Familial Bilateral Cancer of the Breast

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THREE sisters, all with bilateral cancer of the breast of comparable histology, were recently seen at the Lahey Clinic Foundation. This rare combination of unusual events emphasizes the genetic implications of breast cancer as well as the problem of bilaterality of breast cancer.

Case Report

A 46-year-old woman was seen in August 1968 with the complaint of a mass in the site of a previous mastectomy. Past history revealed that in October 1964, at age 42, a left radical mastectomy had been performed for a mass that had been known to be present for over 3 years. A bilateral oophorectomy was performed in November 1964 for prophylaxis. She was well until May 1967 when a mass in the right breast, present for at least 2 years, proved to be carcinoma. Right radical mastectomy was performed. A mass that was noted in the right mastectomy field shortly after operation had gradually increased in size.

Physical examination was remarkable only in demonstrating a mass, 2 cm. × 2 cm., in the posterior axillary line at the level of the seventh rib. Results of laboratory studies were entirely normal. The pathological material was reviewed at the Laboratory of Pathology, New England Deaconess Hospital. The mass found in the left breast in 1964 was described as "a distinctly anaplastic and pleomorphic adenocarcinoma with high mitotic rate, foci of necrosis, and a moderate amount of fibrous stroma." Lymph nodes were all free of metastatic disease.

The mass found in the right breast in 1967 was described as "anaplastic adenocarcinoma of the breast." Lymph nodes were free of metastases. An excisional biopsy of the mass in the site of the right mastectomy was described as "poorly differentiated adenocarcinoma consistent with breast primary."

The family history revealed her mother died at age 36 in childbirth, and two of the patient's sisters each had bilateral mastectomies for breast cancer. The clinical history and pathological material from the patient's sisters were reviewed.

At the age of 31, the younger sister had a right radical mastectomy in January 1956 for a mass, 1.3 cm. in diameter, in the lower medial quadrant. Review of the pathologic material at the Laboratory of Pathology, New England Deaconess Hospital, revealed a "pleomorphic anaplastic adenocarcinoma with a high mitotic rate, heavy fibrous stroma and inflammatory reaction." Seventeen lymph nodes were free of tumor.

In March 1957, when she was 32, a left radical mastectomy was performed for a mass in the upper outer quadrant. Review of this pathologic material revealed a "poorly differentiated adenocarcinoma with a more solid medullary pattern with some lymphocytes and plasma cell response. It would *not* be classified as medullary carcinoma with a lymphoid stroma, however." Fourteen lymph nodes were free of tumor. In addition, a thyroid nodule was excised in November 1956, which on review showed both adenomatous goiter and chronic thyroiditis.

In May 1961, a hysterectomy for interruption of a 12-week pregnancy was performed, and no evidence of metastatic disease was noted. During August 1962, progressive ascites developed. Microscopic analysis of the ascitic fluid revealed tumor cells. The patient's condition deteriorated and she died. No details of the terminal illness are known, and necropsy was not performed.

At age 32, an older sister had a left radical mastectomy for carcinoma in 1952. Review of the pathological material revealed a "solid, medullary, poorly differentiated, adenocarcinoma with a high mitotic rate, focal necrosis and scant stroma." Twelve lymph nodes were negative for tumor. In January 1965 at age 45, she had a right radical mastectomy for a carcinoma, 1.0 cm. in diameter, that on review of the pathological material revealed a "pleomorphic anaplastic adenocarcinoma with fibrous stroma, inflammatory reaction, and a moderate mitotic rate." Six lymph nodes were without evidence of metastases. At present, she is living without evidence of metastatic disease.

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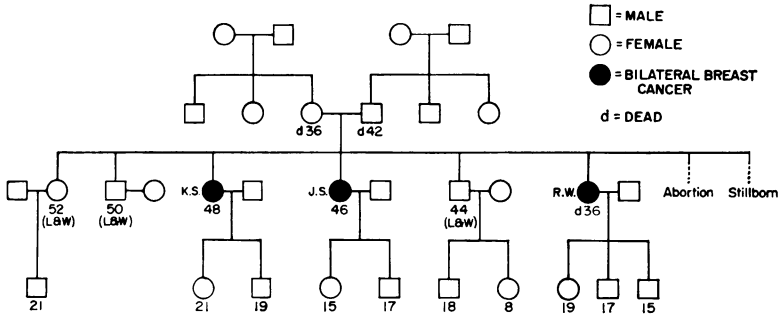

FIG. 1. Outline of genealogy.

The remainder of the family history for two previous and one subsequent generation revealed no other instances of breast cancer on either maternal or paternal side. All six siblings were nursed by the patient's mother for periods of several months. The genealogy is outlined in Figure 1.

Representative photomicrographs of two of the six breast cancers reported are shown in Figures 2, 3, and 4. The six cancers were similar in general histology and revealed no evidence of dermal or other lymphatic invasion nor any other criteria of metastatic disease and therefore were each believed to be primary cancers.

Comment

Both bilaterality and familial incidence, especially among mothers, daughters, and sisters, are well-known aspects of breast cancer. Many articles have been written about the bilateral incidence, the earliest comprehensive report being that of Kilgore[8] in 1921 and the most thorough and provocative article being one by Robbins and Berg[12] in 1964. In an extensive statistical analysis of a large group of patients with breast cancer who were observed prospectively over a 20-year period of follow-up, they found development of an independent cancer in the second breast of 91. It was noted that the risk of development of a second breast cancer was ten times that of the normal population if the first cancer developed before the age of 50 but only twice the normal risk if the first cancer developed after the age of 70. Beside age, the other most obvious factors that increased the risk of bilateral breast cancer were the presence of a multifocal cancer in the first breast (in one of every five such cancers a second primary developed, thus tending to indicate a "field cancerization"), the presence of anaplastic duct cancer with node metastases (in which the poor prognosis still failed to mask what must be a very high risk), comedo, colloid, medullary and lobular types of cancers (in which the prolonged survival enabled a relatively low risk to be manifest), and the presence of a small diameter, unifocal duct cancer, or duct cancer with negative axillary lymph nodes (also the result of low risk but prolonged survival).

In contrast, the groups with a low rate of second breast cancer were those with well-differentiated duct cancers in which excellent prognosis was coupled with extremely low risk, those with extensive axillary metastases in which extremely short survival probably masked a very high risk, and elderly patients with their first breast cancers.

Usually, the second cancers were discovered at an earlier stage when they were smaller and the patient had fewer nodal metastases. Robbins and Berg[12] found a clear tendency for the second cancer to mimic the first in terms of location within the breast, cell type, size, and lymph node involvement. The prognosis after a second cancer should have been better than after the first cancer alone, but was observed to be worse. When analyzed, it is apparent that the continued 20 per cent deficit in

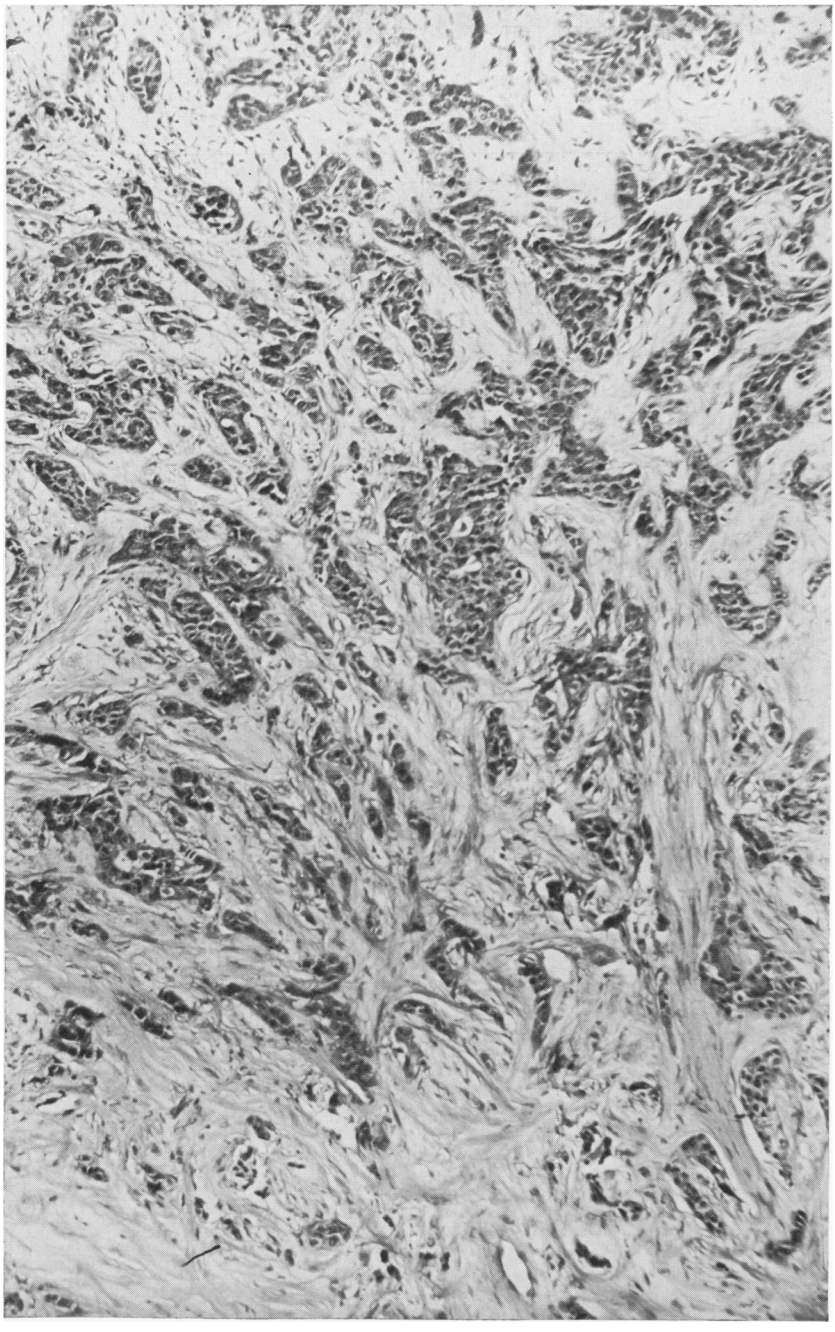

FIG. 2. Right breast cancer of patient. (H & E ×125.)

survival compared with matched controls with one cancer at 5, 10, 15, and 20 years can be accounted for by the continual risk of late metastatic disease from each of the separate breast cancers. This fact was emphasized by appropriate matching of patients for *each* of the two cancers. The theoretical mortality curve thus created overlays exactly the observed mortality curve of patients with bilateral cancer. Other patients in whom there is a high risk of second breast cancer are those who become

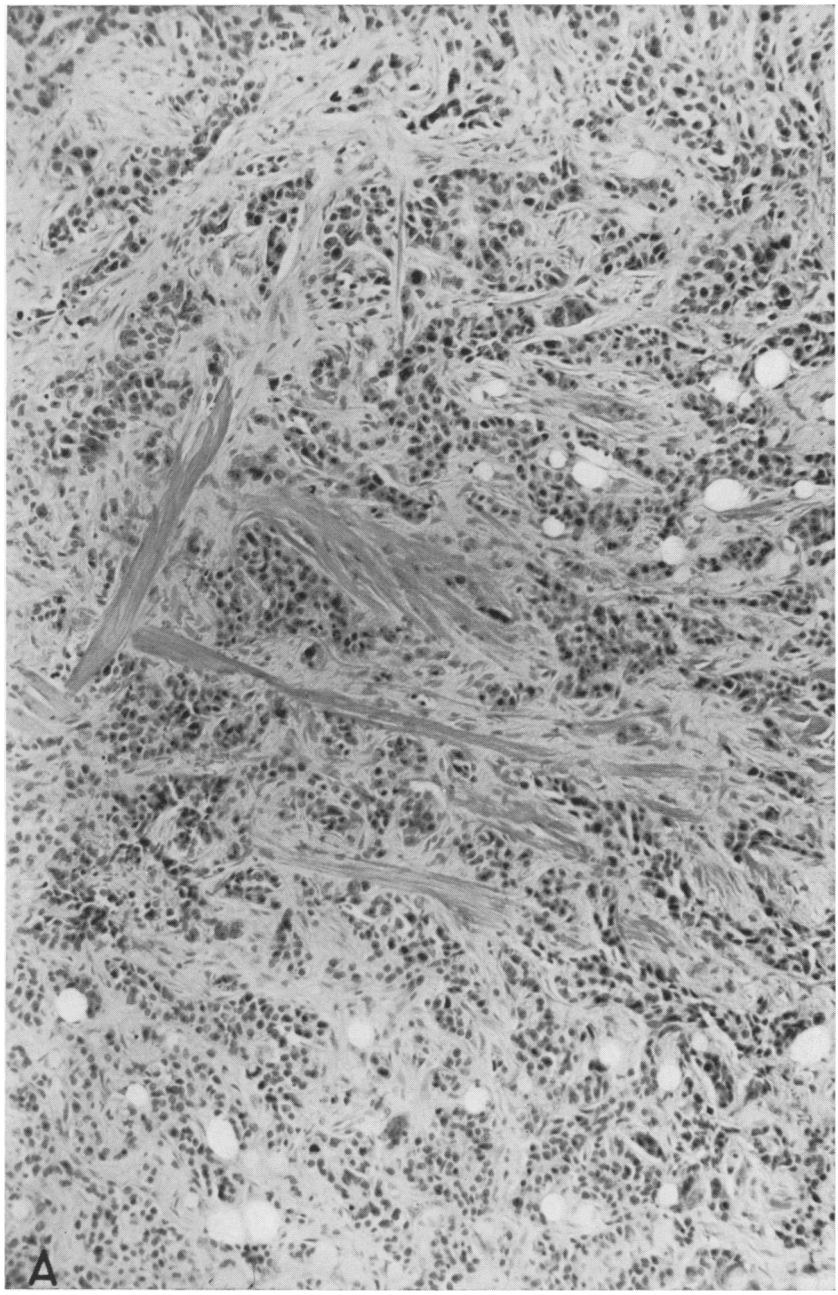

FIG. 3A. Right breast cancer of patient. (H & E ×125.)

pregnant after the first breast cancer, as noted by Hubbard[6] and others. Here the factors of good prognosis and young age, rather than the pregnancy itself, may be operating.

The hereditary aspects of bilateral breast cancer were first alluded to by Handley[5] in 1938. He reported a family of five sisters, two of whom had bilateral breast cancer documented by operation; another sister was noted to have a mass in the remaining breast just before death from other causes after having previously had a unilateral mastectomy. The remaining two sisters had

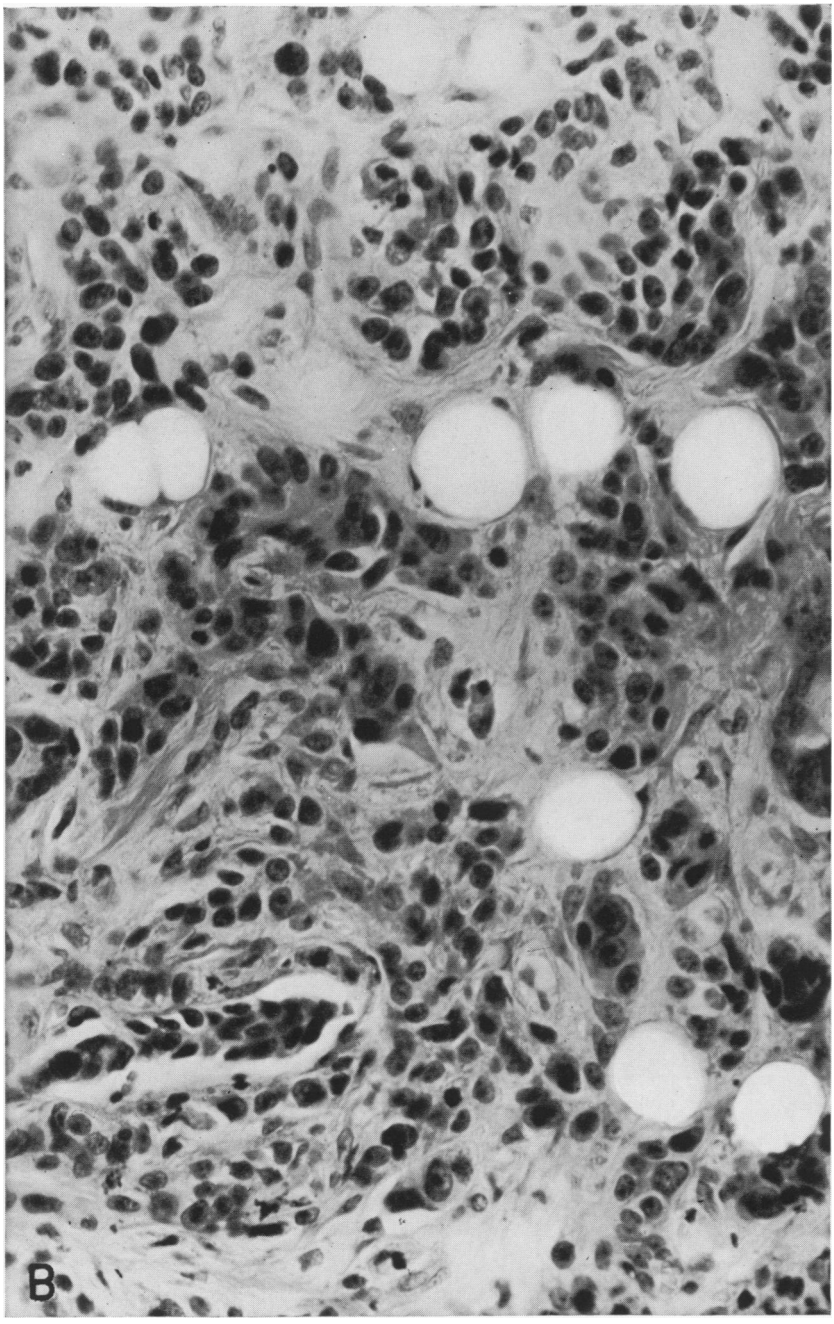

FIG. 3B. H & E ×400.

benign breast tumors. The ages of the three sisters with bilateral breast cancers at the time of their two diagnoses were 37 and 41 years, 48 and 41 years, and 50 and 62 years.

Wood and Darling[16] in 1943 reported a family of three sisters, two of whom had bilateral and one unilateral breast cancer. In addition, the daughter of one sister with bilateral disease had a breast cancer at age 18. The ages at diagnosis of individual breast cancers of the sisters were 22 and 23 years, 35 and 41 years, and 50 years. Smithers[14] in 1948 reported a family in

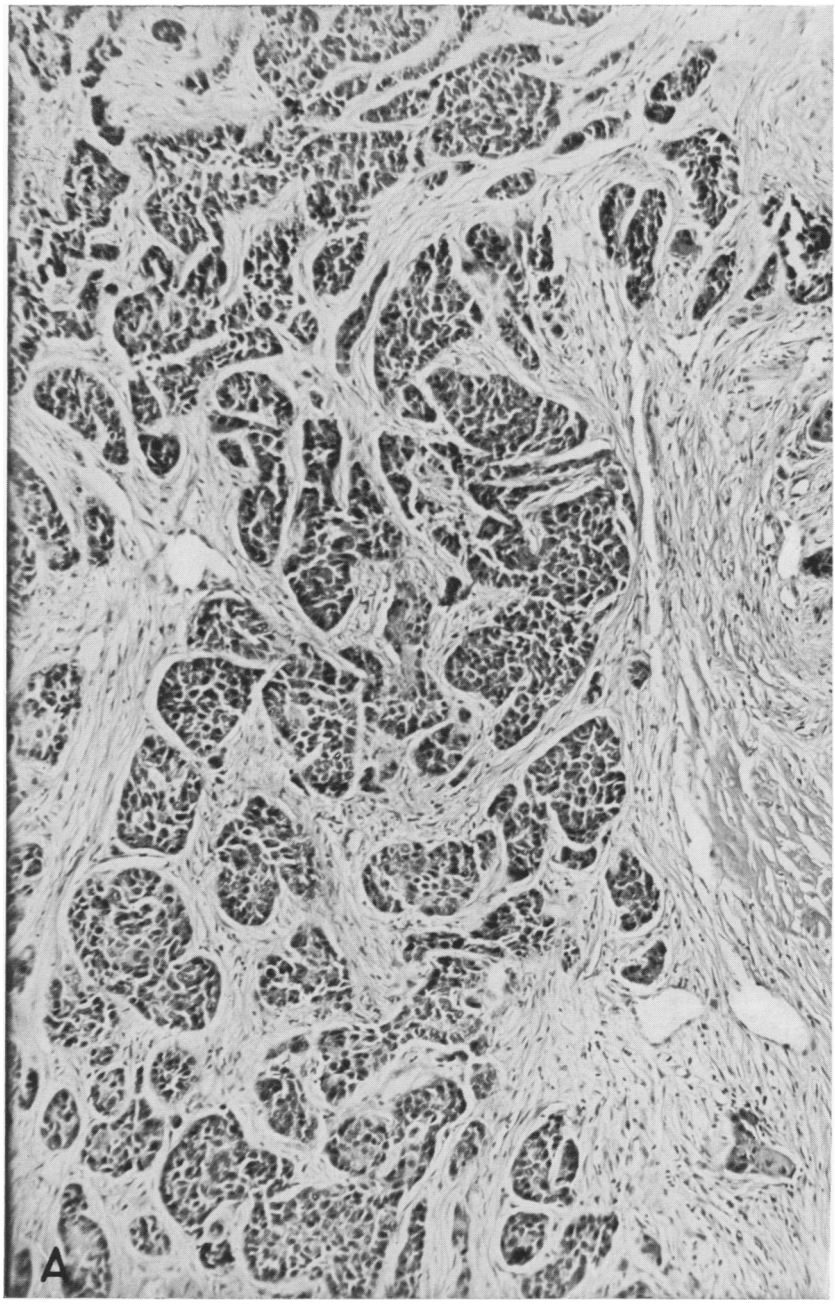

FIG. 4A. Right breast cancer of older sister. (H & E ×125.)

which among 11 siblings there were six women, four of whom had breast cancer; two of the four women had bilateral primary breast cancers. Ages were not stated.

Kerr and Ross [7] in 1967 reported a family in which all three siblings had breast cancer; in one patient it was bilateral. A daughter of one also had unilateral breast cancer. They noted all five tumors to be similar histologically.

Morse [11] reported 33 families in which both mother and daughter had breast cancer; three of the daughters had bilateral cancers. The interval of years between the

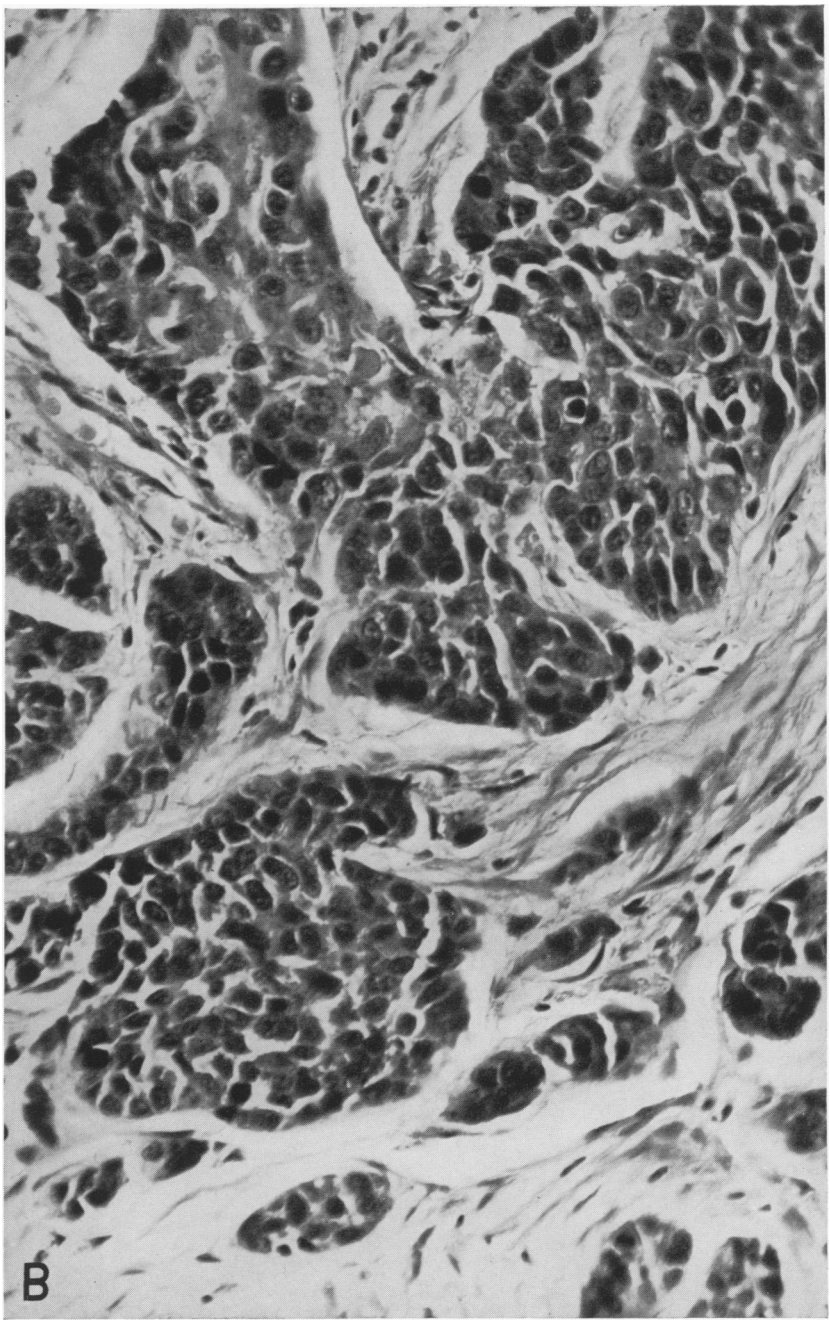

FIG. 4B. H & E ×400.

separate cancers in those instances were 0 (simultaneous), 11, and 13 years. Smith [13] reported a mother and daughter, both of whom had bilateral breast cancer. The ages at the time of diagnoses were 40 and 50 years for the mother and 44 and 45 for the daughter. Stephens *et al.*[15] studied one family intensively for five generations and found 14 breast cancers, one of which was bilateral. In 1953, Hubbard [6] reviewed 24 cases of bilateral breast cancer where a family history could be obtained. He noted

that in mothers and sisters with bilateral breast cancer the incidence was 25 per cent and 21.4 per cent, respectively, but only 3 per cent and 6.8 per cent, respectively, in those with unilateral breast cancer. Without presenting actual ages, he also noted that bilateral breast cancer tended to occur in women at a younger age than did unilateral breast cancer. Of 31 patients with bilateral breast cancer, five had a family history of disease as reported by Kilgore[9] and co-workers in 1956. Farrow[4] noted a family history of breast cancer in 14.3 per cent of simultaneous and 11 per cent of nonsimultaneous bilateral breast cancers. In a series of cases of bilateral breast cancers reported by Leis *et al.*,[10] 28 per cent showed a family history of the disease.

After analyzing their extensive statistical study of a large population in Minnesota, V. E. Anderson *et al.*[3] stated, ". . . the increase in risk (of second breast cancer) is apparently not modified by the presence of breast cancer in one of her close relatives . . . ." However, D. E. Anderson[1] recently has compiled data on a large group of families in which there were many members with breast cancer. He has noted a 15 per cent incidence of bilaterality of breast cancer in those patients with a family history of breast cancer in contrast to a 3 per cent incidence of bilaterality in those instances of breast cancer without a family history of the disease. He[2] also described a set of twins both of whom had bilateral breast cancer, occurring at the ages of 31 and 46 and 31 and 36. The twins' mother, aunt, and a niece also had breast cancer. Thus it appears that in patients with breast cancer having a family history of the disease, the incidence of bilaterality may be greatly increased, and this may have implications in advising patients as to risk. Further, in such patients the addition of histologic features such as Robbins and Berg[12] mention may also help in advising patients in whom there is an extremely high risk of a second primary breast cancer developing.

One feature of the familial cases of bilateral breast cancer reported in the literature in sufficient detail is the young age of the patients both at the time of the first and the second breast cancer. Thus in 13 patients whose ages were given, the mean age at the time of the first breast cancer was 34.1 years and at the time of the second, 40.3 years, both far below the mean age of breast cancer in general. Robbins and Berg[12] note that the risk of a second breast cancer developing is in part a function of years at risk and, therefore, women who are young at the time of onset of the first breast cancer also have a higher risk that a second breast cancer will develop as compared with older women having a first breast cancer. The development of a second breast cancer may only be a problem in women who are premenopausal at the time of the first cancer. Robbins and Berg[12] pointed out, for instance, that women over 50 have only twice the incidence of bilaterality of the normal population, whereas women below 50 years of age have ten times that risk. The ages of patients discovered in this review bears this out. Thus physicians should be alert to the unusually early risk in such family constellations and undertake appropriate detection measures such as self-examination of the breast, mammography, random biopsy, or prophylactic simple mastectomy or subcutaneous mastectomy at an early age.

In regard to the family reported here, speculation can include only the genetic factors involved. Does the appearance of bilaterality in three sisters merely represent a chance occurrence, or are specific genetic factors being displayed? Chromosomal studies of our patient and her older sister both revealed a normal female karyotype with a modal number of 46 chromosomes in each. No aberrations or marker chromosomes were found. No other family

members for one subsequent and two previous generations were known to have had breast cancer. All of the daughters of these three sisters are less than the age of 21, and therefore not yet at great risk. The mother died at age 36 in childbirth and thus was not at great risk herself.

Of interest also is the fact that histologically all six cancers were similar, and clinically all six cancers were small (less than 2 cm. maximum diameter), and in none of these six axillas was there evidence of lymph node metastases—both of which features themselves carry a higher than usual risk of bilaterality.

Summary

Bilateral breast cancer developed in three sisters. The presence of such a family constellation has not previously been reported. Familial breast cancer has a considerably higher risk of bilaterality compared with nonfamilial breast cancer. Bilateral breast cancer, both familial and nonfamilial, tends to occur in younger patients than does unilateral disease, and familial bilateral breast cancer may have its onset at exceptionally young ages. Vigorous detection and perhaps prophylaxis are recommended in such high-risk families.

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