The Synergism between Radiation and Estrogen in the Production of Mammary Cancer in the Rat

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SUMMARY

A X C rats, in which continuous administration of diethylstilbestrol produces a high incidence of mammary carcinoma as opposed to their essentially zero spontaneous incidence, were given radiation of one mammary chain while they were under the systemic influence of diethylstilbestrol. The animals irradiated without the diethylstilbestrol, with the same dose and at the same time, developed fewer mammary carcinomas after a much longer latent period (minimum, 75 weeks), but those animals irradiated while under the influence of the estrogen had many more mammary carcinomas (the first at 18 weeks) than those given the diethylstilbestrol alone. This is interpreted as substantial synergism between the two modalities in mammary carcinogenesis.

INTRODUCTION

We have been interested in the reason for the increasing incidence of breast cancer observed in this country. The induction of breast cancer in animals by radiation has been reported by Shellabarger et al. (4). Huggins and Fukunishi (2), and Shellabarger and Schmidt (5). The role of radiation in the production of breast cancer in humans has been suggested by the increased incidence of mammalian carcinoma in women with repeated fluoroscopies to evaluate pneumothorax treatment of advanced pulmonary tuberculosis, reported by Myrden and Hiltz (3). In addition, the recent report by Wanebo et al. (6) of an increased incidence of breast carcinoma among the survivors of the Hiroshima-Nagasaki bombings, where the radiation dose was greater than 90 R, adds support to the hypothesis that radiation has a role in the induction of breast carcinoma. From these reports, it is apparent that radiation alone could be the causative agent in the rising incidence of breast carcinoma, but we were concerned about the possible additive effects in individuals exposed to both estrogenic hormonal stimuli and radiation.

Because of these considerations, we designed a study to determine whether estrogen and radiation are synergistic for the production of mammary carcinoma. In the animal studies cited above, radiation sources with a higher half-value layer than that used in diagnostic studies were used. We therefore felt that it was important to determine the effects of lower-energy radiation, such as that now being used for X-ray mammography.

MATERIALS AND METHODS

For the study of the synergistic effect of estrogen and radiation in the production of mammary carcinoma, the A X C strain of rats bred by littermate matings in our laboratory was selected. This strain has an essentially zero incidence of spontaneous mammary cancer but is very susceptible to the rapid induction of mammary cancer by continuous administration of estrogen (1).

Female A X C rats weighing between 40 and 50 g at weaning were hysterectomized at 28 to 30 days to prevent fatal estrogen-induced uterine infections. The ovaries were left intact. The animals were divided into 3 groups. Group 1 received an estrogen pellet and radiation; Group 2 received an estrogen pellet alone; Group 3 received radiation alone. The estrogen pellets for Groups 1 and 2 were implanted intrascapularly when the rats were 8 weeks old. These 20-mg pellets contained 25% diethylstilbestrol and 75% cholesterol and remained in place until the animals died or were sacrificed. Two days later all animals, whether they were to be irradiated or not, were anesthetized. The anesthetic used was urethane (ethyl carbamate), 1 mg/g of body weight. When feasible, tumors were removed at a size of 1.5 to 2.0 cm in order to permit sufficient survival time.

Radiation was given only to the left mammary chain of each animal by carefully screening the opposite chain with a lead shield. Therefore, in the animals receiving radiation, 1 mammary chain was irradiated, and the other chain acted as a control. The radiation dose was delivered with a superficial radiation therapy unit at 50 kV with a half-value layer of 0.75 mm of aluminum and a target skin distance of 21.5 cm. This unit was calibrated with a Victoreen Model 570 R meter with the use of a chamber, Model No. 651. The output of the unit at 21.5 cm was 169 R/min at the center of the field of treatment.

The area of treatment was defined by an irregular quadrangular opening 3 x 4 x 11 x 12 cm in a one-sixteenths-inch lead shield. Measurement of the radiation at each end of the field showed a falloff of approximately 10%. The dose delivered was 800 R to the center of the mammary chain in a period of 285 sec. The lead shield protected the thyroid and the pituitary.

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### Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>No. of rats</th>
<th>At 1st tumor seen</th>
<th>Rats with tumors</th>
<th>Mammary chains at risk</th>
<th>Total gross tumors</th>
<th>First palpable tumor (wk)</th>
<th>Median time for 1st tumor (wk)</th>
<th>No. of tumors/ chains at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (irradiated side)</td>
<td>Diethylstilbestrol + cholesterol pellet + radiation</td>
<td>22</td>
<td>14</td>
<td>12</td>
<td>14</td>
<td>78</td>
<td>18</td>
<td>26</td>
<td>5.6</td>
</tr>
<tr>
<td>1 (shielded side)</td>
<td>Diethylstilbestrol + cholesterol pellet</td>
<td>22</td>
<td>12</td>
<td>6</td>
<td>12</td>
<td>17</td>
<td>29</td>
<td>38</td>
<td>1.4</td>
</tr>
<tr>
<td>2</td>
<td>Diethylstilbestrol + cholesterol pellet</td>
<td>21</td>
<td>16</td>
<td>15</td>
<td>32</td>
<td>54</td>
<td>20</td>
<td>33</td>
<td>1.7</td>
</tr>
<tr>
<td>3</td>
<td>Radiation alone</td>
<td>21</td>
<td>11</td>
<td>8</td>
<td>11</td>
<td>12</td>
<td>75</td>
<td>80</td>
<td>1.1</td>
</tr>
</tbody>
</table>

**RESULTS**

There were 14 animals in Group 1. Of these, 12 developed multiple mammary cancers of the irradiated side, for a total of 78 grossly palpable tumors. The 1st tumor appeared at 18 weeks on the irradiated side, while the 1st tumor on the reference side appeared at 29 weeks. All the animals with tumors developed multiple mammary carcinomas in the chain receiving radiation, with only a few tumors developing in the nonirradiated chain; 6 animals developed 17 tumors in the nonirradiated side. On initial examination, it seemed that the tumors developing in the irradiated mammary chain were single, discrete tumors. However, when the tumors had reached a size of 2 cm and were removed or in animals that were autopsied, it became apparent that what was thought to be a single tumor was generally multiple small tumors. Fig. 1 illustrates the striking contrast between the irradiated and nonirradiated sides; the former had undergone essentially total carcinogenesis. Chart 1 shows the incidence curve for the development of mammary cancers. For Group 1, the 2 chains are compared (Curves 1 and 3). Group 2 shows the cumulative incidence in both chains exposed to the estrogen (Curve 2). Group 3 still has 6 animals alive at 110 weeks (Curve 4). Here the 1st mammary tumor appeared at 75 weeks, and a total of 12 palpable tumors has been seen.

The basic neoplasm is similar in all groups. The basic pattern is a poorly differentiated, solid (medullary), infiltrating carcinoma with little desmoplastic reaction, showing a variable degree of glandular and papillary differentiation. The predominant solid carcinomas contain large central zones of necrosis within nodular aggregates of tumor cells. Lumen formation within some tumor nodules produces a cribriform pattern. In others, there are irregular areas of duct and papillary formation, lined by columnar cells with inspissated secretion within lumens.

The solid areas consist of aggregates of large ovoid and polyhedral cells with nuclear crowding, moderate pleomorphism, and occasional gigantocytome nuclei. The nuclei are hyperchromatic, with coarse chromatin clumps, prominent nuclear membranes, and 2 or 3 nucleoli.

The cells of the neoplasm are several times the diameter of the adjacent normal ductal and alveolar cells. Mitoses are frequent (often 3 or 4/high-power field), and occasional abnormal mitotic figures are seen.

The neoplasms usually show mixed patterns, solid and glandular. Metastases in regional lymph nodes show similar histological patterns.
been reported. Not only was there a much higher incidence of tumors, but their absolute and mean latent periods were less.

REFERENCES


DISCUSSION

The preliminary data from the experiment conducted to evaluate the synergistic production of mammary carcinoma demonstrated that, in the animals receiving both estrogen and radiation, the irradiated mammary chain underwent essentially total carcinogenesis. This type of effect has not previously been reported. Not only was there a much higher incidence of tumors, but their absolute and mean latent periods were less.
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