Foster Nursing and Genetic Susceptibility for Tumors of the Breast in Mice*

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The object of this experiment was to determine whether foster nursing, with a decrease in the incidence of spontaneous carcinoma of the mammary gland, might produce any change in the genetic constitution of mice of an inbred strain. By genetic constitution is inferred the inherited susceptibility for the development of cancer of the breast.

All the mice used in the experiment were members of the A stock, a strain which has been inbred, brother-to-sister, since 1918. A female of the A strain (41st generation), No. 38432, and fostered by a female of the CBA or X stock gave rise to the line called the A\(\checkmark\)low Ax\(\checkmark\)o \(\times\) FY and low Ax\(\checkmark\)o \(\times\) high A\(\checkmark\)o \(\times\) FY. The mice of the second and following generations were usually produced by brother-to-sister matings.

The animals of the Ax strain available for the cross were members of the 47th to 53rd generations (7 to 12 generations since fostering of the ancestral female) and the mice of the A strain were from the 53rd to 58th generations. The controls were selected from the 54th to 61st generations (Table I). Observations on the incidences of tumors in the mice of the hybrid generations are given in Table I.

<p>| Table I: The Incidence of Mammary Carcinoma and Average Ages Observed in Breeding Females of the A Stock, Fostered Females of the A Stock (Ax), and Hybrids Derived from Crossing Mice of the Two Lines |
|---|---|---|---|</p>
<table>
<thead>
<tr>
<th>Stock</th>
<th>Incidence in maternal stock</th>
<th>Cancer incidence, per cent</th>
<th>Average age in months</th>
</tr>
</thead>
<tbody>
<tr>
<td>A(F54-F61)</td>
<td>High</td>
<td>98.0</td>
<td>9.4</td>
</tr>
<tr>
<td>Ax</td>
<td>Low</td>
<td>3.1</td>
<td>13.9</td>
</tr>
<tr>
<td>AxAF1</td>
<td>Low</td>
<td>0.0</td>
<td>...</td>
</tr>
<tr>
<td>AxAF2</td>
<td>Low</td>
<td>0.7</td>
<td>11.5</td>
</tr>
<tr>
<td>AAxF1</td>
<td>High</td>
<td>94.0</td>
<td>9.1</td>
</tr>
<tr>
<td>AAxF2</td>
<td>High</td>
<td>95.5</td>
<td>9.5</td>
</tr>
<tr>
<td>AAxF3</td>
<td>High</td>
<td>96.6</td>
<td>8.8</td>
</tr>
<tr>
<td>AAxF4</td>
<td>High</td>
<td>98.4</td>
<td>9.3</td>
</tr>
<tr>
<td>AAxF5</td>
<td>High</td>
<td>93.5</td>
<td>9.6</td>
</tr>
<tr>
<td>AAxF1-F5 (Total)</td>
<td>600</td>
<td>95.8</td>
<td>9.2</td>
</tr>
</tbody>
</table>

* Only depleted litters.

Ax strain (1, 4). All the females were continued as breeders.

The females of the Ax strain have a low incidence of mammary cancer while the females of the A (control) stock have a high incidence. The average age at death of the noncancerous females of the Ax strain was 8 months later than the average cancer age of the mice of the A stock (Table I).

Reciprocal matings were made between representatives of these two sublines. To distinguish between the hybrid generations, the maternal line is mentioned before the paternal stock in the designations; e.g., high A\(\checkmark\) low Ax\(\checkmark\)o \(\times\) AAxF1 and low Ax\(\checkmark\)o \(\times\) high AAxF1. The mice of the second and following generations were usually produced by brother-to-sister matings.

The animals of the Ax strain available for the cross were members of the 47th to 53rd generations (7 to 12 generations since fostering of the ancestral female) and the mice of the A strain were from the 53rd to 58th generations. The controls were selected from the 54th to 61st generations (Table I). Observations on the incidences of tumors in the mice of the hybrid generations are given in Table I.

One mammary carcinoma was observed to develop in the hybrids descended from females of the fostered line. The noncancerous mice of the AxAF1 and F2 generations survived to an average age of 17.6 months; the single growth was observed at 11.5 months. The number of mice observed was 259.

The hybrids descended from maternal parents of the control strain had high incidences of mammary carcinoma. The results are complete for mice of the first 3 generations. In the 4th and 5th generations the observations include only litters in which all the mice have died. There has been no significant reduction in the incidence of breast tumors in any generation.

The total number of mice tabulated from the AAxF1 to AAxF5 generations was 600 and 95.8 per

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* This investigation was aided by grants from the National Cancer Institute and The Jane Coffin Childs Memorial Fund for Medical Research.
cent of these developed tumors of the mammary glands. The average age at the time of recording the tumors in the controls was 9.4 months and in the hybrids 9.2 months. Twenty-five of the hybrids were noncancerous. Of this number only 8 lived to the average age for cancer.

DISCUSSION

There may be two (or more) classes of spontaneous carcinoma of the mammary glands in mice, inherited and noninherited (2). Tumors of the breast may be said to be inherited or transmitted when the strain has a high incidence and the progeny of both cancerous and noncancerous mothers have high incidences characteristic of the strain.

For the development of inherited tumors in mice it has been assumed that at least three "influences" must be present and active (2). These may be: (a) An inherited susceptibility for breast cancer. (b) An active influence in the milk. (c) An adequate hormonal stimulation of the mammary tissue.

Tumors developing in individuals having an inactive influence in the milk or which are not proven to be susceptible for mammary tumors generally are of the noninherited type. In such strains the incidence in the progeny of cancerous mothers is usually low and does not differ from the normal low incidence of the stock (3).

Breeding tests may be needed to determine the genetic constitution of mice of strains which have a low incidence of carcinoma of the breast. It is possible to have a strain in which the mice are susceptible for the development of breast tumors but which have an inactive influence in the milk. Should the influence in the milk become active \textit{de novo} such a strain will change from low to high cancer (4). Also, a strain that is nonsusceptible for tumors of the breast but which has obtained an active influence by nursing will have a higher incidence than the unfostered mice of the strain. This incidence is low, however, when compared with the incidence observed in strains having a high incidence because of a combination of genetic factor and milk influence. On the other hand, fostered mice derived from the strain with a low incidence, having an active milk influence but usually noncancerous, may be used to nurse susceptible animals and a high incidence will result (3).

It is also possible to have a strain of mice developing few spontaneous tumors which have an active milk influence but do not possess the proper genetic constitution for the appearance of tumors. Only by mutational changes in genetic factors would this strain be expected to give a high incidence.

For the development of tumors induced by estrogenic hormones there is evidence that if the influence in the milk is active, the genetic susceptibility factor may not be required (8). Few tumors will develop in animals which have the proper genetic constitution but which have obtained an inactive influence when nursing (5, 7).

The data given above on the cross between cancerous females and males of a noncancerous line of the same strain showed that the incidence remained the same in the hybrids as in the controls. This demonstrates that foster nursing does not alter the inherited susceptibility for breast cancer in mice.

Whether or not we may consider the genetic constitution for the development of mammary cancer in mice as a quantitative or qualitative character is problematical. It may manifest itself by making the individual susceptible to the active influence in the milk usually obtained by nursing potentially cancerous females. This hypothesis may be reasonable if it is determined that the influence in the milk is a virus (6) and, to date, no evidence to the contrary has been observed. It is not claimed, however, that the hypothesis provides proof of the virus-nature of the influence.

CONCLUSION

In mice foster nursing does not influence the genetic susceptibility of an individual for the development of spontaneous mammary carcinoma.

REFERENCES

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