Breast Carcinoma in Uganda
Microscopic Study and Receptor Profile of 45 Cases

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Breast cancer is an important health issue, not only in the developed world but also in resource-limited nations. Although the incidence is low in these nations, it is associated with a poor prognosis and a high mortality, at least in part due to late presentation at advanced stages. Although low in incidence, breast carcinoma is the most common cancer in Nigerian women. The rate of breast carcinoma in some resource-limited countries is estimated to be increasing at a rate of 5% per year. It has been estimated that worldwide most breast cancer deaths occur in resource-limited countries. In Uganda the incidence of breast cancer has doubled since 1960 and is now the third most common cancer, after AIDS-related Kaposi sarcoma and cancer of the cervix. A lack of resources has limited research on the histologic and biomarker features of breast cancer in Uganda, as well as many other African countries. Immunohistochemistry is primarily a research tool and hormonal receptor status is not available for most patients. Hormonal treatment decisions are therefore clinically based.

During a recent sabbatical in Uganda, a project was carried out to study the histologic and receptor characteristics of invasive breast carcinoma in Ugandan women, with some clinical correlation. These findings were subsequently presented at a clinical conference to the general surgeons of Mulago Hospital in Kampala, Uganda.

**METHODS**

During a recent sabbatical in Kampala, Uganda, 64 cases of breast carcinoma were randomly selected, based on a review of bound pathology reports with a diagnosis of breast carcinoma, accessioned from 2000 to 2004, at St. Francis Nsambya Hospital. The reports provided the age and gender of the patient. One hundred four paraffin blocks with corresponding surgical numbers and deemed likely to contain carcinoma, based on a simple visual inspection of the block, were selected for further study in Montreal, Canada. Hematoxylin-eosin slides were prepared from these blocks and invasive breast carcinoma with adequate tissue for study was identified in 47 cases. Two of these were carcinomas in men and were excluded. The remaining 45 cases form the study set. The other cases were rejected for the following reasons: lack of microscopically identifiable carcinoma on the hematoxylin-eosin slide (9 cases, probably because the wrong block was selected), identification only of duct carcinoma in situ (1 case), disagreement with the original diagnosis (4 cases), identification of a malignancy not thought to be a breast primary (2 cases), and mislabeled block (1 case).

The histologic subtype of invasive breast carcinoma and Nottingham histologic grade were defined. Immunostaining was done for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2 (HER2/neu) using a Ventana Benchmark immunostainer (Tucson, Arizona), using the manufacturer’s supplied antibodies (clones 6F11 for anti-ER, 1A6 for anti-PR, and 4B5 for HER2/neu). Estrogen receptor and PR were considered negative if nuclear staining was completely absent. The PR results are not further presented in this study, except as part of the “triple-negative” data (ER negative, PR negative, HER2/neu negative). HER2/neu stains were assessed as 0, 1+, 2+, and 3+ using the

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**Context.—**Histologic and receptor data on breast carcinoma in Uganda are scarce. Estrogen receptor status is not routinely available. Breast cancer blocks from Uganda were studied in Montreal, Canada, and clinical correlations subsequently discussed in Kampala, Uganda.

**Objective.—**To correlate histologic features (tumor type, histologic grade), receptor profile (estrogen receptor, progesterone receptor, and HER2/neu), and age in Ugandan women.

**Design.—**Pathology reports for 2000–2004 from Nsambya Hospital, reporting invasive breast carcinoma, provided 45 microscopically confirmed cases.

**Results.—**Seventy-three percent of patients were 50 years or younger. Histologic types were invasive ductal carcinoma (78%) and “good” prognosis types (11%). Overall 40% were grade 3, but 48% of invasive ductal carcinomas were grade 3. Estrogen receptor was positive in 60% overall and in 51% of invasive ductal carcinomas. HER2/neu was overexpressed in 11%; 36% were “triple” negative (estrogen receptor, progesterone receptor, HER2/neu negative).

**Conclusions.—**Breast carcinoma in Ugandan women presents at a younger age and is histologically and by receptor profile more aggressive than carcinoma in Caucasian women.

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College of American Pathologists guidelines. Specifically, 3+ represented uniform intense membrane staining of more than 30% of the tumor cells and considered positive for HER2/neu overexpression. A lesser degree of staining was considered negative for overexpression. Fluorescence in situ hybridization for HER2/neu gene amplification was not performed.

RESULTS

There were 45 cases of microscopically confirmed invasive breast carcinoma in women, for which there was adequate tissue for histologic and receptor studies. Most (32 of 44; 73%) women were 50 years or younger at diagnosis. Seventeen (39%) women were 40 years or younger (Table 1). In one patient the age was not stated, although she was described as an adult.

Most (35 of 45; 78%) were invasive ductal carcinoma, not otherwise specified (IDC, NOS) (Figure, A through C) (Table 2). There were 5 (11%) “good” prognosis subtypes of invasive carcinoma, including tubular/cribriform carcinoma (Figure, D), colloid carcinoma (Figure, E), and papillary-cystic carcinoma. Other types of breast carcinoma included micropapillary invasive ductal carcinoma (3 cases) (Figure, F) and invasive ductal carcinoma with lobular features (2 cases) (Figure, G).

Overall, 16% were histologic grade 1, 44% were histologic grade 2, and 40% were histologic grade 3 (Table 3). Of the 35 cases of IDC, NOS, only one was grade 1, 17 were grade 2, and 17 were grade 3. Thus, almost half (48%) of the IDC, NOS were grade 3. Most of these patients (13 of 17; 76%) were 50 years or younger. The good prognosis subtypes were all grade 1. The micropapillary invasive ductal carcinomas and invasive ductal carcinomas with lobular features varied from grades 1 to 3.

Estrogen receptor studies showed that overall ER was positive in 60% and negative in 40% of all the carcinomas (Table 4). All 5 of the good prognosis carcinomas were ER positive. The 2 invasive ductal carcinomas with lobular features and 2 of the 3 micropapillary invasive ductal carcinomas were also ER positive. In the IDC, NOS subtype, half (18 of 35; 51%) were ER positive and half (17 of 35; 49%) were ER negative. Most ER-positive IDC, NOS cases were histologic grade 2 (12 of 18; 67%) and a minority were grade 3 (6 of 18; 33%). By contrast, most ER-negative cases were grade 3 (11 of 17; 65%), and a minority grade 2 (5 of 17; 29%). One ER-negative case was grade 1 (Table 4).

HER2/neu could be assessed in 44 cases. In 1 case there was insufficient tissue left in the block for HER2/neu assessment. Overexpression was identified in 5 (11%) cases, all of which were IDC, NOS. Most (4 of 5; 80%) were grade 3 and weakly ER positive (10% or less nuclear stain). Three patients were older than 50 years (Table 5). Overall, 16 of 44 (36%) breast carcinomas were triple negative (Table 6). These were almost all (15 of 16; 94%) IDC, NOS. One was a micropapillary invasive ductal carcinoma. Thus, almost half of the patients with IDC, NOS (15 of 35; 43%) were triple negative. Most (11/16, 69%) triple-negative patients were 50 years or younger at diagnosis.

χ² test for statistical significance was used when comparing with published data.

COMMENT

This study is retrospective and depends on the accuracy of archived patient records. The tissue processing may not have been uniform and therefore may have affected the immunostain results (prolonged formalin fixation is thought to affect antigen preservation). The data may not apply to all Ugandan women because the study material was obtained only from patients treated at St Francis Nsambya Hospital, which serves predominantly the region around Kampala. In addition, lack of data regarding tumor size and stage might bias the results. Within these limitations, however, the study shows that Ugandan women with breast cancer present at a younger age when compared with American women of both European and African origins. Seventy-three percent of Ugandan women were 50 years or younger at diagnosis, compared with 25% of European American (P < .001) and 33% of African American women (P < .001). These findings are similar to reports of Ethiopian, Nigerian, South African, Kenyan, and Central Sudanese women who also present at a younger age.1,2,10–12

Good prognosis subtypes were slightly more frequent when compared with European and African American women (11% versus 5.8% and 7.3%, respectively); however, they represented only a small proportion of the breast cancers. The incidence of IDC, NOS in Ugandan women (78%) was similar to European and African American women (ranging from 68% to 82% and 67% to 86%, respectively)9,13 representing the large majority of invasive breast carcinoma. This is also reported in other African women.14,15

Overall, 40% of the carcinomas were grade 3. The proportion of grade 3 carcinomas (without distinction as to subtype) reported for African American women ranges from 44% to 48% and for European American women from 37% to 40%.1,6,17 Thus, the overall proportion of grade 3 carcinomas in Ugandan women is in the range between European and African American women. However, there is a tendency for a higher frequency of grade 3 IDC, NOS in Ugandan women compared with British women (P = .08).18 As for Ugandan women, breast carcinoma reported for Nigerian, South African, Kenyan, and Central Sudanese women are also often high grade.2,10,11,12

Overall 40% of carcinomas in Ugandan women in this study were ER negative. This compares with the percent-
ages ER-negative carcinomas (22% and 37%) in 2 studies for European American women (P < .001 and P = .006, respectively). When compared with African American women (ranging from 36% to 48%) there is no significant difference (P = .99 and P = .32, respectively). African American women also have a significantly higher proportion of ER-negative breast carcinoma compared with European Americans. Comparison is difficult, however, because uniform methods for assessing ER status are not used in different studies. In our study half of the IDC, NOS major subtype was ER negative. Ugandan women therefore have significantly more ER-negative carcinomas, likely to be resistant to hormonal treatment, as compared with European American women. Similar higher rates of ER-negative carcinomas have been reported in Central Sudanese women. This could impact treatment decisions in Africa, because ER testing is usually not available or is too expensive and patients are sometimes treated empirically with tamoxifen. Based on the data from this study, such empirical treatment in many Ugandan women would be expected to have minimal impact on survival (eg, in half of the women with IDC, NOS). If patients are stratified using readily defined histologic subtypes of invasive carcinoma or by histologic grade, an overall good response to antiestrogen treatment might be expected in good prognosis carcinomas and lower histologic grades of IDC, NOS. However, even within the histologic grade 3 IDC, NOS group, a minority could theoretically benefit, because 6 of 18 (33%) were ER positive, several strongly so (data not shown).

The proportion of breast carcinoma with HER2/neu overexpression (11%) tends to be lower, although not statistically significant (P = .08), when compared with African American (25%) and European American (23%) women. Similar findings have been reported in Nigerian and Central Sudanese patients. Thus, the more aggressive breast carcinomas reported in African women do not appear to be due to HER2/neu overexpression.

Triple-negative breast carcinoma is a recently recognized type of breast carcinoma with a poor prognosis. In our study there was a greater proportion of the triple-negative breast carcinoma in Ugandan women (36%), especially compared with its prevalence as found in 2 other studies among European American women (10%, 14%, P < .001 for each value) and African American women (21%, 24%, P = .02 and P = .08, respectively). This type of carcinoma is also characterized by frequent expression of basal/myoepithelial cell markers such as cytokeratin 5/6 and p-cadherin, and the term “basal” type of carcinoma is sometimes used interchangeably with triple-negative carcinoma. Using these basal cell markers, a recent study of Ugandan women with breast carcinoma showed that 34% expressed the basal phenotype, a proportion that is significantly higher than the 12% to 19% reported for most non-African patients. The 36% triple-negative carcinoma incidence in our study is almost identical to the study’s finding of a 34% basal phenotype incidence. In addition 65% of cytokeratin 5/6 expressing carcinomas, compared with 67% of triple-negative carcinomas, were histologic grade 3. Furthermore, almost all (94%) of the basal phenotype carcinomas were IDC, NOS, an identical figure to the proportion of triple-negative carcinomas in our study. This suggests that Ugandan women have an excess of the triple-negative, basal phenotype of poor prognosis breast carcinoma. A study of breast carcinoma in Nigerian women also suggested an excess of biologically aggressive breast carcinoma, based both on the identification of a higher frequency of basal phenotype of breast carcinoma and a high proportion of p53-expressing carcinomas. The molecular events that underlie these findings may be the recently reported high variability of BRCA1 and BRCA2 gene sequences identified in young Nigerian women with breast cancer. Further study is needed to understand the precise molecular basis for the associated aggressive breast carcinoma. Caution should be used in generalizing these findings to other African countries, however, because a recent study showed no excess of the basal phenotype in Central Sudanese women as compared with Italian women with breast cancer. The poor prognosis of the Central Sudanese women with breast cancer was thought to reflect the advanced stage at diagnosis, rather than intrinsic biologic

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**Table 3. Histologic Grade of Invasive Carcinoma**

<table>
<thead>
<tr>
<th>Histologic Subtype</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subtypes</td>
<td>7/45 (16)</td>
<td>20/45 (44)</td>
<td>18/45 (40)</td>
</tr>
<tr>
<td>“Good” prognosis</td>
<td>5/5 (100)</td>
<td>0/5 (0)</td>
<td>0/5 (0)</td>
</tr>
<tr>
<td>Colloid</td>
<td>2/2 (100)</td>
<td>0/2 (0)</td>
<td>0/2 (0)</td>
</tr>
<tr>
<td>Tubular/cribriform</td>
<td>2/2 (100)</td>
<td>0/2 (0)</td>
<td>0/2 (0)</td>
</tr>
<tr>
<td>Papillary-cystic</td>
<td>1/1 (100)</td>
<td>0/1 (0)</td>
<td>0/1 (0)</td>
</tr>
<tr>
<td>IDC, NOS</td>
<td>1/35 (3)</td>
<td>17/35 (48)</td>
<td>17/35 (48)</td>
</tr>
<tr>
<td>Micropapillary invasive ductal</td>
<td>1/3 (33)</td>
<td>2/3 (67)</td>
<td>0/3 (0)</td>
</tr>
<tr>
<td>Ductal with lobular features</td>
<td>0/2 (0)</td>
<td>1/2 (50)</td>
<td>1/2 (50)</td>
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</tbody>
</table>

Abbreviation: IDC, NOS, invasive ductal carcinoma, not otherwise specified.
Table 4. Estrogen Receptor (ER) Status of Breast Carcinoma

<table>
<thead>
<tr>
<th>Type of Carcinoma</th>
<th>ER Positive/Total (%)</th>
<th>ER Negative/Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>27/45 (60)</td>
<td>18/45 (40)</td>
</tr>
<tr>
<td>“Good” prognosis types</td>
<td>5/5 (100)</td>
<td>0/5 (0)</td>
</tr>
<tr>
<td>Micropapillary invasive ductal</td>
<td>2/3 (67)</td>
<td>1/3 (33)</td>
</tr>
<tr>
<td>Invasive ductal with lobular</td>
<td>2/2 (100)</td>
<td>0/2 (0)</td>
</tr>
<tr>
<td>IDC, NOS</td>
<td>18/35 (51)</td>
<td>17/35 (49)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>0/18 (0)</td>
<td>1/17 (6)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>12/18 (67)</td>
<td>5/17 (29)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>6/18 (33)</td>
<td>11/17 (65)</td>
</tr>
</tbody>
</table>

Abbreviations: ER, estrogen receptor; IDC, NOS, invasive ductal carcinoma, not otherwise specified.

Table 6. Features of “Triple-Negative” Breast Carcinoma (Estrogen Receptor, Progesterone Receptor, and HER2/neu Negative)

<table>
<thead>
<tr>
<th>Feature</th>
<th>Cases/Total (%)</th>
</tr>
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<tbody>
<tr>
<td>Total number of triple-negative cases</td>
<td>16/44 (36)</td>
</tr>
<tr>
<td>Proportion IDC, NOS</td>
<td>15/16 (94)</td>
</tr>
<tr>
<td>Histologic grade 1</td>
<td>0/15 (0)</td>
</tr>
<tr>
<td>Histologic grade 2</td>
<td>5/15 (33)</td>
</tr>
<tr>
<td>Histologic grade 3</td>
<td>10/15 (67)</td>
</tr>
<tr>
<td>Micropapillary invasive ductal carcinoma</td>
<td>1/16 (6)</td>
</tr>
<tr>
<td>Other types of carcinoma</td>
<td>0/16 (0)</td>
</tr>
<tr>
<td>Age 50 years or younger at diagnosis</td>
<td>11/16 (69)</td>
</tr>
</tbody>
</table>

Abbreviation: IDC, NOS, invasive ductal carcinoma, not otherwise specified.

Factors. Indeed, factors other than intrinsic biology are probably important—factors such as a lack of patient education regarding breast carcinoma, reduced availability of adequate medical care, including mammographic screening, and distrust of Western style medicine. For example, on the basis of the available evidence, it is likely that a high incidence of genetically driven, biologically aggressive breast carcinoma, occurring in a resource-limited setting, best explains the poor prognosis of breast carcinoma in many parts of Africa, particularly in young women.

A precursor high-grade ductal carcinoma in situ with comedonecrosis and a basal immunophenotype has been identified and represents hope that future screening mammography, instituted earlier than for white patients, might detect the associated microcalcifications, allowing surgical intervention before invasion develops. Adjunct medical treatment options, particularly once invasion has developed, are more limited, because these carcinomas do not respond to either hormonal therapy or targeted antibody therapy. On the other hand, neoadjuvant chemotherapy for these triple-negative breast carcinomas more often results in complete pathologic response (with no residual invasive tumor in the resected specimen) compared with non–triple-negative breast carcinomas. The subsequent prognosis in these complete pathologic responders is similar to non–triple-negative breast carcinomas.

In summary, the findings suggest the possibility that Ugandan women in the Kampala region more often have genetically driven, histologically aggressive breast carcinomas at a young age, likely to be less susceptible to conventional hormonal and targeted antibody treatment. Similar findings in other parts of Africa suggest that this may be a more widespread phenomenon. Detecting and treating this increasingly important cause of mortality in young African women will be an enormous challenge. The Breast Global Health Initiative is an international effort to address this challenge and recognizes expertise in pathology as a key requirement. Its proposals include training pathologists and organizing international pathology services. Only a focused and sustained international effort of this type could hope to effectively deal with this disease.

References


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**Submissions Now Accepted for CAP ’11 Abstract Program**

Abstracts and case studies are now being accepted for the College of American Pathologists (CAP) 2011 meeting, which will be held September 11th through the 14th in Grapevine, Texas. Submissions for the CAP ’11 Abstract Program will be accepted through Friday, April 1, 2011.

Accepted submissions will appear in the September 2011 issue of the *Archives of Pathology & Laboratory Medicine*. Visit the CAP ’11 Web site at www.cap.org/cap11 for specific abstract program information as it becomes available.