Pathology Update

Bilateral and Multifocal Breast Cancer

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Introduction

Widespread mammography and the increasing use of breast-conserving therapy make bilateral and multifocal breast cancer more important issues in patient care. The biologic mechanisms of these two cancer types differ. Bilateral breast cancer results from independent primaries in the two breasts, while multifocal breast cancer can result from either intramammary spread from a single index tumor or, probably less commonly, from multiple synchronous primary tumors. This article discusses in situ cancer from the point of view of multifocality and bilaterality, as well as the biologic differences between ductal carcinoma in situ and lobular carcinoma in situ. The term “multifocal” is used in this report to describe cases in which two or more discrete tumors can be detected clinically, radiographically, or pathologically in the same breast, and the term is used without etiological implications. In some articles, the words “multifocal” and “multicentric” may be used interchangeably. In other articles, the term “multicentric” may describe multiple independent primary tumors in one breast, and “multifocal” may describe multiple tumor nodules derived from a single primary tumor that occur close to the primary lesions. In this article, synchronous bilateral tumors are those detected within one year of one another, whereas metachronous tumors are detected after an interval greater than one year.

Multifocal breast cancer was noted by John Hunter in 1837 in *Lectures on the Principles of Surgery*. Historically, bilateral carcinoma was regarded as little more than a curiosity, but it became recognized that the incidence was significant and that some of these cases were familial and carried a devastating prognosis. Several factors heighten interest in this subject, including the isolation of the BRCA genes,[1] as well as the widespread use of mammography, which has led to the discovery of many small, nonpalpable tumors and a fivefold rise in the incidence of in situ carcinomas. The effect of these factors is twofold: First, because the survival of patients with small, nonpalpable breast tumors is approximately 95% at 10 years,[2] the window of opportunity for cancer in the contralateral breast to manifest itself is larger. Second, bilateral disease is more readily detected by mammography. Before the widespread use of breast-conserving surgery, multifocal disease was of interest only to pathologists, but now it is of considerable clinical and therapeutic importance. While it is likely that small numbers of residual malignant cells can be eradicated in many patients by radiotherapy, measurable independent tumor foci are clinically significant.

Clinicopathologic Features

The pathogenesis of multiple breast cancers, whether in one breast or two, is not well understood and may be the extremes of the same phenomenon. Given that both breasts share common genetic information and are exposed to the same hormonal and environmental influences, it is conceivable that one is dealing with multiple independent primaries. However, the mode of spread of breast cancer within the ipsilateral breast and the rate of metastasis to both the ipsilateral and contralateral breast are not well understood.

Recent biologic data suggest that bilateral cancer is commonly due to the occurrence of two independent primary tumors, whereas multifocal breast cancer may be due to either intramammary metastases or multiple synchronous primary tumors.

Bilateral breast cancer accounts for 5% to 10% of breast cancers.[3] In patients with breast cancer, the risk of a second primary is approximately fivefold that for other women, and the cumulative risk of bilateral breast cancer is approximately 1% per year.[4,5] Synchronous tumors occur in one fifth of cases, and bilateral tumors present within two years of one another in 50% of cases.[6] These data are derived from women referred to large centers; however, population studies show the risk to be lower. For example, Prior and Waterhouse[7] calculated that in Birmingham, England, the risk of bilaterality in women with one tumor was increased 2.6-fold. In this group, those with bilateral cancer had a median age of onset of three to five years younger than in women with unilateral carcinoma and without a known family predisposition. Although the data are limited, Ringberg et al[8] found malignant lesions in half of the contralateral breasts removed as part of reconstructive breast surgery. The majority of these were in situ, which led them to postulate that the difference between their findings and the incidence of bilateral cancer observed clinically is due to the slow rate of progression of in situ carcinoma.

Bilateral breast cancer may have two major forms, each with different outcomes. A family history of breast cancer frequently is present in premenopausal women, and the mortality is high. Cases of families such as that reported by Cady,[9] in which three sisters aged 31, 32, and 42 years at the time of diagnosis of the first tumor developed bilateral breast cancer before the age of 45 years, make a dramatic impact but are rare. Anderson and Badzioch[10] estimate that in premenopausal breast cancer patients with a positive family history of breast cancer, the probability of developing a primary in the contralateral breast is 35% to 38%. If the first diagnosis was made after the menopause, the probability of a second primary fell to between 11% and 26% compared with 13% in women without a family history. However, cases with a strong family history account for only 5% to 10% of all bilateral breast cancers. The majority of bilateral cases occur in postmenopausal women. The age of onset in this group is a few years younger than in women with unilateral disease, but the interval between the two tumors can span many years.

Pathologically, bilateral breast disease is indistinguishable from unilateral disease. The majority of cases are infiltrating ductal carcinomas (NOS). However, several authors[4,6] have noted an increase in the frequency of lobular carcinoma that is not statistically significant. There is no relationship between the histologic type of tumor in one breast and that in the other.[6]

Survival after bilateral breast cancer is a controversial subject. Robbins and Berg[4] state that the mortality of the two tumors was additive and almost halved the expectation of life, a finding that was subsequently confirmed at the same institution[4] and elsewhere.[11] Others[12,13] reached the opposite conclusion, possibly because patients with favorable primary tumors are more likely to live long enough to develop a second primary. Data from the Surveillance, Epidemiology, and End Results Program[14] suggest that a localized primary in the contralateral breast did not adversely affect prognosis. Conversely, a population-based study on a smaller group of patients[15] showed that survival rates of such patients were worse. One explanation for these discrepancies is the variance in proportion of young patients with familial breast cancer in the various studies, since the young fare worse. Another factor is the stage at which the second primary was diagnosed. Since women with...
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Attempts to elucidate the mechanisms involved in bilateral breast cancer based on histologic examination were unsuccessful due to the difficulty in separating primary tumors from metases as well as the inadequacies of a histologic classification that includes 70% of cases among infiltrating ductal carcinomas (NOS).

We have studied 51 patients using a series of monoclonal antibodies applied to the paired (left and right) breast tumors.[6] Formalin-fixed, paraffin-embedded sections were reacted with monoclonal antibodies B72.3, DF3, H59, c-erb B-2, Sp-1, and carcinoembryonic antigen (CEA) using standard avidin-biotin techniques, and the immunologic profile was determined for each tumor. We saw no relationship between the two carcinomas in each patient, and the immunocytochemical profile was the same on both sides in only one of the 51 patients. These results indicated that bilateral breast cancer probably resulted from two independent neoplastic events.

Alterations in the p53 gene also have been studied in bilateral breast cancer. Lidereau and Soussil[16] screened DNA from lymphocytes of 19 patients with bilateral breast cancer for p53 mutations by single-strand confirmation polymorphism. They could not detect germ-line mutations in exons 5, 6, 7, and 8 and concluded that p53 was not generally involved in bilateral breast cancer. Subsequently, Ackerman et al[17] studied the expression of p53 in bilateral breast cancer by immunocytochemistry on formalin-fixed, paraffin-embedded sections with antigen retrieval (Fig 1). Because the mutant p53 gene product has a longer half-life than the wild type, it can be readily detected by this method, whereas normally, insufficient wild-type is present for detection. Table 1 summarizes the expression of mutant p53 among 38 patients with bilateral breast cancer. The rate of expression (22%) is similar to that found in unilateral breast cancer. There were no differences in incidence of p53 expression between synchronous and meta-chronous tumors or between the first and second tumor. If p53 protein was overexpressed in the first cancer, the probability of overexpression in the second was 60%, whereas if mutant p53 protein was absent in the first tumor, it was unlikely to be present in the second. In the three cases with bilateral expression of mutant p53 protein, the mutations were amplified and sequenced by polymerase chain reaction and single-strand confirmation polymorphism. Among synchronous cases, one showed a mutation in exon 2-3 bilaterally (Fig 2), and the other had a mutation in exon 8-9 in both tumors. In the third (metachronous) case, a mutation could be demonstrated in only one breast, possibly for technical reasons. The authors concluded that p53 mutations rarely play a role in bilateral breast cancer.

These data indicate a lack of congruity between the tumors in the two breasts. The data also suggest that two independent neoplastic events are involved and that metastatic spread from one breast to another is rare, except perhaps with widely disseminated disease. Substantial data on the latter point are unavailable due to the difficulty in histologically distinguishing a primary breast carcinoma from a metastasis from the contralateral side.

Multifocal Cancer

With the advent of breast-conserving therapies, multifocal breast cancer has become more important.[18–20] The incidence of multifocal breast cancer depends on how hard one looks for it.[21] Fisher et al[22] studied single random sections from each quadrant and found multifocal breast cancers in 13.4% of cases. Lesser et al[23] examined two sections per quadrant and found multifocality in 30% of cases. Using a more sophisticated technique - freezing the breast, cutting it into slices, and taking radiographs - Egan[24] found multifocal tumors in 60% of cases. Multifocality not only is found in patients with advanced disease, as was the case in many earlier studies, but also has been observed in nearly half of patients with nonpalpable, mammographically detected tumors.[25,26] Generally, if the index tumor was invasive, the distant foci of tumor were invasive in 10% to 30% of cases. If the index tumor was in situ, so were the other foci in the breast.

The distinction between intramammary spread and multiple separate primary tumors is difficult to establish and has been based largely on location of the tumors, histologic differences among tumors, and the presence of adjacent intraductal carcinoma.[27] In an investigation[28] of the pathogenesis of multifocal breast cancer using a battery of immunocytochemical stains similar to those used in their bilateral breast cancer studies[6,17] (B72.3, DF3, c-erb B-2, CEA, SP-1, and p53), 24 cases of multifocal breast carcinoma were retrieved from the files of the H. Lee Moffitt Cancer Center & Research Institute. In each instance, two or more discrete synchronous tumors were identified within the same breast by the surgeon, radiologist, or pathologist. This study included only those cases in which the distance between the mass was actually measured on the mammogram by the radiologist or on the specimen by the pathologist or clearly described as in separate regions of the breast. In four instances, the tumors were separated by 1 cm to 2.5 cm of grossly normal breast; in eight, the intervening normal breast tissue exceeded 2.5 cm. In the remaining 12, the tumors were in different regions of the breast (ie, the four quadrants and the subareolar area). The histologic findings and immunoreactivity were compared, and the results are summarized in Table 2. Fifteen of 24 cases were histologically and immunocytochemically identical or were histologically identical but differed in their immunoreactivity to only one antibody (in two of these cases, the difference was only focal). In seven of the remaining nine cases, the tumors were histologically and immunologically different. In three of four cases in this group, the discrete tumor foci were from 1 cm to 2.5 cm apart. The two remaining cases were equivocal with histologically different tumors showing identical immunoreactivities. The observations are strengthened by the fact that the same technique applied to bilateral breast cancers[6] yielded different findings: the immunocytochemical profile was different between the left and right breasts of every patient but one. The investigation concluded that multifocal tumors either could result from intramammary spread from a single primary tumor or could represent multiple synchronous primary tumors.

In the seven cases in which a lymph node metastasis was assessed, the immunoreactivity was identical with at least one of the tumors in the breast. Although others have shown consistency in expression of both p53 and c-erb B-2 between primary breast cancers and their nodal metastases,[29,30] and others[31,32] have noted such factors as tumor heterogeneity, genetic drift and clonal selection might influence the results.

A genetic approach has been used to address the problem of multifocality. This is based on an analysis of tumor cloning using a technique developed by Vogelstein[33] of restriction fragment length polymorphism analysis of the X-chromosome-linked phosphoglycerate kinase (PGK) gene and on random inactivation of the gene. Noguchi et al[34] analyzed 30 breast carcinomas and found that every one was monoclonal and that one of the two PGK genes was inactivated at random in each tumor. The authors concluded that p53 mutations rarely play a role in bilateral breast cancer.

In all three cases with bilateral expression of mutant p53 protein, the mutations were amplified and sequenced by polymerase chain reaction and single-strand confirmation polymorphism. Among synchronous cases, one showed a mutation in exon 2-3 bilaterally (Fig 2), and the other had a mutation in exon 8-9 in both tumors. In the third (metachronous) case, a mutation could be demonstrated in only one breast, possibly for technical reasons. The authors concluded that p53 mutations rarely play a role in bilateral breast cancer.

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These studies collectively establish through different methodologies that multifocal tumors generally represent intramammary spread, although discrete independent primaries occasionally may arise synchronously in one breast.

**In Situ Breast Cancer**

Before the 1970s, in situ disease accounted for approximately 5% of all cases of breast cancer, split equally between intraductal carcinoma or ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS). Since only large intraductal tumors could be palpated, the smaller and nonpalpable foci of DCIS and LCIS were detected only incidentally. Widespread mammographic use has resulted in approximately 30% of all breast cancers in the United States now being detected at the in situ stage. No specific mammographic pattern exists for LCIS, and it is recognized only because of its association with fibrocystic changes in the breast.

DCIS and LCIS are biologically and clinically distinct. DCIS is analogous to other forms of in situ carcinoma in that the cells already possess the malignant phenotype but lack the ability to invade. Originally, lobular carcinoma was similarly regarded, but LCIS is now generally believed to be fundamentally different in that lobular in situ cells have not progressed so far along the pathway to neoplasia that progression to invasive carcinoma is inevitable and that the condition is best regarded as a marker of high risk for the development of breast cancer. As a result, many prefer the term lobular neoplasia and include both cases of atypical lobular hyperplasia and LCIS.

**Ductal Carcinoma In Situ**

Multifocality has long been recognized in DCIS and occurs with a frequency of 30% to 60%.[37–39] Since local excision, if complete, is curative in DCIS, this multifocality may explain the 10% to 15% risk of recurrence within a four- to five-year period following treatment by local excision alone.[40] Pathologists recently have begun to separate several different subtypes of DCIS, including comedo carcinoma, cribriform, papillary, solid, and micro-papillary forms (Fig 3). Kinne et al.[41] have shown that of these forms, comedo carcinoma is most likely to be multifocal and to have areas of microinvasion, whereas the cribriform and solid variants are least likely to be multifocal. The probability of multifocality also correlates with the extent of the lesion. Schwarz et al.[42] confirmed these findings, although they found that a significant number of cases exhibited at least two different histologic subtypes so that predication of behavior from histology may be hazardous.

Little investigation has been conducted to determine the pathogenesis of multifocal in situ breast carcinoma. Noguchi et al.[43] recently applied to DCIS their method of detecting clonality based on restriction length polymorphism of the X-chromosome-linked PGK gene and on random inactivation of the gene by methylation, which has been discussed in connection with invasive carcinoma. They examined seven cases of extensive intraductal carcinoma and obtained the intraductal cells by microdissection of frozen sections to obviate contamination by stromal cells. All the samples that were analyzed, including those from widely separated areas of individual breasts, were monoclonal, indicating origin from a single primary focus. While DCIS can spread widely in the breast, it is not clear that all widely separated foci of DCIS in a breast would be necessarily monoclonal. They also noted that areas of atypical duct hyperplasia also were monoclonal, suggesting that somatic cell mutation had already occurred at this stage in the progression from proliferative breast disease to carcinoma.

**Lobular Carcinoma In Situ**

Multicentricity in LCIS has been recognized since the earliest descriptions of the entity. However, the significance of multifocal LCIS differs from multifocal DCIS as there is considerable doubt as to the malignant potential of the cells in LCIS. Long-term follow-up of cases of LCIS shows that the risk of developing invasive carcinoma is relatively low and is equally divided between the ipsilateral and contralateral breasts. In a study[44] of 535 cases of LCIS or atypical lobular hyperplasia with long-term follow-up, invasive carcinoma developed in the ipsilateral breast in 71 cases (13%) and in the contralateral breast in 59 cases (11%). Page et al.[45] estimate the relative risk of developing breast cancer after a biopsy that shows LCIS to be 10.8 times the risk of invasive carcinoma in women lacking proliferative breast disease, or 17% at 15 years. Given these data, does the presence of LCIS adjacent to an invasive carcinoma have clinical significance in terms of multifocality or bilaterality? Haagensen et al.[46] compared the risk of contralateral cancer in cases with invasive breast cancer with or without adjacent LCIS treated by mastectomy and found the risk to be two to three times greater in women with accompanying LCIS.

Scientific investigation of LCIS at the cellular or molecular level does not appear to have been reported, presumably because of the difficulty in detecting foci of LCIS within the breast parenchyma, as well as the microscopic size of the lesions. There is, however, a general lack of the common breast cancer markers.[44]

In the case of in situ carcinoma, the probability of bilateral disease and its clinical significance is highly dependent on whether it is DCIS or LCIS. As already discussed, histologic examination of the contralateral breast reveals a higher incidence of occult disease in situ cancer than is suspected clinically.[8,47] This is particularly true of LCIS where studies based on mirror-image biopsies of the contralateral breast yielded an incidence as high as 35%.[48] While if a contralateral mastectomy specimen is studied, the incidence may reach 67%.[49] The clinical significance of these findings is uncertain as LCIS does not represent a true in situ malignancy but rather an indicator of increased risk of carcinoma in both ipsilateral and contralateral breasts. Close observation has been suggested as an appropriate treatment.[49]

Follow-up studies in patients with DCIS have yielded a lower incidence of contralateral breast cancer. Webber et al.[50] followed 116 patients with DCIS for a mean of nine years, four of whom (3.4%) developed carcinomas in the contralateral breast. This incidence is similar to that expected in patients in whom the initial carcinoma is invasive. Cataliotti et al.[51] reported 13 cases (7%) of cancer in the contralateral breast among 175 patients with a median follow-up of 81 months, although three of these preceded the in situ carcinoma in the opposite breast and four were synchronous. Silverstein et al.[39] found an 11% incidence of bilaterality with a median follow-up of 45 months, while Temple et al.[52] in a population-based study in Alberta, Canada, observed a frequency of 6%, the majority of which were invasive among 226 patients with mean follow-up of six years.

Three points emerge from these data. (1) The incidence of clinically significant bilateral breast cancer in patients with DCIS appears to be approximately the same as that following a diagnosis of invasive breast cancer; however, this does not obviate the need for close follow-up. (2) The disparity between this clinical figure and that reported when the contralateral breast is removed (or a biopsy is done) and examined histologically suggests that what histologically is called in situ carcinoma (particularly LCIS) may not always represent an irreversible condition and that progression to invasive carcinoma may be slow. (3) An increased awareness of the low biologic potential of LCIS, coupled with the fact that the risk of invasive carcinoma is low and equal in the ipsilateral and contralateral breasts, has led to a more conservative approach to treatment of both unilateral and bilateral LCIS.

**Conclusions**

The effects of invasive and in situ bilateral and multifocal breast cancers are different. Invasive bilateral breast carcinoma appears to have two basic forms: one has a genetic basis, affects young women, and carries a poor prognosis, while the other occurs sporadically in generally older breast cancer patients and has probably little additional effect on life expectancy. Lifelong surveillance of the contralateral breast is indicated. Multifocal carcinoma is present in the ipsilateral breast in at least one third of cases of breast carcinoma and is particularly significant in women who undergo breast conservation therapy.

Generally, bilateral breast cancers represent independent primary tumors, and metastases to the contralateral breast are unusual. Multiple tumors found synchronously...
Multifocal and bilateral in situ carcinoma present different problems, depending on whether the lesion is ductal or lobular. DCIS represents fully committed malignant cells that have not yet invaded but, given enough time, will probably do so. LCIS is best regarded as a preneoplastic state from which progression may not be inevitable, although when invasive carcinoma does develop, it is as likely to occur in the contralateral breast as in the ipsilateral one. The frequency with which both are detected pathologically appears to exceed that of clinical disease, which suggests that some lesions may not inevitably progress to invasive carcinoma or may do so very slowly.

References