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The Other Breast: Indications for Biopsy and/or Mastectomy

Charles S. Rogers, MD*

A search for malignant and premalignant lesions in 162 contralateral biopsy and/or mastectomy specimens yielded 45 (27.8%) malignancies and 54 (33%) premalignant lesions (atypical epithelial hyperplasia, Wellings grades III and IV). In those with no palpable or mammographic suspicion of malignancy, the cancer incidence was 13.8%. Eight malignancies occurred one month to three years after antecedent biopsies which revealed premalignant lesions. No cancer has been detected after biopsies which revealed hyperplasia of grade II or less. Cancer size at time of discovery varied significantly with the method of detection: average 2.7 cm by palpation; 1.6 cm by mammography; 0.5 cm by biopsy. Axillary metastasis was present in 30%, 20%, and 10%, respectively. Axillary metastasis from occult contralateral cancer occurred in three instances where none was found from ipsilateral, clinically evident cancers; synchronous in two; asynchronous in one by eight years. In a subgroup of one hundred prophylactic biopsies performed by the author, patients with Wolfe P2-DY patterns (vs. N1-P1) had a high incidence of malignancy (20% vs. 12.5%) and at a younger age (average: 53 vs. 73 years). Routine contralateral biopsy synchronous with ipsilateral mastectomy is recommended. Patients with contralateral severe epithelial atypia should have the option of prophylactic mastectomy.

Breast cancer is frequently a multicentric and bilateral disease. Clinically, these characteristics may be absent or obscure but readily apparent to those who study serial sections of whole breast specimens (1-3). A segmental resection may remove only a small part of the disease, and even a radical mastectomy leaves 50% of the target tissue at risk. If, like the thyroid, the breast(s) had a small strip of tissue between the two lobes, it would be considered one organ rather than two.

Malignancy begins at the same time or asynchronously in multiple terminal ductal lobular units (TDLU) and evolves from epithelial hyperplasia, to anaplasia, to in situ carcinoma, and finally to invasive malignancy (1). The time interval from hyperplasia to in situ malignancy is unknown, but studies of growth rates indicate that invasive breast cancers, on the average, double in volume in one hundred days (4-5). At this growth rate, it takes six to eight years for one cancer cell to become one billion cells in a mass 1.0 cm in diameter, but only another three hundred days before it grows to eight billion cells in a 2.0 cm mass.

Despite this long latency period, we are able to detect less than 10% of breast cancers while they are still smaller than 1.0 cm and less than 3% while they are still noninvasive (6). The short interval required for a cancer to double in size explains, in part, why so many “interval” cancers are detected by patients between annual physical and/or mammographic examinations. Except for data from the Breast Cancer Detection Demonstration Projects (BCDDP), scant evidence exists that we are detecting breast cancer earlier (7). Until we discover better early detection methods, most women who develop breast cancer will eventually die from it (8). A reduction in mortality may require a more aggressive use of biopsies in those at known high risk. We need to know if, and how often, this aggressive approach would detect lesions significantly earlier—and if the benefits exceed the risk. Additionally, we need to know how often, and under what circumstances, epithelial atypia proceeds to invasive malignancy. One such clue may be the demonstration that some epithelial hyperplasias can stimulate neovascularity (5).

This communication reports an analysis of 162 consecutive biopsies and/or mastectomies in a group of 450 patients who had known cancer in one breast.

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Materials and Methods

We analyzed 162 consecutive contralateral biopsies and/or mastectomies (in a group of 450 patients at risk) at Bay Medical Center between January 1977 through August 1982. Indications for the procedures varied with the individual surgeon and with time. Specimen size varied from minimal biopsies to the entire breast. Most biopsies consisted of a full thickness segment of breast tissue, about one half of a quadrant, or the subareolar segment. In the absence of palpable abnormalities, the location of prominent ducts, dysplasias, and asymmetries indicated by mammograms was used to determine where to perform the biopsy.

Two physicians, instructed in Wolfe’s system of classification of mammographic patterns (9), interpreted the mammograms. When elements of both P2 and DV existed, the pattern was usually classified as P2. Only a few prominent ducts resulted in a PI rather than N1 classification.

Epithelial hyperplasias were graded by the method of Wellings (1). Thoroughness of histopathologic study of specimens varied with the individual pathologist and with time. During the course of the study, Dr. Thomas Cajigas and associates, with the aid of Dr. Wellings, developed a rapid, subgross method of studying serial sections of breast specimens (unpublished), which increased the incidence of premalignant, in situ, and microinvasive lesions.

Results

Forty-five of 162 (27.8%) contralateral biopsies or mastectomies resulted in a diagnosis of malignancy: 33 were invasive; 12 in situ. Fifty-three patients (33%) had premalignant lesions or atypical epithelial hyperplasia (Wellings grade III [27] or IV [26]). A cancer incidence of 13.6% was found in those with no palpable or mammographic suspicion of malignancy. This finding is consistent with the studies reported by Urban and Leis (10).

The size of the cancer and incidence of axillary lymph node metastasis varied significantly with the method of detection (Table I). Only 20% of the 20 palpable cancers were less than 2.0 cm in diameter, and 30% had axillary metastasis. The five nonpalpable cancers detected by mammography were earlier cancers and illustrate the value of mammographic surveillance. Twenty of the 45 cancers, however, were discovered by biopsy in patients with no palpable or mammographic evidence of malignancy. Of these 20 cancers, 70% were 0.5 cm or less in diameter, and only two had axillary metastasis. Three patients with pathological stage I ipsilateral cancers had axillary metastasis from occult cancers in the contralateral breast: synchronous in two cases and asynchronous (eight years) in one case.

During this study, one in situ and seven invasive cancers have been discovered following 61 antecedent biopsies that revealed moderate or severe epithelial atypia. Thus far, no contralateral malignancy has been detected in patients in whom the highest grade of epithelial hyperplasia in a biopsy specimen was Wellings grade II or less. This is consistent with evidence that severe epithelial atypia in abnormal terminal ductal lobular units is, indeed, preneoplastic (1,2).

In a series of one hundred consecutive prophylactic biopsies performed by the author as a subgroup in this study, patients with prominent ducts (Wolfe P2 pattern) or generalized coalescent dysplasia (Wolfe DY) had a higher incidence of contralateral invasive cancers and severe epithelial hyperplasia than those with N1-P1 patterns (Table II). These results are consistent with those of Wellings and Wolfe (9), who reported that xeroradiographic and histological risk grades correlate closely. In biopsies of breasts without malignancy, the highest grades of precancerous epithelial abnormality were found in those with P2 and DY patterns, seldom in P1, and rarely in those with N1 patterns (10).

In patients whose biopsies had Wolfe P2-DY patterns, detection of the first cancer occurred at an average age of 49 years, and the second at age 53. In those with N1-P1 patterns, the corresponding ages were 61 and 73. The reason for this age discrepancy remains unclear, although it is tempting to speculate that the breasts containing

<table>
<thead>
<tr>
<th>Detection Method</th>
<th>No.</th>
<th>% with nodes</th>
<th>Average</th>
<th>2.0 cm or &lt;</th>
<th>0.5 cm or &lt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palpation</td>
<td>20</td>
<td>30%</td>
<td>2.7 cm</td>
<td>25%</td>
<td>5%</td>
</tr>
<tr>
<td>Radiography</td>
<td>5</td>
<td>20</td>
<td>1.6 cm</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>Biopsy</td>
<td>20†</td>
<td>10</td>
<td>0.5 cm</td>
<td>85</td>
<td>70</td>
</tr>
<tr>
<td>TOTALS</td>
<td>45*</td>
<td>20%</td>
<td>1.6 cm</td>
<td>58%</td>
<td>38%</td>
</tr>
</tbody>
</table>

*33 invasive and 12 in situ cancers
†All 20 nonpalpable and not visible on mammography
prominent ducts and severe dysplasias have been subjected to more virulent and/or greater quantities of carcinogen(s). Patients with a family history of breast cancer had cancer at an earlier age than the entire group but no younger than those with P2-DY patterns.

An attempt to correlate cancer bilaterality with multifocal lesions in the first breast failed because of marked variance among pathologists in searching for additional lesions. The incidence ranged from 6% to 58%. The latter figure is more consistent with the incidence recently reported by Egan (3). Attempts to correlate multicentricity with the Wolfe patterns failed for the same reason. No attempt was made to correlate the incidence of bilateral nature of breast cancer with the histological grade or type of the tumor in the first cancer, nor with the presence or absence of estrogen receptors in the first cancer.

Discussion

Many investigators (1-3), including Samhouri, Block, and Kambouris (10), have documented the multicentric and bilateral nature of breast cancer. Urban and Leis (11) have demonstrated that significant numbers of occult contralateral breast cancers can be detected by routine contralateral biopsies, and greater numbers by selective contralateral prophylactic mastectomies. The incidence of bilaterality is higher than reported in those studies when cancers evident by palpation or mammography are included. Our study and others (10) indicate that the incidence varies with the method(s) of detection. It also varies with the size of the specimen, diligence of the pathologist, and length of follow-up (9).

If epithelial atypia is present in biopsy specimens, the patient is at a significantly higher risk of developing invasive cancer (12-14). In this study, eight patients with these lesions in antecedent biopsy specimens developed malignancies within three years after the biopsy was performed. Thus far, none of the patients with epithelial hyperplasia, Wellings grade II or less, have developed contralateral cancer. These data support the pathological evidence that severe atypical epithelial hyperplasia in abnormal terminal ductal lobular units is premalignant (1,2). It also supports the clinical studies of others indicating that patients with atypical epithelial hyperplasia are at considerably higher risk than those without hyperplasia (12-14). The method of grading used in this study is similar to that of Black (13). It indicates whether cellular abnormalities of mammary epithelium are mild, moderate, or severe. In the author's view, it is somewhat analogous in both method and significance to the classification of dysplasias of the uterus and cervix made by means of the Pap smear. It is helpful in making decisions about the management of the disease.

Patients who have had cancer of one breast require constant surveillance. There is scant evidence, however, that such a procedure actually results in discovering the second cancer any earlier than the first one. Most patients in our study had not practiced routine self breast examination (SBE). In those with palpable cancers, the patients rarely had yearly mammograms. However, all twenty of the patients with cancer detected only by biopsy had had "negative" mammograms within one year before biopsy. There seems little doubt that SBE, frequent physical examinations, and screening mammography can discover more cancers and at an earlier stage. If the patient and physician remain unconcerned, however, the result too often yields an incurable cancer in the contralateral breast. Contralateral biopsy at the time of the mastectomy requires only a small amount of additional effort, time, and cost; it results in little, if any, additional morbidity and no mortality. It allows detection of some additional cancers and premalignant lesions and provides worthwhile information which may well influence decisions about management of the disease.

In our institution, 65-70% of the patients with prevalent cancers have P2 or DY mammographic patterns. Over 90% of our false negative mammographic diagnoses also occur in these patterns. Patients with these patterns are also more difficult to evaluate by palpation. In this study, they were found to have a higher risk of invasive contralateral cancer or premalignant lesions. In the absence of palpable abnormalities, the locations of prominent ducts and areas of asymmetry aided considerably in choosing where to perform the biopsy. In patients who had no palpable abnormalities but diffuse symmetrical prominent ducts or dysplasia, the biopsy was performed in mirror image locations, or the upper outer quadrant.

In all breast cancer patients except in those with a known short life expectancy, valuable information can be provided by mammography, knowledgeable interpretation.
of the Wolfe parenchymal patterns, contralateral biopsy, and a diligent search for premalignant and obscure malignant lesions by an informed and interested pathologist. These procedures all are needed to make logical decisions about therapy and surveillance. Serial sectioning of the specimen and rapid subgross preparation (or radiography) of the slices helps considerably in identifying significant lesions. The presence of severe atypical epithelial hyperplasia in terminal ductal lobular units puts the patient at a high risk of subsequent invasive cancer. In such patients, prophylactic mastectomy with reconstruction seems a logical alternative to constant surveillance.

References

1. Wellings SR, Jensen HM, Marcum RG. An atlas of subgross pathology of the human breast with special reference to possible precan-