td>
<td>1/16 = 6% (694)</td>
<td>4/17 = 24% (766 ± 92)</td>
<td>6/13 = 46% (749 ± 140)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0/15 = 0% (698 ± 129)</td>
<td>0/15 = 0% (724 ± 108)</td>
<td>0/17 = 0% (723 ± 138)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Numbers in parentheses, average days ± S.D. from injection to death for those plutonium-injected animals that developed osteosarcomas and for all of the control mice.
cancer was similar in the neutered animals of both sexes (Table 3, in which the number of tumor sites was significantly increased, resembled that of the intact females (Tables 2 and 3). The frequency of tumors in the axial skeleton was approximately twice that in the appendicular sites in both intact and neutered mice. Thus, castration did not appear to change the regional distribution of radiation-induced bone cancer.

Although the incidence of bone tumors induced in humans by internal emitters is approximately equal in both sexes (23), as it is in the beagle (15) and the rat (2), subtle sex-related differences in the incidence of naturally occurring bone cancers are well established. For example, the incidence is slightly higher in men than in women (19). Also, the peak incidence associated with puberty occurs approximately 2 years earlier in girls than in boys. This coincides with the approximately 2-year-earlier onset of puberty in girls (9). Thus, the sex factor associated with bone neoplasia in mice has at least a subtle counterpart in humans.

REFERENCES

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