

Women at High Risk for Breast Cancer:

Preventive Strategies

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Abstract

Prevention of breast cancer is a high priority for women at risk for the disease. Management options for this group include close surveillance, chemoprevention, and prophylactic mastectomy (surgical prophylaxis). The optimal method remains to be determined. However, at the present time, close surveillance, which include breast self-examination, annual or semiannual physical examinations, and annual mammography starting at age 30, remains the most widely accepted method.

Key Words: Breast cancer, surveillance, chemoprevention, prophylactic mastectomy.

Introduction

BREAST CANCER IS THE MOST COMMON cancer among women, with the exception of skin cancer. It was estimated that almost 175,000 new cases would be diagnosed in the United States in 1999 (1). Despite diagnostic and therapeutic advances, about one-fourth of these women will die of the disease. This underscores the limitations of current approaches to breast cancer diagnosis and treatment, and emphasizes the need for prevention of this potentially lethal disease, at least for women in the high-risk groups.

Defining the “High-Risk Group” for Breast Cancer

Breast carcinogenesis is a multistep, multifactorial process. Both endogenous and exogenous factors are involved in this phenomenon and contribute to breast cancer risk. Recognizing these factors and identifying precancerous lesions are of crucial importance for developing effective preventive strategies. Recent progress in molecular biology and human genetics, and accurate estimation of the cancer risk in benign breast disease have enabled a more logical approach to the management of women at high risk. Clearly, defining “high risk” is the first significant step toward effective prevention. Family history is the most widely recognized

risk factor for breast cancer development. Most women with a family history of breast cancer do not have the genetically transmitted form of the disease, and, therefore, their risk is much less. While this risk increases as the number of relatives with breast cancer increases, it rarely exceeds 30% (2). About 5–10% of breast cancers are due to a specific inherited mutation, most frequently *BRCA1* or *BRCA2* mutation, that confers an extremely high risk of developing breast cancer (ranging from 40–85%, depending on the population) (3–5). Proliferative lesions of the breast are associated with a modest (1.5- to 2-fold) increase in risk. Atypical hyperplasia is associated with a 4- to 5-fold increase in breast cancer risk (6). In the presence of other risk factors, the cumulative risk is further increased. For example, women having atypical hyperplasia and a first-degree relative with breast cancer have an 11-fold increase in risk over those without proliferative atypical changes (6). In contrast, non-proliferative lesions carry no increased risk of developing into invasive cancer. Lobular and ductal carcinoma *in situ* (LCIS and DCIS, respectively) are also associated with an increased risk. LCIS is associated with a 7- to 12-fold increase in risk and is considered a “marker” rather than an anatomical precursor of invasive carcinoma. In contrast, DCIS is an “anatomic precursor” of invasive breast cancer (7, 8). Finally, women with a prior history of breast cancer are at an increased (5-fold) risk for developing cancer in the contralateral breast; this risk is about 1% per year of survival and is significantly increased in the presence of other associated risk factors, such as hereditary or familiar breast cancer and atypical proliferative changes in the remaining breast (2).

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To help increase the accuracy of breast cancer risk estimates, Gail et al. proposed, in 1989, a tool based on the number of first-degree relatives with breast cancer, the age at first live birth, the age at menarche, the number of breast biopsies, and a history of atypical hyperplasia (9). The relative risk for each of these factors is multiplied to provide a composite risk (i.e., the Gail model). Women are considered to have a “high” risk for breast cancer when their risk is equal to or greater than that of the average 60-year-old woman. While the Gail model may be useful in predicting numbers of breast cancer cases in specific risk factor strata, it has only modest discriminatory accuracy at the individual level (10). This finding has obvious implications for use in clinical counseling of individual women.

Management Options for the High-Risk Group

Three options are available in the health care management of high-risk women (Table 1):

Surveillance

The majority of these women will choose the option of surveillance, which includes monthly breast self-examination, annual or semiannual physical examination, and annual mammography, starting at age 30 (11). Because of safety concerns relating to repeated radiation exposure starting at a relatively young age, breast ultrasonography may be a valuable alternative method for breast imaging in these women. The rationale for surveillance is early detection of breast cancer — if it develops — resulting in a much better prognosis.

TABLE 1
Women at High Risk for Breast Cancer: Management Options

Surveillance
Breast self-examination (monthly)
Physical breast examination (annually or semiannually)
Mammography (annually)
Breast ultrasonography
Chemoprevention
Prophylactic mastectomy (total mastectomy)

Chemoprevention

Chemoprevention, mainly using tamoxifen, has been shown to be an effective method for primary prevention of breast cancer. The NSABP P-1 project found that tamoxifen reduced the risk of invasive cancer by 49% during a median follow-up period of 55 months (12). This conclusion is in contrast with the recent interim reports of two European trials (13, 14). However, the larger number of patients in the NSABP P-1 and its prohibition of hormone-replacement therapy among participants add to the strength of its findings.

Based on the results of this study, tamoxifen has been approved in the U.S. for reduction of breast cancer risk in women at high risk for this disease. However, chemoprevention by the use of tamoxifen should be considered only for women at increased risk based on National Cancer Institute criteria (Table 2) (9, 15). This therapy should be continued for five years. The relative benefit of tamoxifen for women on hormone-replacement therapy and for those with specific breast cancer genotypes remains to be determined. Long-term side effects of tamoxifen include endometrial cancer, stroke, pulmonary embolism, and deep venous thrombosis, particularly in women 50 years of age or older. However, tamoxifen is also associated with some beneficial side effects, including a reduction in hip, radius, and spine fractures, probably due to the maintenance of bone mineral density. Interestingly, in a recent study, the risk of invasive breast cancer was decreased by 76% during three years of treatment with raloxifene — another antiestrogen — among postmenopausal women with osteoporosis (16). Of note, in this study the use of raloxifene has not been associated with an increased risk of invasive uterine cancer. The effectiveness of chemoprevention by the use of tamoxifen and raloxifene is currently being evaluated in an ongoing trial (STAR trial; Study of Tamoxifen and Raloxifene).

TABLE 2
Factors Used to Determine the Risk of Breast Cancer

Age
Race
Age at menarche
Age at first live birth
Number of breast biopsies
Atypical hyperplasia
Number of first-degree relatives with breast cancer

Surgical Prophylaxis (Prophylactic Mastectomy)

Surgical prophylaxis (prophylactic mastectomy) is another option for primary prevention of breast cancer. However, prophylactic mastectomy is considered too drastic an option, especially in an era of breast conservation therapy, in which one breast with cancer is preserved (albeit irradiated), while two normal breasts are amputated in the name of "prophylaxis." Existing data suggest that prophylactic total mastectomy significantly reduces (by ~ 90%), but does not totally eliminate, the risk of subsequent cancer development, probably from the residual amount of breast tissue that remains after prophylactic mastectomy. This is the "Achilles' heel" of surgical prophylaxis. Survival improves by 2.8–6 years over surveillance alone (17–20).

At present, prophylactic mastectomy should be considered only for a relatively small number of carefully selected patients. The decision to perform a prophylactic mastectomy should be a multidisciplinary one and must be based on the objective risk for breast cancer development, the woman's personal values and experiences within her family, and her concerns about developing breast cancer. Detailed patient counseling is very important and the patient should understand the limitations of prophylactic mastectomy, the irreversibility of the decision, and the need for postoperative follow-up. Furthermore, she should be well informed about the alternative strategies.

The role of diet in the development of cancer (including breast cancer) has been evaluated in many epidemiological studies. However, although diet may have an impact on breast cancer risk, dietary modification alone is not likely to be sufficient to prevent breast cancer (21).

No data exist comparing prophylactic mastectomy vs. surveillance vs. chemoprevention. Thus, despite significant advances in our understanding of the biology of breast cancer, many questions remain concerning the optimal health care management of high-risk women. Patient counseling has a central role in the decision-making process and should be based on a multidisciplinary approach. The individual woman will make the final decision, according to the amount of risk she is willing to accept. For the future, other preventive methods may become available which will more accurately estimate the risks associated with developing breast cancer.

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