

Breast Cancer: Overview of Current Management Considerations of Economic Impact

Based on a presentation by Sandra E. Brooks, MD, FACS, FACOG

Presentation Summary

Most women who are diagnosed with breast cancer have either no risk factors or only one. Recommendations for breast cancer screening for women between the ages of 40 and 49 are controversial, because the National Institutes of Health (NIH) Consensus Conference made no specific recommendation regarding the frequency of screening. In so

doing, a possible reduction in mortality or morbidity is balanced against known false-positive or false-negative rates and the detection of ductal carcinoma in situ. Although genetic testing is available, many questions surround its use, including its likely emotional and financial impact on the patient and her family and the unresolved issue of how to interpret the results.

Providing a foundation for a discussion of the economic impact of diagnostic and management concerns related to breast cancer, Sandra E. Brooks, MD, FACS, FACOG, Director of the Division of Gynecological Oncology at the University of Maryland Medical System in Baltimore, briefly presented an overview of some of the issues that confront a woman diagnosed with the disease.

"Women who are diagnosed with carcinoma of the breast are faced not only with the initial diagnosis and treatment decisions but with other considerations that are important throughout their lives," Dr Brooks said.

"Although we focus very closely on those women who have an obvious familial or historical risk, most women who are diagnosed with breast cancer really have no risk factors or only one," she added.

Screening Recommendations Vary

According to Dr. Brooks, there has been a great deal of controversy over recommendations for breast cancer screening for women between the ages of 40 and 49. The National Institutes of Health (NIH) Consensus Conference failed to make recommendations for these patients.

To illustrate, she noted that the recommendations of the American Cancer Society (ACS) and the National Cancer Institute (NCI) differ, with the former recommending monthly self-examinations for women older than 20, clinical examinations at 3-year intervals for women younger than age 40, and annual clinical examinations for those 40 and older.

The ACS also recommends mammography annually for women between the ages of 40 and 49, but the NCI recommends it every 1 to 2 years

for the same age group, as well as annual mammography for those age 50 and older.^{1,3}

Because of the lack of consensus, the question remains: Should all women between the ages of 40 and 49 undergo regular mammography? "The NIH Consensus Conference really tossed the decision-making process back to the healthcare provider and the patient when it stated that the available data do not warrant a single recommendation for mammography for all women in their 40s and advised that each woman in this age group consult with her healthcare provider and decide for herself whether she should get a mammogram," Dr. Brooks said.

"Such a recommendation balances a possible reduction in mortality or morbidity with the known false-positive and false-negative rates and the detection of ductal carcinoma in situ with mammography with these patients," she explained, adding that genetic testing for breast cancer and ovarian cancer could be considered in high-risk groups of women as well.

Value of Genetic Testing

"Genetic testing is clearly available," Dr. Brooks said, "but how should we use it, what is the potential impact on the patient and her family, what is the likely financial impact, and how should we act on the results?" she asked.

Five percent to 10% of all breast cancer is inherited, with BRCA1 and BRCA2 being the most clearly linked with hereditary breast cancer. "Once we have diagnosed breast cancer," Dr. Brooks said, "we must remember that these women also need to undergo surveillance and screening for other types of cancers, such as carcinoma of the colon and ovaries." Screening guidelines for ovarian cancers are in the process of evolution, she noted, however, screening is certainly effective for colon cancer.

"Eighty-five percent to 90% of all inherited breast and ovarian cancer is caused by a BRCA1 mutation," Dr. Brooks said, noting that "numerous mutations have been identified, and it is estimated that about 1 in 200 to 400 women carries them." The incidence of BRCA1 mutations in the Ashkenazi Jewish population is approximately 1%,⁴ she noted.

Who Should Be Tested?

According to Dr. Brooks, women who should be tested include those who developed breast cancer before age 45; those with 2 or more first-degree or second-degree affected relatives; those with one affected relative who was diagnosed with breast cancer before age 45; those who have multiple primary cancers, such as colon or ovarian, or who have bilateral breast disease; and those who have a documented BRCA1 or BRCA2 mutation in the family.

"Breast cancer touches not only the patient but her family as well," Dr. Brooks said, "because each person within that family must make decisions about testing. Currently, the cost of testing ranges between \$1500 and \$3000, depending on its comprehensiveness." Some of this expense is covered by insurance, she explained, adding that some patients have concerns about having insurance companies pay for such testing.

"So how should we act on the results if a patient has a BRCA1 mutation?" Dr. Brooks asked, adding that chemoprevention is now an option for such patients, but it could potentially be offered to the patient on the basis of risk factors or utilizing modeling techniques, such as the Gail model, for selected populations.⁵

"Prophylactic surgery is an option," she pointed out, noting that it reduces the risk of breast cancer by approximately 90%, but is a drastic option and does not eliminate the risk of developing breast cancer entirely. Other options include frequent mam-

mography for women who are mutation carriers, testing of other relatives, and lifestyle changes that would principally involve weight control and reduction of alcohol intake.

In the tamoxifen breast cancer prevention trial, more than 13,000 women who were at increased risk for breast cancer were studied. The reduction in breast cancer was 45% with tamoxifen use, Dr. Brooks reported. "If the economic considerations of this were applied to the population at large, the costs involved would include the therapy and treatment of side effects or complications of therapy." For example, she explained, "Patients on tamoxifen for more than 1 year are at approximately 3 times the relative risk of developing endometrial cancer." According to Dr. Brooks, most endometrial cancers that occur in patients on tamoxifen are well-differentiated cancers that are confined to the uterus and are typically associated with very good survival rates.

Is Prophylactic Treatment Necessary?

"The question is," Dr. Brooks said, "do we recommend prophylactic treatment for a patient who is at risk for breast cancer and then ask that patient to undergo surveillance for possible development of a second cancer, such as carcinoma of the endometrium?"

It has not been established whether such surveillance is necessary, cost effective, or associated with a reduction in morbidity and mortality from endometrial cancer, Dr. Brooks said. The survival rates for endometrial cancer are quite good for the majority of women.

According to Dr. Brooks, the principal method of surveillance is the endometrial biopsy. However, she noted that in a postmenopausal population, the incidence of not being able to obtain a specimen is approximately 15% to 25%. Although ultrasound is a noninvasive modality, it is nonspecific.

There has been concern that tamoxifen might be related to the development of aggressive endometrial cancer; however, this has not been validated, and it now does not appear that the types of tumors that develop are unusual. Although abnormal bleeding should always be aggressively evaluated, Dr. Brooks said, clinicians are "more likely to find benign problems such as polyps, hyperplasia, growth of fibroid tumors, or adenomyosis in patients on tamoxifen." Once the breast cancer trial was under way, she noted, there was concern about the possibility of endometrial abnormalities, so an annual endometrial biopsy was recommended for women receiving therapy while in the study. According to Dr. Brooks, that step has not translated into a recommendation that all women undergo an annual biopsy. "So it is really at the discretion of the healthcare provider and the patient as to whether routine surveillance is undertaken," Dr. Brooks observed.

Therapeutic Choices Available

Therapy options for patients include modified radical mastectomy or lumpectomy and radiation. Patients with locally advanced lesions may undergo neoadjuvant chemotherapy. Dr. Brooks described the 4 stages of breast cancer development (Table).

Table. Breast Cancer Staging

Stage	Tumor Size	Nodes	Metastases
I	<2 cm	No	No
II	<2 cm	+Axillary	No
	2-5 cm	+/-Axillary	No
	>5 cm		
IIIa	<5 cm	+Axillary	No
IIIb	Any	+/-	+chest wall
IV	Any	+/-	any distant

Risks for Recurrence

Dr. Brooks identified the main risk factors for recurrence as receptor status, nodal status, tumor size, and histology. Patients who have very small tumors or tumors that are estrogen receptor-positive or well differentiated, and patients who are older are in the lower-risk categories.

Tumor size, histologic grade, nodal status, estrogen receptor status, and patient age are criteria that determine postsurgical treatment as they are related to prognosis, according to Dr. Brooks. Patients who are considered to be at minimal or low risk can be offered no treatment or tamoxifen if the tumor is estrogen receptor-positive. "Patients who are in moderate-risk categories can be offered either tamoxifen or chemotherapy," Dr. Brooks said. In addition, she added, "it is always beneficial if such patients can be offered enrollment in clinical trials. Approximately 5% of women in the United States are actually enrolled in clinical trials," she noted, which clearly limits a physician's ability to use clinical trial data to make definite decisions about small subgroups. "Naturally," she noted, "high-risk premenopausal patients will be counseled to receive chemotherapy and postmenopausal women will be counseled to receive tamoxifen, chemotherapy, or both."

Very high-risk patients, with positive axillary lymph nodes should receive 4 cycles of doxorubicin plus cyclophosphamide followed by 4 cycles of paclitaxel, Dr. Brooks added.⁶

Tamoxifen Trial Results

The Early Breast Cancer Trial Initiative Group evaluated tamoxifen use for 1 or 2 years in women with early breast cancer and found a 26% reduction in the recurrence of tumor and a 17% reduction in mortality for postmenopausal women with estrogen receptor-positive

tumors, Dr. Brooks said. Premenopausal women who received chemotherapy also experienced a reduction in recurrence and mortality.⁷

With tamoxifen use, the risk of contralateral breast cancer is reduced also. Dr. Brooks explained that for premenopausal women with nodal disease, treatment options include chemotherapy or ovarian ablation, which can be accomplished through surgery, radiation therapy, or hormonal therapy.

According to Dr. Brooks, ovarian ablation is not efficacious for postmenopausal women, and therefore, these women are offered tamoxifen, chemotherapy, or a combination of the 2 for treatment. Recent trials have demonstrated that tamoxifen used in combination with chemotherapy is beneficial.⁷⁻⁹

Length of Trials Controversy

Controversy still exists as to whether 5 years of tamoxifen use is adequate, Dr. Brooks noted. The pivotal study evaluating this issue demonstrated that 5 years of therapy was more efficacious than 2 years of therapy. Thus, the trial was stopped. Whether 5 years of therapy is sufficient treatment for all patients remains to be seen.

Tamoxifen analogs are the subject of newer studies. According to Dr. Brooks, preliminary reports reveal that response rates, time to progression, survival, and quality of life were similar. She indicated that the side-effect profile of the analogs is similar to that of tamoxifen.

"The role of the newer drugs, such as the aromatase inhibitors anastrozole and letrozole, is principally in the treatment of postmenopausal women who have disease progression," Dr. Brooks said. She explained that the role of these drugs or the newly introduced drug capecitabine, an oral pro-drug of 5-fluorouracil, might be in the treatment of metastatic disease that is resistant to front-line therapy.

Dr. Brooks mentioned that several trials have evaluated the taxanes in the treatment of breast cancer. These preliminary trials showed efficacy in patients with advanced or recurrent disease.¹⁰⁻¹² Current studies are evaluating the correct dose, infusion schedule, and incorporation of the taxanes into front-line therapy.

Risks in Her2/Neu Overexpression

Recently investigators have developed the drug herceptin in recognition that Her2/Neu overexpression occurs in about 25% to 30% of women who have primary breast cancer. There also appears to be a fourfold higher risk of recurrence in such patients. This finding appears to exist independent of tumor size, grade, patient age, and estrogen receptor status, so it must be an independent poor prognostic factor in women with breast cancer.

"Herceptin is a humanized monoclonal antibody, that targets the Her2/Neu growth factor receptor and induces antibody-dependent cellular cytotoxicity," Dr. Brooks explained. "Early trials¹³⁻¹⁵ show promise in that the overall response rate in heavily pretreated breast cancer patients treated with herceptin is 16% for 9 months. This demonstrates that herceptin has some activity in patients with metastatic disease." According to Dr. Brooks, cardiotoxicity is an area of concern when herceptin is added to anthracycline drugs, an effect that needs to be followed closely.

Other types of supportive therapy include pamidronate and related drugs that decrease skeletal morbidity in patients with advanced or recurrent disease. These drugs decrease the number and incidence of bony metastasis in this patient population.

In summary, there are many considerations for the potential economic impact of breast cancer. The important issues, Dr. Brooks concluded, include frequency and intensity of screening, whether or not to test

women for genetic aberrations, the scope of primary prevention efforts, initial therapy considerations, the choice of adjuvant therapy, the prevention of recurrence, and the treatment and complications of disease.

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