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Case 28-2003: A 51-Year-Old Premenopausal Woman with Newly Diagnosed Breast Cancer and a Strong Family History of Breast Cancer

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PRESENTATION OF CASE

A 51-year-old, premenopausal woman came to this hospital with a newly diagnosed breast carcinoma and a strong family history of breast cancer.

Three months earlier, on physical examination at another institution, a mass in the upper outer quadrant of the right breast had been found. Examination of a fine-needle aspirate showed atypical ductal cells. An excisional biopsy, also performed elsewhere, revealed a 0.2-cm invasive lobular carcinoma (stage T1a), with ductal carcinoma in situ and lobular carcinoma in situ (Fig. 1).

The patient came to this hospital for further treatment of her breast carcinoma. The results of routine hematologic and blood chemical tests were normal. Bilateral mammographic examination revealed heterogeneously dense breast tissue; there was no evidence of a mass, of microcalcifications suggesting a malignant process, or of architectural distortion. Evaluation of the right breast was inadequate because it was difficult to compress it after the recent surgery. Radiographs of the chest were unremarkable.

After a discussion of options, the patient elected to undergo axillary staging by biopsy of a sentinel lymph node. Lymphoscintigraphic study of the right breast with a gamma probe after the injection of technetium-99m–labeled sulfur colloid around the previous biopsy site indicated the presence of a focal "hot spot" in the lower part of the right axilla. An incision in this part of the axilla yielded two radioactive lymph nodes and, adjacent to them, a third, palpable node. Examination of these lymph nodes revealed no evidence of cancer by standard pathological analysis or by cytokeratin immunostaining.

Previously, the patient had undergone biopsy of the left breast twice; both biopsies revealed benign lesions. Menarche had occurred at the age of 13 years, and she had been pregnant twice (first pregnancy at the age of 32 years) and given birth once. She had used oral contraceptives for six years and had never received exogenous hormone-replacement therapy. She had a 10-pack-year history of cigarette smoking, before having stopped smoking at the age of 26 years, and drank one to four alcoholic beverages weekly. She had no history of weight loss, headache, or neurologic problems. Her mother

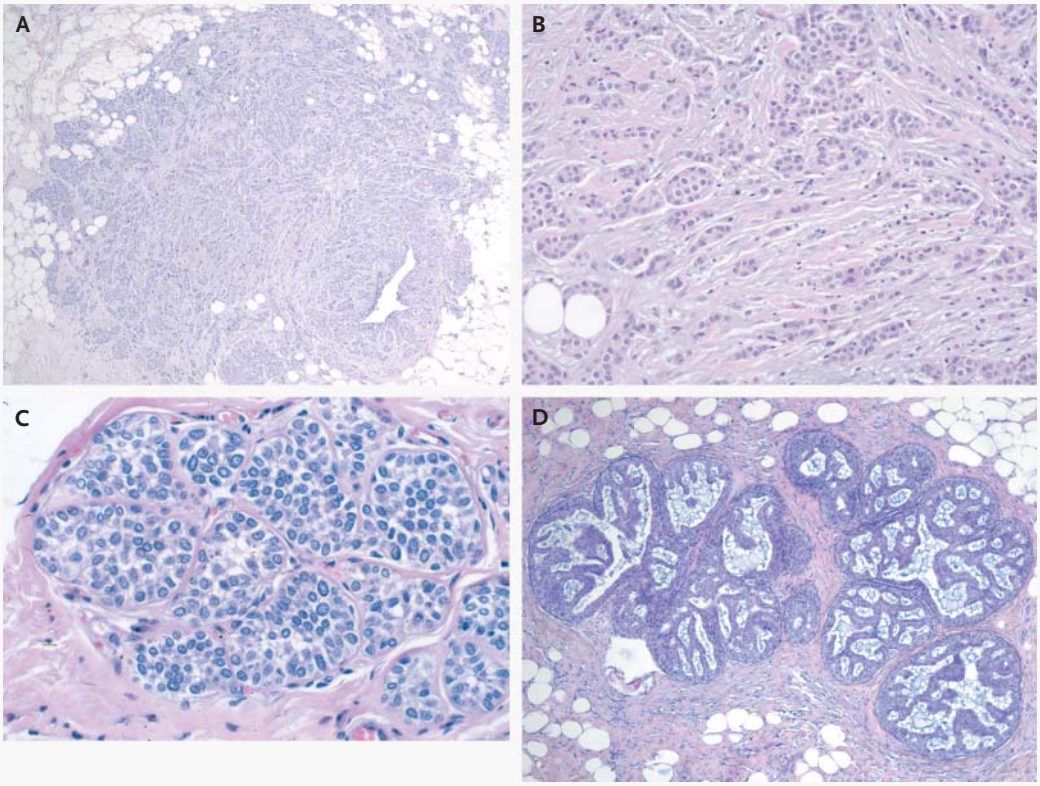

Figure 1. Biopsy Specimen of the Right Breast (Hematoxylin and Eosin).

There is a 0.2-cm invasive carcinoma (Panel A, ×62), with infiltration of small cells in the single-file and clustered alveolar patterns that are characteristic of lobular carcinoma (Panel B, ×250). In the adjacent tissue, there are foci of lobular carcinoma in situ (Panel C, ×500), characterized by small cells that fill the acini of the lobules, and there is low-grade ductal carcinoma in situ (Panel D, ×200), characterized by a complex papillary and cribriform cellular proliferation within the ducts.

had had breast cancer at the age of 48 years and now had lymphoma at the age of 72; her maternal grandmother had had breast cancer at the age of 47 years and had had lung cancer as well (Fig. 2). A paternal first cousin currently had breast cancer, at the age of 30 years; a paternal aunt was known to have had breast cancer at a "very young age" and had died from the disease. Another paternal aunt had had lung cancer, and the patient's father, who was of Ashkenazi Jewish descent, had had colon cancer.

PATHOLOGICAL DISCUSSION

Dr. Melinda J. Fan: Excisional biopsy of the mass in the right breast revealed an invasive lobular carcinoma, 0.2 cm in diameter, with tumor cells infiltrating in single-file and clustered alveolar patterns (Fig. 1A and 1B). The invasive tumor expressed estrogen and progesterone receptors but did not overexpress HER2/neu. Lobular carcinoma in situ (Fig. 1C), low-grade ductal carcinoma in situ (Fig. 1D), and extensive atypical ductal hyperplasia were present in the adjacent tissue. Resection margins were free of invasive tumor, with the closest margins of invasive tumor 0.4 cm away and of ductal carcinoma in situ 0.2 cm away. The mass that was clinically palpable was attributed to fibrocystic changes, with the carcinoma representing an incidental finding.

The patient's family history raised the possibility of a genetic susceptibility to breast cancer. Tumors associated with germ-line mutations in *BRCA1* have characteristic, but not unique, morphologic features. They are often high-grade, invasive ductal carcinomas, with sheet-like growth, marked nuclear pleomorphism, and a high degree of mitotic ac-

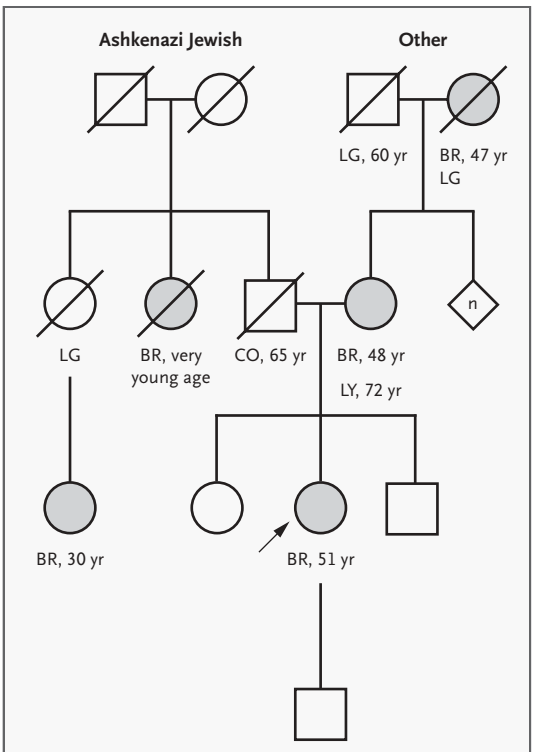

Figure 2. The Patient's Pedigree.

The patient's father was of Ashkenazi Jewish descent. Her maternal grandmother, her mother, a paternal aunt, and a paternal first cousin (shaded symbols) all had breast cancer (BR). Circles indicate female family members, squares male family members, slashes deceased family members, and the diamond multiple persons (exact number [n] unknown). An arrow indicates the proband. LG denotes lung cancer, CO colon cancer, and LY lymphoma.

tivity. There is an increased incidence of medullary and atypical medullary breast carcinomas.[1] The tumors are often negative for expression of estrogen and progesterone receptors; HER2/neu is overexpressed.[2] This patient's breast tumor did not have the typical features of a *BRCA1*-associated carcinoma. Breast carcinomas in patients with *BRCA2* mutations do not have a distinct histologic pattern,[3] although these patients may have an increased incidence of carcinomas with lobular features.[4,5]

Dr. Paula D. Ryan: The patient underwent evaluation for mutations in the *BRCA1* and *BRCA2* genes. Germ-line mutations in *BRCA1* or *BRCA2* are rare in the general population (estimated prevalence, 0.1 to 0.2 percent), and together these mutations account for only approximately 3 to 5 percent of all cases of breast cancer. However, these mutations are present in approximately 10 percent of women in whom breast cancer develops before the age of 40 years and in approximately 50 percent of women who have a strong family history of breast cancer, ovarian cancer, or both.[6] Carriers of a mutation in *BRCA1* have a 50 to 85 percent lifetime risk of breast cancer and a 20 to 40 percent lifetime risk of ovarian cancer. The upper limits of these risk estimates were derived from studies of familial cases and the lower limits from population-based studies.[7] Carriers of *BRCA2* mutations are estimated to have a similar lifetime risk of breast cancer and a 10 to 20 percent risk of ovarian cancer. In the current case, the patient's family history of breast cancer strongly suggested that she had a mutation in either *BRCA1* or *BRCA2*, making genetic testing appropriate in her case.

Founder mutations in *BRCA1* and *BRCA2* that are correlated with ethnic background are important to consider. Such mutations may increase the prior probability that a patient carries a germ-line mutation and suggest a strategy for the detection of specific mutations. Founder mutations include the 999del5 *BRCA2* mutation, which is carried by approximately 0.6 percent of the Icelandic population; a chromosomal deletion initially reported in the Dutch population; and three founder mutations that together are present in 2.5 percent of the Ashkenazi Jewish population (185delAG and 5382insC mutations in *BRCA1* and the 6174delT mutation in *BRCA2*).[6] Given the relatively high prevalence of these mutations among Ashkenazi Jews who have familial breast cancer, the first genetic study to undertake in persons of this ancestry is analysis to detect any of the three founder mutations, before full sequencing of *BRCA1* and *BRCA2* to search for novel mutations is considered.

A person's predisposition to breast cancer is inherited as an autosomal dominant trait, and this patient's family history is unusual in that cases of early-onset breast cancer were present in both her paternal and maternal lineages (Fig. 2). Because of her father's Ashkenazi Jewish ancestry, she underwent initial screening for the known founder mutations.

Kristen M. Shannon: In a family that appears to have an inherited susceptibility to breast cancer, an affected person should be tested first. This maximizes the chance of identifying the mutation that is responsible for the familial predisposition. If a deleterious mutation is identified, the affected

carrier can be counseled that he or she is at risk for a second cancer. Testing of unaffected family members for this specific mutation may then be performed to help identify those among them who carry the mutation and thus are at increased risk for breast cancer, ovarian cancer, or both. Testing can also identify noncarriers, whose risk of breast cancer is similar to that of the general population.

A negative test result in a family member who does have cancer can be difficult to interpret and can be explained in any of three ways. First, despite a strong family history, a person who does not have any genetic predisposition may have sporadic breast cancer. Second, although the *BRCA1* and *BRCA2* genes may be intact, the patient may have a mutation in another gene that has yet to be identified and that predisposes her to cancer. Third, the patient may have an alteration in the *BRCA1* or *BRCA2* gene that is not detectable by standard techniques (e.g., chromosomal deletions or mutations in the promoters or regulatory regions of the genes).

Finally, genetic testing may identify a mutation in *BRCA1* or *BRCA2* that encodes an amino acid substitution of unknown functional significance. Most deleterious mutations in these genes are premature stop codons that result in protein truncation and are readily identified as pathological. Only a small number of amino acid substitutions are known to be deleterious; most are of unknown functional significance. If a patient harbors one of these variants, genetic counseling is difficult, and the inconclusive results may cause the patient considerable anxiety.

Genetic testing for a predisposition to breast cancer brings with it the responsibility of discussing appropriate clinical recommendations with persons who carry the mutation and of addressing the possibility of emotional distress in both carriers and noncarriers ("survivor guilt"). Uninformative test results must also be interpreted. Although concern about potential genetic discrimination persists, more than 40 U.S. states have enacted legislation to protect persons against employment or health insurance discrimination on the basis of the results of genetic testing.

Genetic counseling is an essential component of the genetic-testing process and most often includes at least two individualized sessions: the first (before testing) to ensure informed consent, and the second (after testing) to discuss the test results in an appropriate context. In the current case, during a pretest counseling session, the patient was provided with information about the inheritance patterns of *BRCA1* and *BRCA2* mutations and the logistics of the testing process itself. We discussed possible test results and their potential impact on her as well as on her family members. She confirmed her interest in undergoing genetic testing, primarily for its potential importance to her own medical care. She also expressed the wish to discuss the test results with her family members, who would then be able to choose whether to undergo testing themselves. A second counseling session was scheduled after the receipt of the test results, which showed that the patient had the 6174delT mutation in *BRCA2*. The second, essential counseling session allowed interpretation of the results to be discussed, clinical recommendations based on the results to be reviewed with the patient, and emotional support to be offered.

Dr. Daniel A. Haber: The proteins encoded by *BRCA1* and *BRCA2* are often considered in parallel when the inherited risk of breast cancer is discussed, but these two proteins have distinct functional properties. *BRCA2* encodes a large protein (3418 amino acids in length), with no similarity in sequence to that encoded by *BRCA1*. The most significant domains within the BRCA2 protein appear to be eight repeated motifs (called BRC repeats) that are responsible for its interaction with another protein, RAD51, which is an integral component of the cellular machinery involved in the homologous recombination of chromosomes and the repair of double-stranded breaks in DNA (Fig. 3). The interaction between these two proteins provided the first clue to the potential function of BRCA2 in the maintenance of chromosomal integrity. BRCA1 is also thought to function in this cellular pathway, although its interaction with RAD51 appears to be indirect; it has been implicated in a number of other cellular responses to DNA damage.[8] Inactivation of either BRCA1 or BRCA2 in cultured cells is associated with decreased repair of chromosomal damage. However, it remains unclear how this global genomic instability results in a specific susceptibility to breast cancer and why inactivation of these genes is restricted to inherited forms of breast cancer.

The most dramatic difference between *BRCA2* and *BRCA1* mutations is the spectrum of cancers with which they are associated. In addition to the high risk of breast or ovarian cancer, which can occur with either of these gene mutations, *BRCA2* mutations confer an increased risk of pancreatic cancer and, in men, male breast cancer and possibly

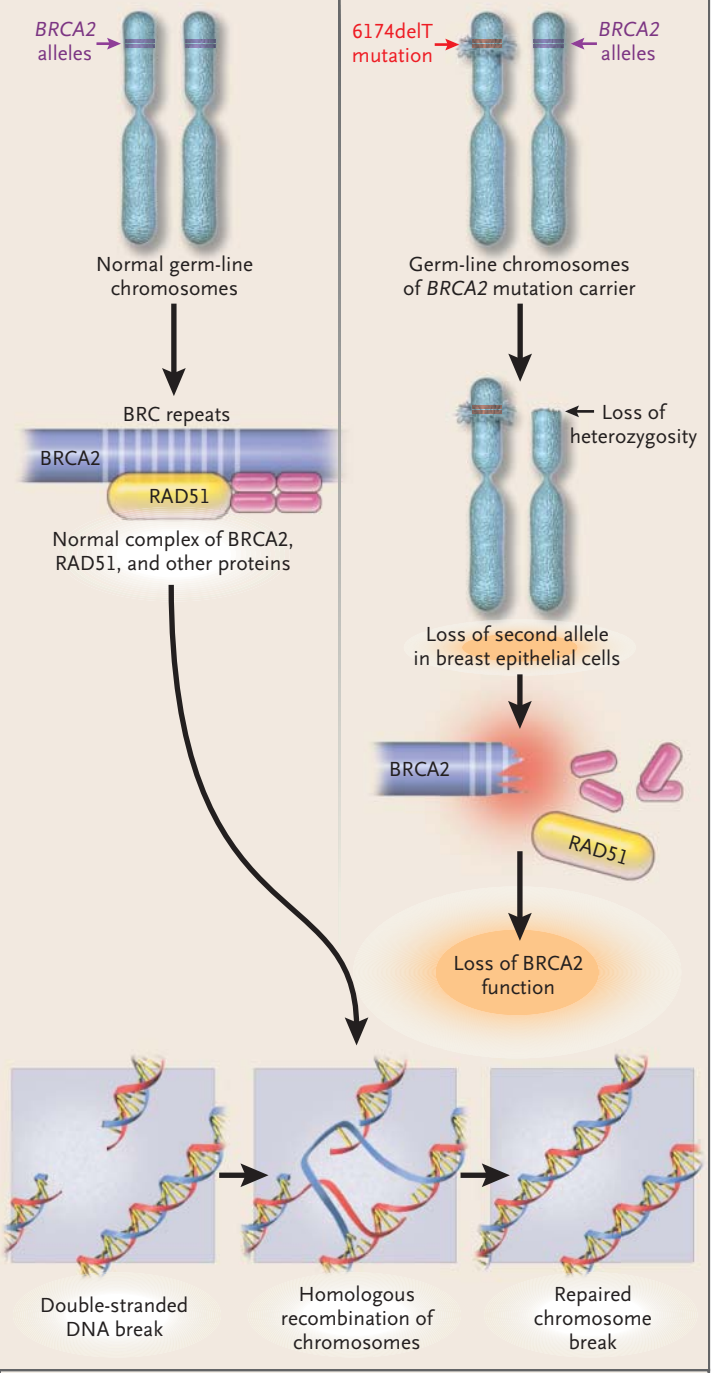

Figure 3. Schematic Diagram Indicating Normal Function of the *BRCA2* Gene and Loss of BRCA2 Function in Breast Cancer.

The BRCA2 protein contains eight repeated motifs, known as BRC repeats, that interact with another protein, RAD51, which is involved in homologous recombination of chromosomes and repair of double-stranded DNA breaks. The location of the patient's mutation is shown, within the ovarian cancer cluster region.

prostate cancer. The patient in this case had the 6174delT *BRCA2* mutation, which is present in about 1 percent of the Ashkenazi Jewish population. This protein-truncating mutation is located within the central exon (exon 11) of *BRCA2*, the so-called ovarian cancer cluster region, which is bounded by the sequences encoding amino acids 3059 to 4075 and 6503 to 6623 and which contains most of the BRC repeats required for binding to RAD51 (Fig. 3). Mutations in the *BRCA2* ovarian cancer cluster region were initially associated with an apparently increased risk of ovarian cancer, but recent epidemiologic data suggest that this may result from a relative reduction in the associated risk of breast cancer within this region.[9] Estimates of the risk of cancer derived from cases of familial breast cancer, such as that in the current case, are higher than those derived from population-based studies of either the *BRCA2* 999del5 founder mutation in Icelanders or the 6174delT mutation in Ashkenazi Jews — a difference that may reflect potential contributions of other genetic factors, diet, or hormonal history.

MANAGEMENT DISCUSSION

Dr. Barbara L. Smith: After extensive discussion, the patient chose to undergo bilateral simple mastectomy, as primary treatment of the carcinoma of her right breast and as prophylaxis against additional cancers. The availability of the results of a genetic test before definitive treatment for breast cancer made this case somewhat unusual. In most women with newly diagnosed breast cancer and a positive family history, genetic counseling and mutational analysis are undertaken once treatment has been completed and long-term concerns can be addressed more comfortably. However, it is probable that mutational status will increasingly have an effect on initial treatment decisions as unaffected carriers are followed in greater numbers and as rapid testing for specific *BRCA1* and *BRCA2* mutations becomes more widely available. The overall prognosis for women with breast cancer who carry such mutations appears to be similar to that for age-matched women with sporadic cancer. Recommendations for surgical and adjuvant treatment of breast cancer in carriers therefore do not differ from those for women with sporadic cancer. Why, then, did the patient elect to undergo bilateral mastectomy?

Prophylactic bilateral mastectomy clearly re-

duces the risk of breast cancer in carriers of *BRCA1* or *BRCA2* mutations. A review at the Mayo Clinic of women with a family history of breast cancer showed, at a median of 14 years of follow-up, a 90 percent reduction in the number of breast cancers in women who had undergone bilateral prophylactic mastectomy, as compared with their sisters who had not undergone surgery.[10] With the advent of genetic testing for *BRCA1* and *BRCA2* mutations, a more recent study has confirmed these observations.[11]

Despite this benefit, the decision to undergo prophylactic mastectomy must be made after careful consideration of both life expectancy and psychological issues. A woman's perception of her risk of breast cancer may be affected by the experience of family members in whom breast cancer has developed, her own attitudes toward breast cancer and breast surgery, and her understanding of the effectiveness of early mammographic detection and treatment of breast cancer. A follow-up study from the Mayo Clinic reported that about 70 percent of women who had undergone prophylactic mastectomy were satisfied with their choice, whereas 10 percent were uncertain and 20 percent were dissatisfied, citing decreased self-esteem, increased emotional stress, a negative effect on sexual relationships, or a combination of these factors.[12]

Prophylactic mastectomy should include meticulous excision of all identifiable breast tissue. Resection of the nipple and areola is commonly performed, although nipple-sparing subcutaneous mastectomy has also been used. Removal of axillary lymph nodes is not required. Many patients elect immediate reconstruction, which has no detrimental effect on the reduction in the risk of breast cancer. The resected breast tissue is analyzed histologically to identify any microscopic cancer present.

In the current case, after genetic counseling, the patient felt certain that she would have elected to undergo bilateral prophylactic mastectomy, even if she had been an unaffected carrier of the 6174delT *BRCA2* mutation. Given her young age and her excellent prognosis with respect to the carcinoma of the right breast, as well as the associated lifetime risk of a second (ipsilateral or contralateral) breast tumor, bilateral mastectomy was offered as both a therapeutic and a prophylactic option. Six months after her initial presentation, bilateral simple mastectomy was performed, and bilateral breast-tissue expanders were inserted; five weeks later, the tissue expanders were removed and saline breast implants were inserted. We did not recommend systemic chemotherapy to this patient, because of her good prognosis. Appropriate treatment of the primary breast cancer should always take precedence over the less immediate need to reduce any additional lifetime risk of cancer.

Dr. Fan: The right-mastectomy specimen in this case contained a second, 0.2-cm focus of invasive lobular carcinoma, located in a different area from that found on the initial biopsy. Lobular carcinoma in situ and atypical ductal hyperplasia were also present. The specimen obtained from the prophylactic mastectomy on the left side contained lobular carcinoma in situ and atypical ductal hyperplasia.

Dr. Ryan: After the mastectomy, the patient was referred for consideration of prophylactic oophorectomy. Two recent studies have validated the recommendation of prophylactic oophorectomy after the completion of childbearing in women with a *BRCA1* or *BRCA2* mutation.[13,14] In both studies, among the women who opted for surveillance, ovarian cancers developed in 7 percent of those followed for a median of two years[15] and 20 percent of those followed for a median of nine years.[16] In both studies, as well, 2 to 3 percent of the women who elected to undergo oophorectomy were found to have early-stage cancer in a removed ovary. In 1 percent of the patients who elected to undergo oophorectomy, a papillary serous carcinoma of the peritoneum subsequently developed, indicating that the risk of this related tumor type remains substantial in patients who have undergone prophylactic oophorectomy. Both of these studies also showed that prophylactic oophorectomy was associated with a 50 percent reduction in the risk of breast cancer. Thus, oophorectomy has emerged as a viable option for reduction of the risk of breast cancer in women who do not wish to undergo prophylactic mastectomy. In the current case, after extensive discussion, the patient opted to undergo laparoscopic bilateral salpingo-oophorectomy.

Dr. Fan: The adnexa were submitted in their entirety for histologic examination, since carriers of *BRCA* mutations are at increased risk for both ovarian and fallopian-tube carcinomas, which may be occult.[15,16] There was no evidence of cancer in the adnexa.

Dr. Ryan: The prophylactic surgical procedures were performed over a relatively short period in this premenopausal woman. The possibility of hormone-replacement therapy was discussed after the oophorectomy, but we did not recommend it, since

she had a history of breast cancer and her estrogen-withdrawal symptoms were manageable. The results of a bone mineral density study were normal. After reviewing her diet, we recommended calcium and vitamin D supplementation.

Dr. Nancy Lee Harris: Dr. Smith, how does the patient feel about the decision she has made to have these ablative operations?

Dr. Smith: Like many of the women we have studied, she is glad that she had the operations in terms of the risk reduction, but she was initially not very happy with the cosmetic results. She subsequently underwent revision of the reconstructive surgery, with replacement of the implants, and is now satisfied with the results. She has a very supportive husband and family.

PATHOLOGICAL DIAGNOSIS

Infiltrating lobular carcinoma of the right breast, two separate foci.
Ductal carcinoma in situ of the right breast.
Lobular carcinoma in situ and atypical ductal hyperplasia in both breasts.
Mutation (6174delT) in the *BRCA2* gene.

Ms. Shannon reports having received a lecture fee from Myriad Genetics.

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