Carcinoma of the Prostate in Irradiated Parabiotic Rats

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ABSTRACT

Twelve hundred fifty-two pairs of male NEDH rats were parabiosed, one partner received a single dose of 1000 R X-radiation, and the other rat was shielded with lead. Eleven hundred twenty pairs survived over 200 days and constitute the basis of this report. Twenty-five of the irradiated partners developed malignant tumors of the prostate, 19 of which were adenocarcinomas. One adenocarcinoma appeared in the shielded partners and one in a control group of 586 parabiosed and single rats. The long-term effect of a single dose of 1000 R whole-body X-radiation is weakly carcinogenic for the rat prostate.

INTRODUCTION

Much of the emphasis in experimental prostatic cancer research has been placed quite properly on hormones and chemicals as etiological agents (1). Radiant energy also has a long-term carcinogenic potential on the rodent prostate. In 1976 Hirose ef al. (6), using local pelvic X-radiation for a total of 8000 R, produced 5 adenocarcinomas in 135 mice surviving the treatment more than 16 weeks. We would like to record the incidence of malignant tumors in a series of 1120 pairs of parabiosed male rats, 1 rat irradiated in each pair that survived over 200 days postirradiation.

MATERIALS AND METHODS

Under barbiturate anesthesia 1252 pairs of 30- to 40-day-old male NEDH rats were parabiosed by a modified Bunster-Meyer technique (3, 16). Approximately 60 to 90 days later, the right partner received 1000 R whole-body unfiltered X-rays from a 250-kVp G. E. Maximar machine operated at 15 ma. The left partner was shielded with lead. The 1120 pairs surviving 200 days postirradiation were included in the study. One hundred thirty-two pairs died prior to this time, mostly from pneumonia, and to a lesser extent from radiation effects. We have not included these animals.

One control series consisted of 129 pairs of parabiosed males receiving no irradiation. Three hundred twenty-eight single nonirradiated males constituted the other controls.

All rats received Purina Checkers and water ad libitum. Only moribund rats were killed prior to their natural death. Complete autopsies were performed. All organs, including the prostate, were sectioned and studied microscopically. Tissues were fixed in Zenker-formalin solution and blocked in paraffin. Sections were stained with hematoxylin-eosin.

RESULTS

Malignant tumors of the prostate occurred in 25 of the irradiated partners. Two of the nonirradiated partners also developed prostatic carcinoma (Table 1). One carcinoma of the prostate appeared in 1 of the 258 parabiosed control partners, and none appeared in the 328 single males.

The life span of the 25 irradiated partners with prostatic cancer averaged 480 days postirradiation, the shortest postirradiation survival being 274 days and the longest 717 days.

Some of the tumors could be seen or felt at autopsy as small, hard nodules limited to 1 lobe of the prostate. A few were not seen grossly. About one-half of the tumors were so large that localization in any lobe was impossible. Gross examination of the prostate failed to disclose any consistent point of localization in a given lobe. Two cancers extended into the colon. In 5 of the larger tumors, i.e. seeding and nodulation were observed; in 3 of these there were pulmonary metastases and in 1 there was a metastasis to the sternum. Four small tumors, not tabulated with the prostatic lesions, were limited to the seminal vesicles, 2 in the irradiated partners and 2 in the shielded partners.

Microscopically, 19 of the tumors were classified as adenocarcinoma. The 4 localized adenocarcinomas were limited to 1 or 2 adjacent glands filled with large, crowded columnar epithelial cells with slightly hyperchromatic nuclei. They formed a trabeculated, cribriform, or bridging pattern similar to that seen in some intraductal breast carcinomas. They are to be distinguished from simple infolding of prostatic epithelium, which is often seen in normal glands. Many prostatic glands, however, were lined with atrophic epithelium. In the 3 spreading types of adenocarcinoma, the neoplastic process had extended to several glands, having broken down the limiting septae (Fig. 1). In the 11 diffuse adenocarcinomas, only traces of a glandular pattern remained, the tumor being composed of strands and clusters of distorted tumor cells arranged around a central lumen (Fig. 2). Fibrous stroma was abundant, and perineural invasion was often observed (Fig. 3). This pattern was reminiscent of that seen in human prostatic carcinoma. As noted above, 1 adenocarcinoma metastasized to bone (Fig. 4). In 1 tumor, a carcinosarcoma, the epithelial cells were so distorted that a search was necessary to establish their identity in the neoplastic stroma. Diagnoses of scirrhous carcinoma and leiomyosarcoma were considered and excluded.

The 3 squamous cell carcinomas formed abundant keratin. Two of them may have originated in or around the prostatic colliculus.

A rhabdomyosarcoma apparently arose near 1 of the ducts deep in a posterolateral lobe. The infiltrating tumor was composed of distorted eosinophilic muscle bundles largely obliterated by densely packed clusters of multiple...
nuclei. Cross-striations were seen rarely in the cytoplasm. The nuclei often appeared as enlarged pleomorphic sacrolemmal nuclei.

The small-cell carcinoma grew in sheets of small cells with clear cytoplasm and round small nuclei. Because of extensive prostatic involvement, this tumor was classified as prostatic and was assumed to have originated here. Widespread i.p. involvement, however, raises the possibility of its origin elsewhere.

The testes of the irradiated partners contained a few to many atrophic tubules lined only with Sertoli cells. Very often, the interstitial cells, when compared to those of the shielded partner, were smaller and had pyknotic nuclei. Other changes suggesting an irradiation effect were slight increases in interstitial fibrosis and capillary wall thickening. Occasionally, and particularly in older rats, no differences between the irradiated and shielded testes could be discerned with light microscopy and hematoxylin-eosin staining.

In all but 5 of the rats with prostatic cancer, primary tumors also occurred in other organs. The most common coexisting tumors were pheochromocytomas of the adrenal gland, sarcomas occurring at the anastomotic site, and islet cell adenomas of the pancreas. Nodular hyperplasia or adenomas of the pituitary occurred only twice coincidentally with the prostatic tumors.

DISCUSSION

A single dose of whole-body X-radiation of 1 partner of 1120 pairs of parabiosed male rats resulted in 25 prostatic cancers, a 2.2% incidence as against 0.2% in their shielded partners and 0.2% in 586 controls. This is interpreted as a weak but significant carcinogenic effect.

The large number of postradiation-surviving pairs is attributed to parabiosis, presumably because of material donated to the irradiated partner by the shielded syngeneic partner (15). Parabiosis has made possible the study of the remote effects of supralethal doses of radiant energy delivered to 1 partner of a pair of rats.

Not included in our 1120-parabiont series are 2 small series in which males received 1000 R whole-body irradiation. In 1 of these, 30 rats were joined as usual, and 1 partner was irradiated. The pairs were then separated surgically and allowed to live out their life spans. In the second small series, 20 single rats that survived the irradiation for 200 days were allowed to live out their life spans. One irradiated rat in each small group developed typical diffuse adenocarcinoma of the prostate.

Spontaneous adenocarcinoma of the rat prostate has been considered a very rare lesion. No cases were found in 3 large series reported prior to 1940 (2, 7, 13). In 1963 Dunning (4) encountered a single spontaneous adenocarcinoma while testing the effect of steroids on chemically induced tumors of the rat prostate.

More recently, Pollard (11) reported 3 adenocarcinomas in a selected group of 31 retired male breeders maintained under germ-free conditions and examined at 32 to 40 months of age and 1 additional carcinoma at 22 months of age. The prostatic adenocarcinomas were sometimes associated with tumors of the endocrine glands. In a later publication the number of prostatic adenocarcinomas was increased from 4 to 8. Three of these were transplanted s.c. and metastasized to lungs and lymph nodes (12). In 1975 Shain et al. (14) reported 7 prostatic adenocarcinomas in a group of 41 rats with a high incidence of gonadal stromal tumors of the testes. More direct evidence of hormonal etiology is presented by Noble (10), who reported in 1977 the incidence of 24 adenocarcinomas of the prostate in a group of 130 male rats treated with pellets of testosterone and estrone injected s.c.

The X-irradiated rats in our series are also subject to the effect of an altered hormonal milieu secondary to coincidental changes in the testes from irradiation. This, plus the association in some of our rats of such endocrine tumors as islet cell and adrenal medullary tumors, suggests the possibility of a contributing hormonal factor.

Direct implantation of chemical carcinogens, benzpyrene, or methylcholanthrene into the prostate following laparotomy usually produces squamous cell carcinomas (5, 9), but Mirand and Staubitz (8) reported 2 adenocarcinomas as well as 30 squamous cell carcinomas in 99 male rats following direct implantation of methylcholanthrene crystals into the anterior prostate.

Thus, recent experience with prostatic carcinogenesis in the rat indicates that this organ, like many others, is subject to chemical, hormonal, and radiation stimuli.

Fig. 1. Adenocarcinoma, spreading. Several glands are involved with atypical hyperchromic cells in cribriform pattern. × 31.
Fig. 2. Adenocarcinoma, diffuse. Replacement of normal glands with cords and distorted neoplastic glands lying in fibrous stroma. × 125.
Fig. 3. Adenocarcinoma, diffuse. Perineural spaces invaded by neoplastic epithelium in adenoid configuration. × 125.
Fig. 4. Adenocarcinoma, metastatic to bone. Vacuolated tumor cells between bony trabeculae. × 312.
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Cancer Res 1978;38:159-162.

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