THE RELATIVE INCIDENCE OF OOPHORECTOMY IN WOMEN WITH AND WITHOUT CARCINOMA OF THE BREAST

WALLACE E. HERRELL, M.D.
(Fellow in Medicine, The Mayo Clinic, Rochester, Minnesota)

In the past two decades numerous discussions and some evidence have appeared regarding the possible effect of ovarian-hormonal activities on the normally functioning as well as on the abnormally functioning breast. It is further true, however, that a close relationship between the activity of the ovary and that of the breast was widely recognized long before an attempt was made to explain such a relationship by modern hormonology. Most of the present conceptions concerning the possible rôle of the ovarian hormones in normal and abnormal activity of the breast are based on the results of animal experimentation. The very nature of the problem prevents, to some degree, the prosecution of studies on human beings. However, convincing results have been obtained in animals, especially mice. The investigations of Lathrop and Loeb (1916) and later of Cori (1927) are especially outstanding as regards an “ovarian-mammary” mechanism in the development of spontaneous carcinoma of female mice.

Lathrop and Loeb, working with a strain of mice in which the incidence of spontaneous cancer in the female was high, found that castration of the females when they were less than six months of age led to marked decrease in the incidence of mammary tumors. In a later report Loeb (1919) was able to confirm and enlarge his previous results. He concluded that the hereditary factors which determine the development of mammary carcinoma in mice depend on the cooperation of a definite quantity of ovarian hormones if cancer is to develop. Such a conclusion was justifiable since the results showed that if the quantity of hormone that was acting exceeded a certain limit, mammary cancer appeared as frequently in the castrated animals as in those which were not castrated.

Cori (1927) in a painstaking study repeated and amplified the work of Loeb. His work seems to establish unquestionably the rôle of ovarian activity in the production or development of mammary tumors in mice. He concluded that castration of female mice between the fifteenth and the twenty-second day of life entirely prevented the occurrence of spontaneous adenocarcinoma of the breast, while among controls the incidence of this tumor was 78.57 per cent. In three of the castrated animals spontaneous spindle-cell sarcoma developed, indicating that the influence of the ovary on the breast is a specific one, since oophorectomy does not lead to resistance against the other types of spontaneous malignant tumor which develop in these animals. Cori further observed that castration between the ages of two and six months led to a marked reduction in the incidence of mammary tumor, though it did not entirely prevent the occurrence of the tumors. He concluded, also, that the

1 Submitted for publication February 8, 1937.
spontaneous cancer of the breast of the mouse is attributable to an hereditary
organ disposition which remains latent in absence of the ovarian function but
which manifests itself when certain amounts of ovarian hormone correspond-
ing to 5 to 30 estrous cycles have acted on the breast tissue.

In view of results to be cited here, the fact that Cori was able to decrease
the incidence of cancer of the breast to an appreciable degree in the group of
mice up to six months of age is of especial interest, since this age corresponds
roughly to the age of the women who are most readily available for study.

Further support for these ideas concerning the rôle of the ovary in the
development of cancer of the breast in mice may be found in the work of
Murray (1936), who was able to show that a decrease in the secretions of
the ovary was instrumental in prolonging life and decreasing the incidence of
mammary tumor. If all ovarian activity is prevented, as in castrates, the
effects are in the same direction and are more striking. Murray concluded
that castration of female mice which were approaching the period of declining
reproductive power has at least two effects on the subsequent life history of
these animals. (1) The average expectation of life is appreciably increased.
(2) The incidence of tumor of the breast is markedly decreased, especially
among animals of older age groups.

In the light of evidence of this sort, some of which has been available for
a short time only, the present study was undertaken to determine, if possible,
whether these findings were in any way applicable to the perplexing problem
of spontaneous mammary adenocarcinoma in women. The magnitude of the
problem of cancer of the breast is evident when it is noted, for example, that
of the 69,893 females who died of carcinoma in the United States in 1933,
12,316 (17.6 per cent) died of cancer of the breast. These figures are taken
from the report of the Bureau of the Census of the United States (1933).

Material Studied

Approximately 3,500 case records have been reviewed. These comprised
two groups: (1) 1,906 consecutive records of women who had received a
diagnosis of, and had been operated on for, malignancy of the breast and (2)
a control group of 1,011 consecutive records of women patients, forty years
of age or older, who had not received a diagnosis of malignancy of the breast.
Later an additional series of control cases was studied. Records in all series
were examined for a history of partial or complete oophorectomy or castration
by roentgen rays or radium to determine the relative incidence of these pro-
cedures. In the course of the examination of the records the relation in time
between the castrating procedure and the examination, as well as the com-
plaints which brought the patients to the clinic, were noted. With due cog-
nizance of the possibly unrepresentative character of a selected group of
individuals such as is found in a clinic population, it was thought, never-
theless, that if the incidence of castration in the control group was consider-
ably different from that in the group in which malignancy occurred, this would
be suggestive of a possible influence of the castration on the subsequent
development of the neoplasm.
THE RELATIVE INCIDENCE OF OOPHORECTOMY

RESULTS

Incidence of Oophorectomy among Patients Who Later Had Mammary Carcinoma: Of 1,906 patients with carcinoma of the breast seen at the clinic in the years 1920–1925 and 1931–1933, only 28 had undergone complete oophorectomy or castration before mammary carcinoma was found (Table I).

<table>
<thead>
<tr>
<th>Year</th>
<th>Cases of Carcinoma</th>
<th>Partial Oophorectomy</th>
<th>Complete Oophorectomy</th>
<th>Total Oophorectomies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Per cent</td>
<td>Cases</td>
<td>Per cent</td>
</tr>
<tr>
<td>1920</td>
<td>206</td>
<td>6</td>
<td>2.9</td>
<td>3</td>
</tr>
<tr>
<td>1921</td>
<td>217</td>
<td>4</td>
<td>1.8</td>
<td>5</td>
</tr>
<tr>
<td>1922</td>
<td>203</td>
<td>6</td>
<td>3.0</td>
<td>1</td>
</tr>
<tr>
<td>1923</td>
<td>226</td>
<td>10</td>
<td>4.4</td>
<td>2</td>
</tr>
<tr>
<td>1924</td>
<td>218</td>
<td>6</td>
<td>2.8</td>
<td>2</td>
</tr>
<tr>
<td>1925</td>
<td>246</td>
<td>10</td>
<td>4.1</td>
<td>6</td>
</tr>
<tr>
<td>1931</td>
<td>222</td>
<td>10</td>
<td>4.5</td>
<td>1</td>
</tr>
<tr>
<td>1932</td>
<td>170</td>
<td>8</td>
<td>4.7</td>
<td>4</td>
</tr>
<tr>
<td>1933</td>
<td>198</td>
<td>7</td>
<td>3.5</td>
<td>4</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1906</strong></td>
<td><strong>67</strong></td>
<td><strong>3.5</strong></td>
<td><strong>28</strong></td>
</tr>
</tbody>
</table>

This is an incidence of 1.5 per cent. If those cases are eliminated in which oophorectomy was performed so short a time before the diagnosis of carcinoma of the breast that the procedure could hardly be said to influence the development of the disease, that is, less than three years before, the incidence of castration or complete oophorectomy falls to the low point of 1 per cent. In other words, in 8 of the 28 cases oophorectomy or castration had been performed less than three years prior to the time at which a diagnosis of carcinoma of the breast was made at the clinic.

Control Series: The original control group of 1,011 cases was divided into subgroups of 504 new cases and 507 old cases, the "new cases," being those in which the first registration at the clinic was in 1935 and the "old cases" those in which, though the patients came to the clinic in 1935, their first registration had been prior to that year. It was evident that among women forty years of age or older, who first became patients of the clinic at that advanced age (new cases), some would have undergone oophorectomy elsewhere, whereas among women of the same age group who had been patients of the clinic in years gone by (old cases), oophorectomy, if it had been done, would probably have been performed by a surgeon of the clinic. By comparing the two subgroups, therefore, it could be determined whether there was a significantly greater or a significantly less tendency to perform oophorectomy within the clinic than without. As is brought out in Table II, there was no evidence of any significant difference in this tendency. New and old cases may therefore be considered as composing a single control group.

In this original control group, the incidence of total oophorectomy was 15.4 per cent, 156 of 1,011 patients. In other words, the incidence of com-
complete oophorectomy or castration was approximately ten times as great among the non-cancer-bearing females as in the group of women with carcinoma of the breast.

**Table II: Incidence of Oophorectomy in Women without Mammary Carcinoma**

<table>
<thead>
<tr>
<th>Cases</th>
<th>Partial Oophorectomy</th>
<th>Complete Oophorectomy</th>
<th>Total Oophorectomies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Per cent</td>
<td>Cases</td>
</tr>
<tr>
<td>New * cases</td>
<td>504</td>
<td>35</td>
<td>73</td>
</tr>
<tr>
<td>Old * cases</td>
<td>507</td>
<td>50</td>
<td>83</td>
</tr>
<tr>
<td>Total</td>
<td>1011</td>
<td>85</td>
<td>156†</td>
</tr>
</tbody>
</table>

* See text.
† In 20 cases castration was performed by means of radium or roentgen rays.

An additional study was made of several hundred control cases encountered in the period of years corresponding with that over which the cases of malignancy of the breast were seen, and the incidence of oophorectomy was found to be essentially the same as in the 1,011 cases of the original control group. This served to verify the dependability, as controls, of the original control group.

**Table III: Initial Symptoms in Control Series of 1,011 Cases**

<table>
<thead>
<tr>
<th>Symptoms on Admission in 1935</th>
<th>Patients Having Partial Oophorectomy</th>
<th>Patients Having Complete Oophorectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Per cent</td>
</tr>
<tr>
<td>Gynecologic</td>
<td>8</td>
<td>9.4</td>
</tr>
<tr>
<td>Cardiovascular and urinary</td>
<td>9</td>
<td>10.6</td>
</tr>
<tr>
<td>Eye, ear, nose, throat and dental</td>
<td>7</td>
<td>8.2</td>
</tr>
<tr>
<td>Gastro-intestinal</td>
<td>11</td>
<td>12.9</td>
</tr>
<tr>
<td>Rectal</td>
<td>8</td>
<td>9.4</td>
</tr>
<tr>
<td>Metabolic</td>
<td>3</td>
<td>3.5</td>
</tr>
<tr>
<td>Bone and joint</td>
<td>8</td>
<td>9.4</td>
</tr>
<tr>
<td>Central nervous system (organic, functional)</td>
<td>14</td>
<td>16.5</td>
</tr>
<tr>
<td>Miscellaneous (general examination negative)</td>
<td>17</td>
<td>20.0</td>
</tr>
<tr>
<td>Total</td>
<td>85</td>
<td>100</td>
</tr>
</tbody>
</table>

To avoid misinterpretation of the findings, the original control series from which the data are drawn were still further examined with regard to the complaint which brought the patient to the clinic. If most of these patients had come to the clinic in 1935 because of gynecologic complaints, they could hardly be taken as a basis for a reliable estimate of the general incidence of oophorectomy or castration in women without carcinoma of the breast. It was found, however, that in most of the cases there had been no complaint in 1935 which was at all related to the previous procedure. Table III indi-
cates the general groups into which the chief complaints fell. Interestingly enough, they varied from functional indigestion to dislocation of the coccyx and ocular refractive errors. We are, therefore, justified in the statement that the figures obtained represent a fair estimate of the incidence of complete oophorectomy (or castration) in a population of women aged more than forty years (cancer age) without carcinoma of the breast. It is to be noted, also, that the oophorectomies or castrations in this original series of control cases were entirely justified both clinically and pathologically and were by no means done on an experimental or unnecessary basis.

**Time Relationship between Complete Oophorectomy and the Development of Carcinoma of the Breast:** In view of the experimental demonstration that the earlier castration is performed the more effective is the procedure in the prevention of spontaneous mammary carcinoma in a cancer-bearing strain of mice, the series of cases of carcinoma of the breast in women was examined in regard to the relationship in time between oophorectomy and the development of carcinoma. The results are shown in Table IV. These figures suggest that the element of time is as important in studies of human beings as it is in animals. Conclusions on this basis, however, are not justified, since it is almost impossible to correlate the ages of mice and of man. One factor is nevertheless significant, and that is that the two groups selected for study in this work are comparable, as is shown by the percentage of cases in both the original control group and in the group of those who had cancer, who gave histories of oophorectomy more than three years before the time when they entered the clinic for treatment in 1935.

**Partial Oophorectomy Followed by Complete Oophorectomy:** Apart from the purpose for which this study was designed, one observation seems of especial interest. In the 1,011 patients in the original control series it was found that approximately 241 oophorectomies, either partial or complete, had been performed. In 85 cases partial oophorectomy was performed, and in 15 of these complete oophorectomy was later necessary. In other words, in about 18 per cent of cases, or in nearly one of every five, in which unilateral or partial oophorectomy was performed for any reason, subsequent completion

### Table IV: Time Relation between Bilateral Oophorectomy or Castration and Examination *

<table>
<thead>
<tr>
<th>Series</th>
<th>Total Cases</th>
<th>Bilateral oophorectomy or castration</th>
<th>Less than three years</th>
<th>More than three years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Number</td>
<td>Per cent</td>
<td>Number</td>
</tr>
<tr>
<td>Carcinoma of breast..</td>
<td>1906</td>
<td>28</td>
<td>1.5</td>
<td>8</td>
</tr>
<tr>
<td>Control</td>
<td>1011</td>
<td>156</td>
<td>15.4</td>
<td>34</td>
</tr>
</tbody>
</table>

*By "examination" is meant the general physical examination in which, in the 1,906 cases, mammary carcinoma was discovered and, in the 1,011 control cases, mammary carcinoma was found to be absent.*
of the procedure was necessary. This merely means, perhaps, that ovarian disease is bilateral. In view of the material which has been presented here relative to the incidence of oophorectomy (complete) in patients of similar age groups with and without carcinoma of the breast, the foregoing finding is especially significant.

Comment

An investigator feels some reluctance in attempting to discuss the possible practical application of findings such as these lest they lead to confusion rather than to clarification. Nevertheless, it is impossible to overlook the accumulating evidence that the ovarian secretions do in some way play a very definite rôle in the development of mammary tumors, not only in mice but also, as these studies strongly suggest, in women. The genetic factor is perhaps the most baffling aspect of the problem as it bears on the human being and indeed, in that bearing, seems beyond control. Yet, the ovarian functions are factors in the internal environment of the individual and, as these results indicate, probably play a definite rôle in the incidence of mammary cancer; these factors are, furthermore, controllable. The study here reported in no way suggests the cause and cure of mammary cancer. It does, however, supply excellent indication that the ovarian rôle may be a very definite one in human beings, as it is in animals whose genetic factors can be more or less controlled at will.

So far as I know, this is the first report of its kind dealing with the ovarian factor in the human being before rather than after the development of carcinoma of the breast. Schinzinger proposed oophorectomy in the treatment of carcinoma of the breast in 1889 and Beatson, independently, had the same conception and reported three inoperable cases so treated in 1896. Following these reports oophorectomy or castration was used rather widely for some time as a therapeutic weapon in inoperable mammary carcinoma. Thomson in 1902 reported 80 cases of inoperable carcinoma of the breast, in 22.5 per cent of which there had been definite improvement following oophorectomy. Lett, in 1905, reported 93 cases, in 36 per cent of which there was decided improvement following oophorectomy. In recent years castration by radiation combined with surgical operation has been regarded with considerable interest by some in the treatment of mammary carcinoma. Taylor (1934) reviewed the entire subject of the treatment of carcinoma of the breast by castration or induction of artificial menopause. Treatment, however, is not the concern of this report. The time to combat cancer is not in the inoperable stage but, if possible, before it develops, and this can be accomplished only when more is known concerning the factors which underlie the genesis of the disease. To add to this knowledge is the purpose of this review.

Summary and Conclusions

1. Something is known of the rôle of the ovary in the development of spontaneous mammary adenocarcinoma in mice.
2. A review of 1,906 records of women treated for carcinoma of the breast, and 1,011 records of women in a similar age group without mammary carcinoma, discloses that in the cancer-bearing group the incidence of complete oophorectomy or castration before carcinoma was diagnosed was 1.5 per cent. The incidence of castration in the non-cancer group was 15.4 per cent, or ten times as great. These findings warrant further study in this field.

REFERENCES


SCHINZINGER: Quoted by Taylor, p. 1138.


THOMSON, ALEXIS: Analysis of cases in which oophorectomy was performed for inoperable carcinoma of the breast, Brit. M. J. 2: 1538–1541, 1902.
