Elastosis in Relation to Prognosis in Primary Breast Carcinoma

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ABSTRACT

The content of elastic tissue has been evaluated in 171 primary breast carcinomas. Of the tumors, 35% had no or very little elastic tissue in the malignant areas, 42% presented with medium elastosis, and 22% had gross elastosis.

The occurrence of elastin has been related to different prognostic factors. An increasing amount of elastin was found with increasing amounts of estrogen receptor (p = 0.0003), while there was only a slight correlation to the progesterone receptor content. Furthermore, the highly differentiated tumors contained more elastin in their tumor tissue than the poorly differentiated tumors (p = 0.003), and parous women had significantly more elastin than nonparous women (p = 0.02). The presence of elastin was not, however, of any demonstrable prognostic significance.

INTRODUCTION

Breast tissue often contains fairly large amounts of elastin in the connective tissue (3, 6, 8, 15, 16, 19, 20, 25). Some studies have claimed that the presence of elastin may indicate cancer (3, 25), whereas others have found elastin in both the normal breast and benign disease (6, 20). Elastin in primary breast carcinomas has earlier been related to parameters that can predict recurrence, such as estrogen receptor content and the grade of anaplasia (9–11, 13, 16, 19). However, it is still uncertain whether elastosis is of any prognostic significance (1, 11, 21, 23, 26).

In an earlier study (19), the occurrence of elastin was compared to the estrogen receptor status in approximately 100 breast carcinomas, and a positive correlation was found. This was corroborated by results obtained by others (9, 11, 13, 16, 22). In the present study, 171 primary breast carcinomas were investigated for possible associations between the occurrence of elastin in the tissue and other histological, biochemical, and clinical parameters, including recurrence-free survival as analyzed in a Cox regression model.

MATERIALS AND METHODS

Materials. Primary breast carcinomas from female patients operated upon between September 1979 and February 1981 were investigated here. The patient population is a representative part of the patients entering the protocolled studies of the Danish Breast Cancer Cooperative Group, a nationwide project for treatment of primary breast cancer in women. The organization, design, and follow-up of the program have been described in detail elsewhere (2). During the period of investigation, a total of 1795 patients entered this study; tumor tissues from 171 of these patients were available for the present study (18).

The clinical status of the patients has been evaluated as of June 1, 1983.

Histological Evaluation. The type of tumor and the grade of anaplasia were evaluated on a hematoxylin-eosin-stained section taken immediately adjacent to tumor tissue used for receptor analysis. The presence of elastosis was determined on a section from the same block stained with Victoria blue (14). The tumor type was determined using the classification recommended by WHO (27). The infiltrating ductal carcinomas NOS were graded according to anaplasia into Grade 1, highly differentiated, Grade 2, moderately differentiated, and Grade 3, poorly differentiated. The grading system is a modification of the method of Bloom and Richardson’s (4), that takes the formation of tubules, nuclear polymorphism, and mitotic activity into account. The amount of elastic tissue was semiquantitatively graded into no or very little elastic tissue, moderate elastosis, and gross elastosis. Only elastin present in the stromal part of tumor tissue was taken into account. Sections with elastin only around normal ducts and vessels were considered negative.

Steroid Receptor Analysis. Analyses of estrogen and progesterone receptors were performed in a single laboratory (the Fibiger Laboratory). Estrogen receptor results were available for all patients, while results from progesterone receptor were obtainable in 110 patients. The dextran-coated charcoal receptor analysis method was used in accord with the recommendations of the European Organization for the Research and Treatment of Cancer (7), and the results were expressed in terms of fmol/mg cytosol protein.

Statistical Analysis. In the statistical analyses, the patients with moderate and gross elastosis were combined. The statistical comparison of the included variables for the groups of patients with very little and with moderate and gross elastosis was made by a likelihood ratio test. The log rank test was used for comparison of life tables. The presence of elastin has also been included as a covariable in a stratified Cox regression model that is identified and explained in detail elsewhere (18).

RESULTS

At the time of primary operation, 31% of the patients were premenopausal, and 69% were postmenopausal. Information about the state of parity was available in 154 patients; of these, 79% had given birth to at least one living child. In 44% of the patients, one or more axillary lymph nodes with metastases were found at the primary operation. The estrogen receptor content was regarded positive in 77%, and 65% had a positive progesterone receptor content. The histological characteristics of the patients with regard to types of carcinoma, and the grade of anaplasia for the infiltrating ductal carcinomas, are illustrated in Table 1. Table 2 shows the frequencies of patients with little, moderate, and gross elastosis. Approximately two-thirds of all the tumors contained some elastin, and nearly one-fourth were rich in elastic tissue. Elastin was randomly dispersed in the stroma and/or localized around ducts in a mantel of varying thickness.

The relations between the degree of elastosis and the various prognostic factors are shown in Table 3. The morphologically...
ELASTOSIS IN HUMAN BREAST CANCER

Relation between elastosis and other prognostic factors

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>No. of patients with no or little elastosis (total n = 152)</th>
<th>No. of patients with moderate or gross elastosis (total n = 60)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menopausal status</td>
<td></td>
<td></td>
<td>0.70</td>
</tr>
<tr>
<td>Pre</td>
<td>19 (34)</td>
<td>32 (53)</td>
<td></td>
</tr>
<tr>
<td>Post</td>
<td>41 (66)</td>
<td>79 (71)</td>
<td></td>
</tr>
<tr>
<td>Parity (n = 154)</td>
<td></td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>Nonparous</td>
<td>17 (31)</td>
<td>15 (25)</td>
<td></td>
</tr>
<tr>
<td>Parous</td>
<td>38 (69)</td>
<td>84 (85)</td>
<td></td>
</tr>
<tr>
<td>No. of positive nodes</td>
<td></td>
<td></td>
<td>0.70</td>
</tr>
<tr>
<td>0</td>
<td>30 (50)</td>
<td>63 (57)</td>
<td></td>
</tr>
<tr>
<td>1-3</td>
<td>18 (30)</td>
<td>29 (26)</td>
<td></td>
</tr>
<tr>
<td>&gt;3</td>
<td>12 (20)</td>
<td>19 (17)</td>
<td></td>
</tr>
<tr>
<td>Grade of anaplasia (n = 152)</td>
<td></td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>1</td>
<td>9 (17)</td>
<td>30 (30)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>16 (30)</td>
<td>43 (55)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>28 (53)</td>
<td>25 (25)</td>
<td></td>
</tr>
<tr>
<td>Estrogen receptor</td>
<td></td>
<td></td>
<td>0.0003</td>
</tr>
<tr>
<td>&lt;10 fmol/mg</td>
<td>22 (37)</td>
<td>16 (14)</td>
<td></td>
</tr>
<tr>
<td>10-100 fmol/mg</td>
<td>24 (40)</td>
<td>39 (35)</td>
<td></td>
</tr>
<tr>
<td>≥100 fmol/mg</td>
<td>14 (23)</td>
<td>56 (51)</td>
<td></td>
</tr>
<tr>
<td>Progesterone receptor (n = 104)</td>
<td></td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td>&lt;10 fmol/mg</td>
<td>21 (43)</td>
<td>16 (26)</td>
<td></td>
</tr>
<tr>
<td>10-100 fmol/mg</td>
<td>10 (23)</td>
<td>19 (31)</td>
<td></td>
</tr>
<tr>
<td>≥100 fmol/mg</td>
<td>12 (23)</td>
<td>26 (43)</td>
<td></td>
</tr>
</tbody>
</table>

* Numbers in parentheses, percentage of total number of patients.

We have found that elastosis is correlated to both the estrogen receptor status of the tumors and to the grade of anaplasia. Both variables are important prognostic factors in breast cancer (10, 13). The relation between elastosis and the estrogen receptor has been evaluated in other studies (9, 11, 16, 19, 22), and all agree that estrogen receptor-positive tumors contain larger amounts of elastic tissue than estrogen receptor-negative tumors. Furthermore, Masters et al. (17) have demonstrated a positive correlation between the amount of elastin in tumor tissue and response to endocrine therapy.

The value of elastosis as a prognostic factor has been investigated in other studies (1, 11, 21, 23, 26), and the results have been contradictory. Thus, Shivas and Douglas (23) found a clear correlation between the grade of elastosis (expressed as "elastic index") and survival. However, Robertson et al. (21) and Wallgren et al. (26) could not confirm this finding, and Anastassiades et al. (1) and Glaubitz et al. (11) found a negative effect of the presence of elastosis on survival. The present study showed no relation between elastosis and recurrence-free survival, regardless of whether the data were analyzed by univariate or multivariate life table methods. The latter method permits appraisal of whether elastosis is important for predicting survival, when the other variables in the model are taken into account.

The observation that elastin is present in greater amounts and in a greater proportion of patients who have given birth is in accord with an earlier observation by Davies (6). He found an increasing amount of elastosis in normal breast ducts with an increasing number of births. During pregnancy and lactation, the breast is under the influence of increased amounts of estrogens and progesterone, and it is therefore conceivable that the synthesis of elastin may be stimulated by high levels of these hormones.

The strongest relationship found between elastin and the sex steroid hormone receptors is with the estrogen receptor, which further indicates that synthesis of elastin may be under regulation of estrogens. Experimental data have shown that the production of the progesterone receptor is stimulated by estrogens (12), and the progesterone receptor has been shown recently to be as important in predicting recurrence-free survival as the estrogen receptor (5, 18).

It has already been noted that the presence of elastin is of no

| Variables: number of positive lymph nodes (0 to 3 versus 4); the estrogen receptor content (<100 versus ≥100 fmol/mg of cytosol protein); and the menopausal status of high-risk patients. When included in this model, the amount of elastic tissue provided no additional prognostic information (p = 0.22).
significance in predicting the prognosis of the disease. Furthermore, while elastin occurs more frequently in tissue of parous women than nonparous women, the progesterone receptor content of tumor tissue from parous women is lower than that in nonparous women (24). These facts together with the observation that there is only a weak relationship between the occurrence of elastin and the progesterone receptor may indicate that the progesterone receptor and elastin are 2 independent products of estrogen stimulation of the tumor tissue. While the former is valuable as a prognostic factor, the latter may merely reflect the presence of both estrogen and its receptor in the tissue.

ACKNOWLEDGMENTS

We wish to thank Charlotte Laustsen, Torhil Rignes, and Ulla Thomsen for excellent technical work and Ellen Margrethe Post for typing the manuscript. We are grateful to Niels Keiding, M. S. (Statistical Research Unit, Copenhagen) for enlightening discussions on the statistical methods.

REFERENCES

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