fib breast cancer

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This issue of *THE CANCER JOURNAL from Scientific American* continues the central purpose of the publication: to serve as a bridge between the laboratory and the clinic and also as a bridge linking the various disciplines of oncology. Pasteur cautioned that "nature favors only the prepared mind." Perhaps these reviews of new and emerging fields will help to prepare our minds for such studies as the one reported in this issue by Dr Peplinski and colleagues. They report on the use of a vaccinia virus containing the human gene for interleukin-1β to treat a pancreatic tumor in a mouse model. The virus proliferates preferentially in the tumor and produces interleukin-1β in the tumor but not in normal tissue, resulting in a significant tumor response. Although this approach has a long way to go before reaching the clinic, it seems to be interesting and at the least prepares us for similar future treatment techniques.

An interesting use of molecular technology in the clinic reported by Ikenberg and colleagues is the recognition that the presence of human papillomavirus DNA detected by polymerase chain reaction in apparently tumor-free lymph nodes is an adverse prognostic marker. We hope this is a harbinger of things to come: molecular markers of prognosis and as guides to therapy. Gynecologic oncologists Gibson et al report in this issue a lack of pathologic changes in the uteri of women taking tamoxifen as a part of their management of breast cancer. This study illustrates the continuing monitoring required with the long-term use of pharmaceutical agents in cancer prevention.

The recurrent questions of how best to integrate treatment modalities are presented in two studies in this issue. Breast cancer is a model of the multi-modality treatment approach. How, when, in what amount, and in what sequence are all relevant and complicated questions when different therapies are combined. McCormick and colleagues observe no significant difference in local recurrence when the order of radiation therapy and chemotherapy is altered following breast-conserving surgery. Although this is reassuring, we recognize the methodological difficulties involved in considering how to handle distant failure when using statistics to analyze the likelihood of local failure.

An encouraging combined chemoradiation approach to laryngeal tumors, which allowed laryngeal preservation and associated continued voice, is reported by Lacava et al. Voice preservation was correlated with complete response to chemotherapy, a result that is becoming the norm when instituting this neoadjuvant approach to organ and function preservation in a variety of sites. Finally, this issue continues the search for new agents effective in the treatment of cancer. Sausville et al find that brefeldin A, a Golgi-apparatus toxin, has in vitro and in vivo antitumor activity.

As managed care emerges as a major form of treatment delivery, we have an additional responsibility to assure optimal cancer care in a cost-effective fashion. We will acknowledge this responsibility by presenting, from time to time, a management plan for specific clinical conditions. The first such plan is presented in this issue by Dr Love. We invite others to submit these kinds of materials for other clinical presentations, and we are especially interested in a lively dialogue with our readers concerning these plans.

As we enter our second year of publication, we'd also like to remind our readers that each issue of the journal is available electronically through the Scientific American page on America Online. You can review new articles, browse past issues, and contribute your comments or questions to an ongoing forum. We encourage you to visit there often, and to add your voice to our plans for the journal. Additionally, in this issue we publish a letter to the editor that comments upon the work by Teicher et al published in our first issue. Again, we encourage all of our readers to submit such letters for consideration.

And so our plate continues to be full to overflowing. We must learn the vocabulary and conceptual advances of the laboratory and apply these to the clinic. We must integrate the disciplines of oncology the way instruments in an orchestra are integrated, and we must always search for new agents.We must add to the discussions of managed care a dialogue that will contribute to the spread of appropriate cancer management guidelines. It is our continued hope that *THE CANCER JOURNAL from Scientific American* helps in these efforts.

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The Revlon/UCLA Breast Center Practice Guidelines for the Treatment of Breast Disease

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Practice guidelines developed by the Agency for Health Care Policy and Research, medical specialty societies, academic centers, and private sector providers and insurers[1] are designed to improve the quality of patient care and to reduce variations in the delivery of care. The increased activity in guideline development coincides with increasing concerns over controlling the costs associated with medical treatment. Practice guidelines have the potential to reduce costs by reducing unnecessary care, although in some cases they may improve the standard of care beyond that observed in current practice. If so, cost savings will be realized only if savings from the elimination of inappropriate care exceed any increased costs that result from raising the standard of care. However, one unambiguous benefit derived from formulating and implementing practice guidelines is that by reducing variations in care delivery we may improve the ability of health care providers and organizations to anticipate and manage care for their patients.

The Revlon/UCLA Breast Center has created a set of clinical pathways for the treatment and management of breast problems, from the abnormal mammogram to the treatment of metastatic disease. These recommendations reflect our current state of knowledge regarding those treatments associated, where scientific information is available, with the most favorable patient outcomes. These guidelines also take into account areas in which uncertainty may exist regarding optimal treatment strategies; in these cases, we suggest a balanced discussion with the patient regarding the pros and cons of various treatments.

OVERVIEW

The Revlon/UCLA Breast Center consists of a coordinated, multidisciplinary effort to treat breast diseases. It comprises several different programs under the umbrella of the center. The first is the High-Risk Program, which evaluates and follows women with a family history of breast cancer or those who are at a high risk of breast cancer because of pathological findings (atypical ductal hyperplasia or lobular carcinoma in situ). These women are initially seen by a nurse practitioner, oncologist, nutritionist, and mental health specialist. After their initial evaluation, they are followed regularly by the nurse practitioner and other specialists as needed.

The Diagnostic Program sees women who have a lump or an abnormal mammogram and who want to be evaluated. They are seen by a breast surgeon, nurse practitioner, or women's health specialist, as well as by a mammographer. Fine-needle aspiration and core biopsies are readily available.

The Follow-Up Program coordinates aftercare for women with breast cancer. Six to 8 weeks following surgery, women are evaluated with the CARES rehabilitation questionnaire. They are seen by a nurse practitioner, a mental health specialist, a nutritionist, and a physical therapist so that any particular rehabilitative needs are addressed. A follow-up plan is then established.

The Multidisciplinary Program gives women who are newly diagnosed with breast disease or those at a new decision point in their treatment the opportunity to see all of the relevant specialists at one time. The patients come in as a group and are seen individually by a breast surgeon, a medical oncologist, a radiation oncologist, a plastic surgeon, and a mental health specialist. While the patients take an hour-long break, the specialists together review each case along with a pathologist who reviews all of the slides and a radiologist who evaluates x-ray films. A recommendation is reached, and one of the doctors who has seen the patient will then return to review the recommendations with her. All patients are given a tape recorder to record the visit, and a summary of the recommendations is faxed to the referring doctor at the end of the day.

When this center was begun in 1992, it became obvious that the participating clinicians had varying approaches to treating breast problems and breast cancer. We felt it was important for the multidisciplinary group to participate in a literature review and to develop a consistent treatment approach. An additional goal of this work was to track our treatment outcomes, as well as our costs, in anticipation of the arrival of managed care.

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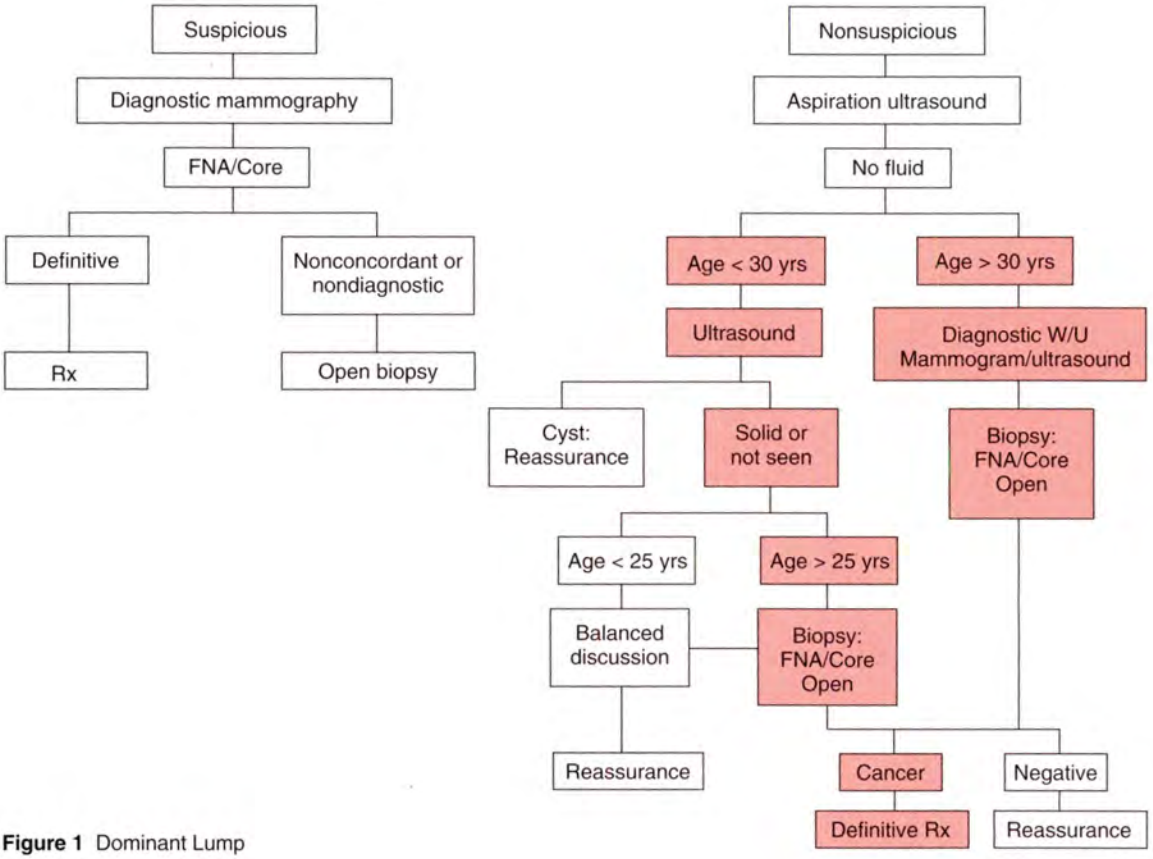


Figure 1 Dominant Lump

DEVELOPMENT

From January 1993 to January 1994, a multidisciplinary group met weekly to develop practice guidelines for the treatment of breast diseases. Initial development of these guidelines was based on evidence of treatment efficacy supported by the medical and scientific literature that focused on the treatment of breast cancer.

The method used for guideline development was a blended approach that included evidence-based evaluation and expert consensus. Although a strict evidence-based approach to guideline development benefits from its rigor, its application is impractical for clinical areas where acceptable study designs have not been produced, as noted by Woolf.[1] Here, guideline development allowed for the use of information from observational studies where randomized studies had not been conducted, and incorporated expert medical opinion explicitly in the decision-making process.

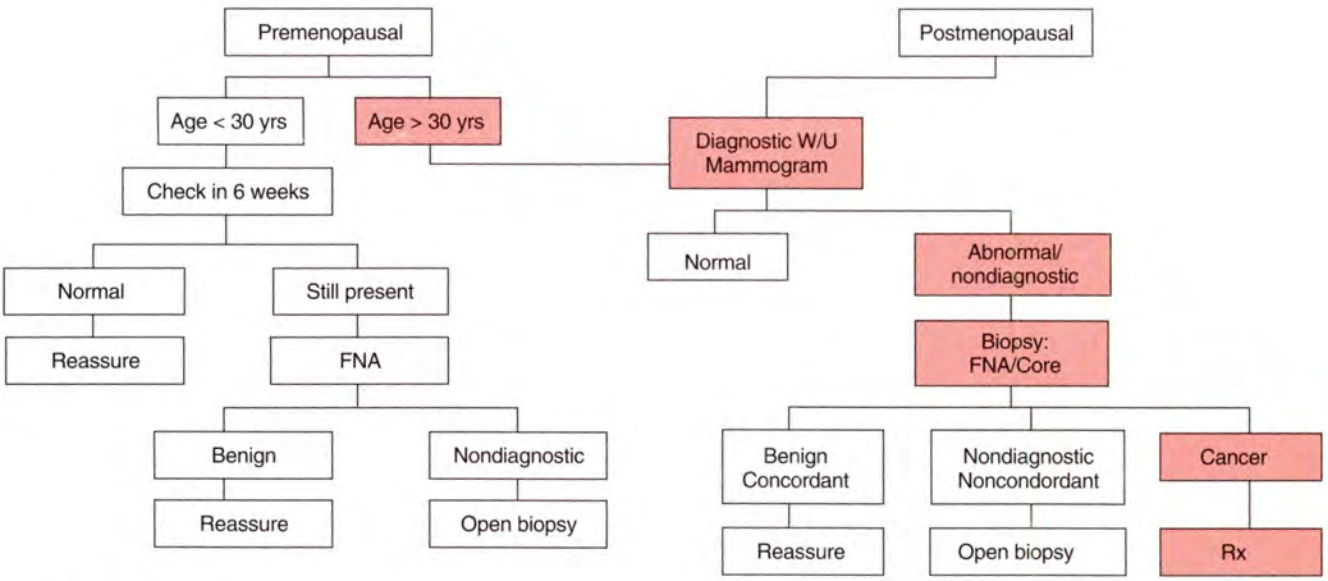


Figure 2 Nondominant Palpable Lump

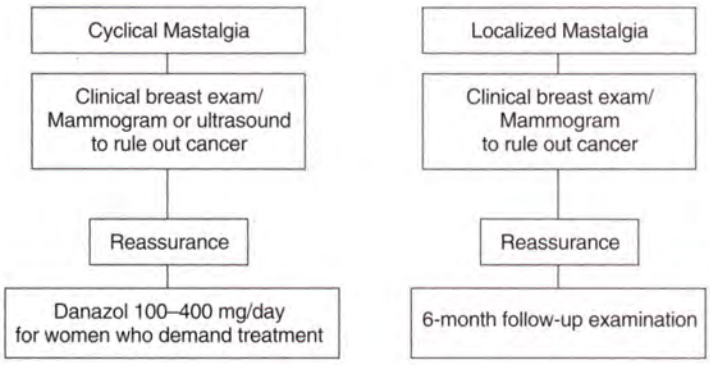


Figure 3 Mastalgia

This process paralleled the recommendations of the American Medical Association for developing practice parameters.[2] These recommendations include: (1) that practice parameters be developed by physicians with scientific and clinical expertise in the content areas; (2) that relevant scientific literature and expert clinical judgment be employed; (3) that practice parameters be as comprehensive and specific as possible, including alternate management strategies where appropriate; (4) that recommendations be based on current information; and (5) that practice parameters be widely disseminated.

The format of the meetings involved presentation of the relevant literature by an appropriate specialist, followed by a group discussion. A first draft of the initial guidelines was circulated to all members of the group for evaluation, and a second meeting incorporated recommended modifications of the specific guidelines.

Initially, the process was complicated by the expression of a polite consensus that did not, however, reflect the actual practice of the participants. As the guidelines were put into practice it quickly became apparent which guidelines had been accepted because of expediency rather than conviction. We reconsidered the topic until all members of the team were comfortable. Any member of the group was allowed to reopen the discussion of any one of the guidelines as new data became available. This insures that the guidelines stay current and are not seen as rigid. Whenever possible, we strove to be data driven. In those areas where data was unavailable or inadequate, we included an option of balanced discussion with the patient of the pros and cons of various treatments. In all circumstances, we favored participation in a clinical trial as the first choice of care. The patient is always considered a participant in the decision making. The guidelines are considered just that—guidelines—and do not dictate our care.

Through this collaborative process we have developed an extensive set of guidelines with which everyone feels comfortable. We have improved the consistency and quality of care to our patients and enabled ourselves to begin to collect outcome and cost data. In the process, we have developed a team approach to breast care that is predictable and reliable.

BENIGN BREAST DISEASE

Dominant Lump. A dominant lump is distinct and persistent. When identified during a physical examination, it must be further evaluated (Fig. 1).[3] If a dominant lump is suspicious for cancer, regardless of the patient's age, a diagnostic mammogram should be done prior to biopsy, to better characterize the lesion and demonstrate other suspicious areas. This should always be followed by a biopsy regardless of the mammographic findings. Either fine-needle aspiration (FNA) or core biopsy can be done. If the results are definitive and concordant with the clinical impression, the patient can go on with treatment. If findings are nonconcordant or nondiagnostic, an open biopsy is required.

A nonsuspicious dominant lump is one suspected by the examiner to be a cyst or fibroadenoma. Aspiration or ultrasound is used to rule out a cyst. If the lesion is shown to be a simple cyst, no further treatment is necessary. If the lesion is solid, further workup is determined according to patient age. In women younger than 30

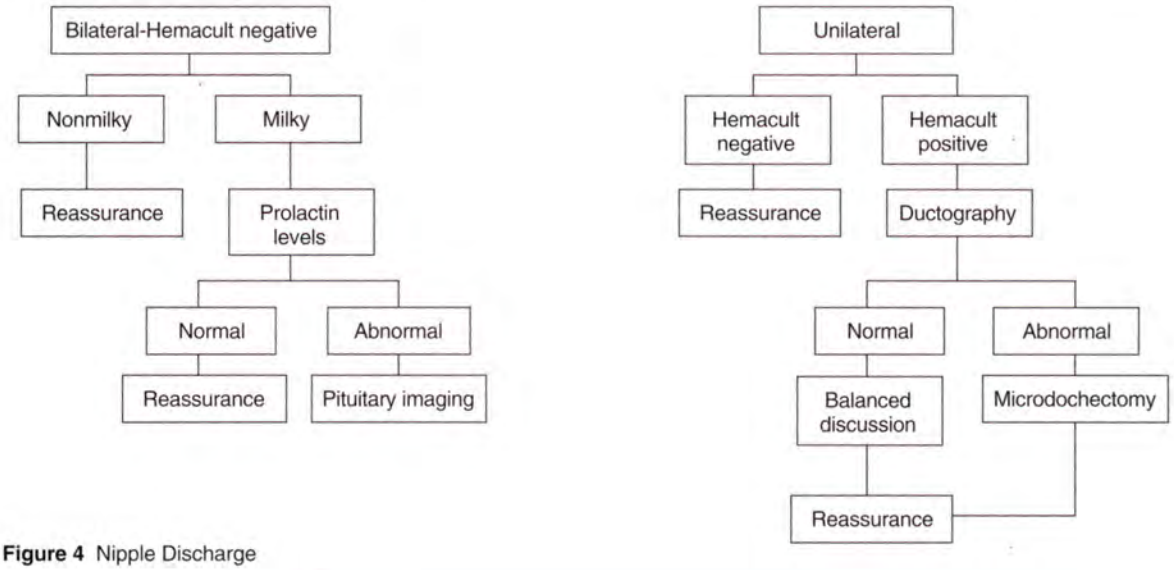


Figure 4 Nipple Discharge

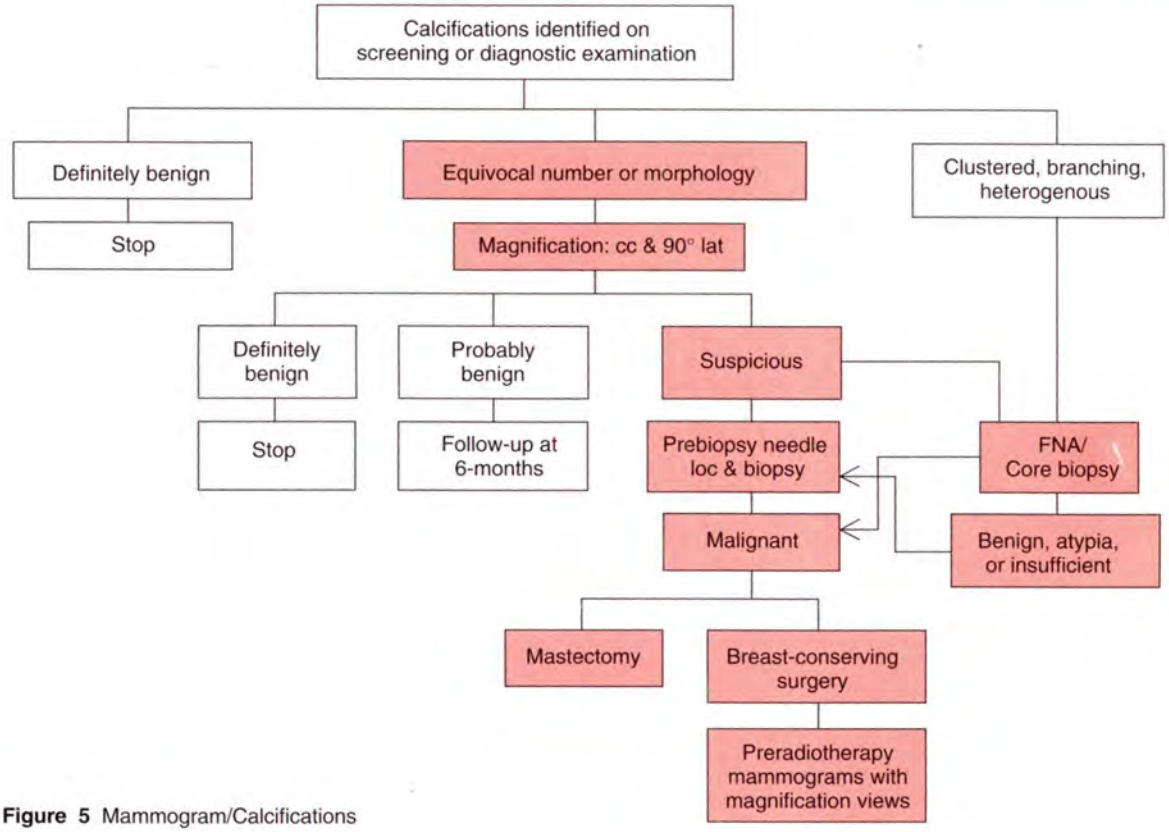


Figure 5 Mammogram/Calcifications

years, an ultrasound can be done. If the lesion is a cyst, no further treatment is necessary. In women younger than 25 years, the likelihood of cancer is very low. The physician should discuss with each woman the options of observation or biopsy. If the woman is older than 25 years or has a strong family history of disease, a diagnostic workup with a mammogram and a biopsy should be done. Fine-needle aspiration, core biopsy, or open biopsy can be used, depending on patient and physician preference. The rule of concordance is very important in all biopsies.[4] The clinical impression, mammographic and ultrasound impressions, and biopsy results should all be concordant. Further workup is necessary when any discrepancy exists.

Nondominant Lumps. Nondominant lumps are those thickenings, areas of asymmetry, or areas of nodularity that are not multiple masses and cysts. Women older than 30 years and postmenopausal women should receive a mammogram and ultrasound (Fig. 2). If these are normal, only regular follow-up examinations are necessary. If these imaging studies are abnormal or nondiagnostic, FNA or core biopsy is required. A concordant benign diagnosis requires no further workup. A cancer diagnosis leads to definitive treatment. Nondiagnostic nonconcordant results require an open biopsy.

Mastalgia. Mastalgia or breast pain is almost always benign. It can be cyclical or localized (Fig. 3).[5] Cancer should be ruled out with a clinical breast exam and mammogram. If these are negative, the patient can be reassured.[6] There is no evidence to support the common use of caffeine restriction[7] or vitamin E[8] in this condition. If a patient demands treatment, Danazol 100–400 mg/day should be used.[6]

Table 1. Staging and Follow-Up Treatment

Staging—Clinical Stage III Patients Only	Breast Conservation & Follow-Up	[a]Mastectomy & Follow-Up
Bone scan	Mammogram before starting radiation	Exam every 6 months for 2 years, then every year
Chest x-ray films	Mammogram within 6–8 weeks of completing radiation	Contralateral mammogram every year
LFTs	Mammogram and exam every 6 months for 2 years, then every year	[We do not recommend contralateral mastectomy.]
CEA & CA 15-3		

[a] We do not recommend routine blood tests or scans in asymptomatic patients.
Abbreviations: LFT, liver function tests; CEA, carcinoembryonic antigen; CA 15-3.

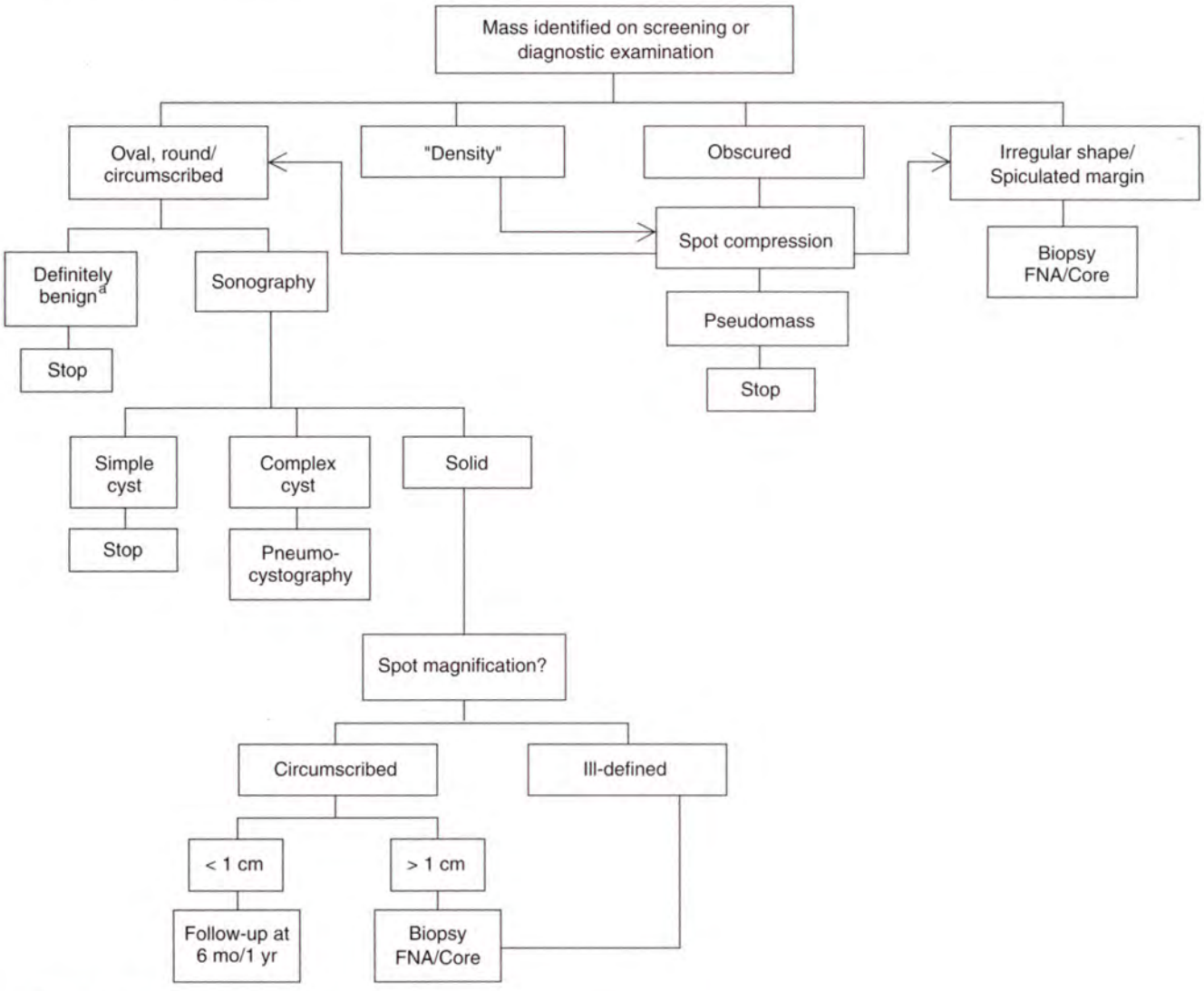


Figure 6 Mammogram/Mass
[a]Multiple, round, circumscribed masses; fat-containing masses; degenerating fibroadenoma.

Table 2. Local Relapse Guidelines: Systemic Therapy[a]

Type of Relapse	Recommendation
1. Local relapse from prior mastectomy, poor prognosis	Strongly consider protocol chemotherapy for ER-negative or premenopausal patients. Tamoxifen may be used in elderly, ER-positive patients.
2. Relapse from BCT, premenopausal, no prior adjuvant treatment	Recommend chemotherapy.
3. Relapse from BCT, postmenopausal, ER-positive	Recommend tamoxifen.
4. Relapse from BCT, diploid, low SPF	No adjuvant treatment.
5. Late (> 4–5 yrs) relapse from BCT	Treated same as a new primary, especially if occurs in a different part of the breast.
6. Local recurrence > 3 cm, short relapse-free interval, or dermal invasion	Strongly consider protocol chemotherapy for ER-negative or premenopausal patients. Tamoxifen may be used in elderly, ER-positive patients.
7. All other patients	Treatment strategy should be individualized, because to date all data available preclude firm conclusions regarding treatment approach.

[a]Local relapse following mastectomy is treated with excision and radiation. Local relapse following BCT requires total mastectomy.
Abbreviations: BCT, breast-conserving therapy; ER, estrogen receptor; SPF, S phase fraction.

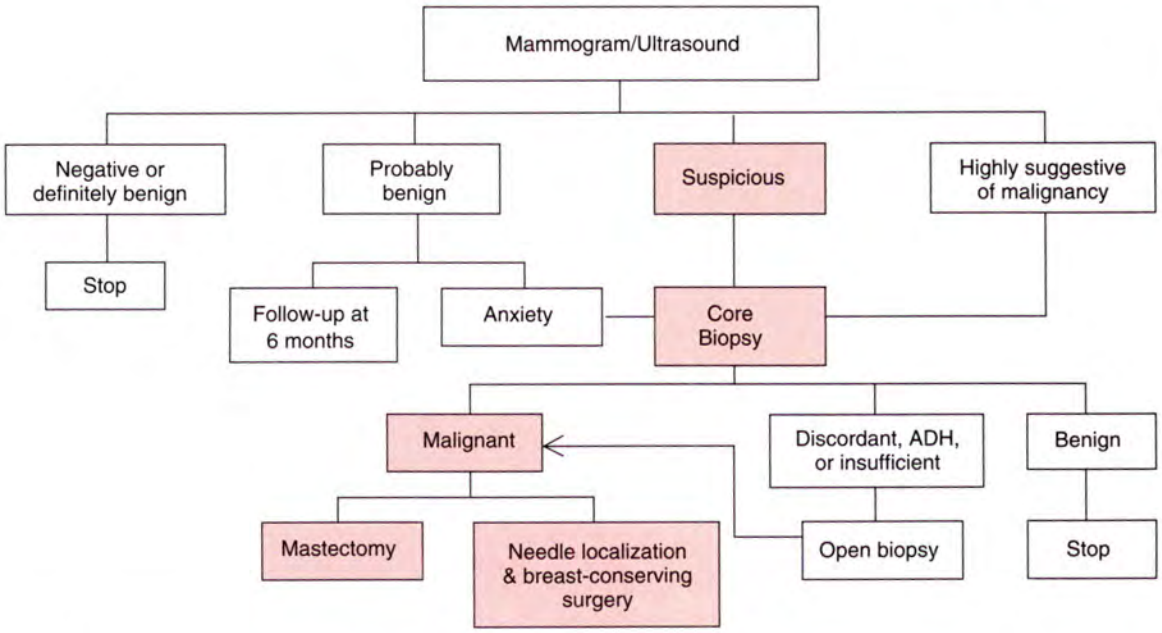


Figure 7 Indications for Core Biopsy

Nipple Discharge. Only spontaneous nipple discharge warrants a workup (Fig. 4). Secondly, only hemacult-positive discharge has any probability of being caused by significant breast pathology.[9] Only if the discharge is bilateral, spontaneous, and milky should prolactin level be measured; if high, the pituitary can be imaged. If the discharge is bilateral, nonmilky, and hemacult negative, the patient can be reassured. Unilateral hemacult-positive discharge requires further examination—preferably with ductography followed by surgery.

Mammographic Lesions. Calcifications identified on a screening or diagnostic mammogram should be classified as definitely benign, equivocal number or morphology (indeterminate), and clustered branching, heterogeneous (suspicious) (Fig. 5). Benign-appearing calcifica-

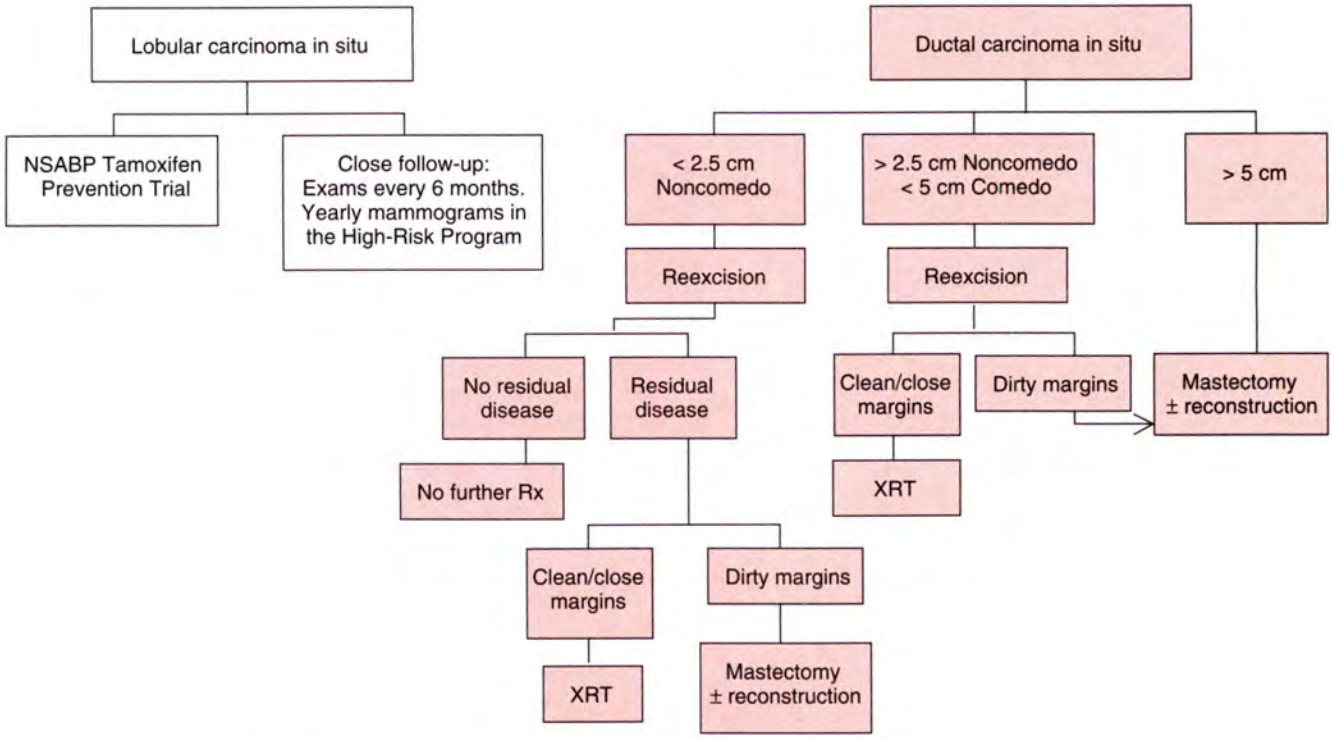
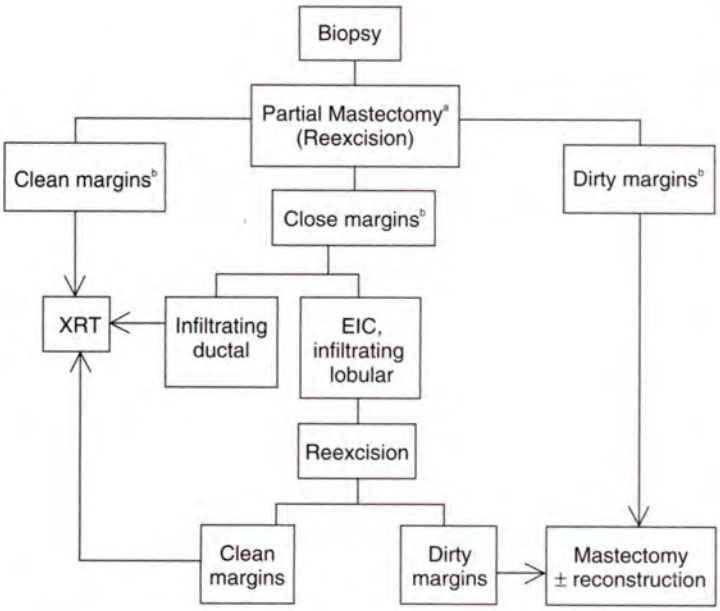


Figure 8 Noninvasive Carcinoma



All biopsies done elsewhere need to re-excised.
All resections need to be inked and tissue sent for ER/PR, DNA flow cytometry and Her 2 Neu.
All women with invasive cancer over 5mm will have a level one and two axillary dissection.

Radiation Therapy: All breast conservation patients are treated with 5000 CGy of external radiation followed by an electron boost.
Post mastectomy radiation with lesions > 5cm; extranodal extension; > positive nodes or extensive lymphatic invasion.

[a]Lesions < 5cm, remove tumor with gross rim of normal tissue. If lesion is too big to be removed cosmetically, then modified radical mastectomy.
[b]Clean Margins: normal breast tissue between the pathology and the ink.
Close Margins: pathology close to the ink in more than three focal areas.
Dirty Margins: pathology at the ink in more than three focal areas.

Figure 9 Local Control

tions do not need further workup or follow-up examination. Indeterminate calcifications should be further evaluated with magnification including craniocaudad and 90° lateral views. If on magnification these appear benign, no further workup is necessary. If they are probably benign, a 6-month follow-up examination can be done. If they are suspicious initially or on magnification, a stereotactic FNA or core biopsy is needed. A definitive diagnosis can be used to discuss options and proceed to treatment. A nonconcordant or nondiagnostic diagnosis indicates the need for an open biopsy.

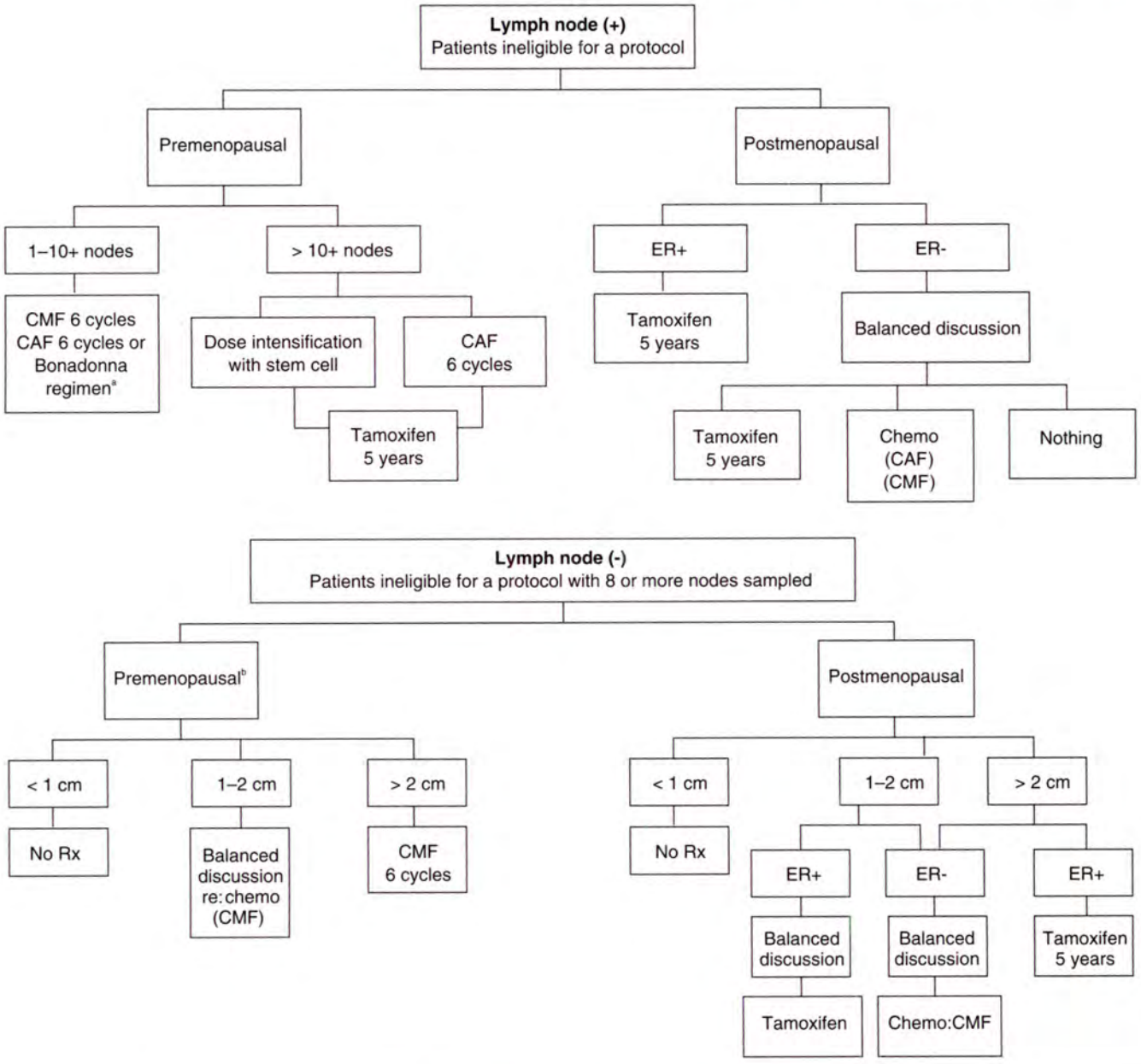
A new mass on mammogram requires a similar workup (Fig. 6). First, compression spot views and ultrasound should be done to better characterize the lesion. If still suspicious, a stereotactic FNA or core biopsy is necessary to establish the diagnosis (Fig. 7). If the diagnosis is benign and concordant, no further workup is necessary. In the rare circumstance where the histopathology is not concordant, an open biopsy may be necessary. In the event that a core biopsy reveals a malignancy, a definitive operation can be performed.

MALIGNANT BREAST DISEASE

Noninvasive Carcinoma. Lobular carcinoma in situ (LCIS) is rarely diagnosed by mammogram or physical exam (Fig. 8). It is usually found incidently in a biopsy specimen that has been removed for some other reason. It is not thought to be precancerous in itself, but rather is considered a marker for an increased cancer risk. The risk is about 1% per year and reaches a maximum at 30 years at 30%.[10] Interestingly, the risk is bilateral and the resulting cancer usually is ductal in nature. The treatment for LCIS does not involve further surgery with wide excision or even clean margins. There is no reason to attempt to remove the LCIS. The treatment is preventive: either close follow-up examination with mammograms once a year and biyearly exams or preventive bilateral simple mastectomies. Our recommendation is the former unless a woman strongly prefers the latter.

Intraductal carcinoma in situ (DCIS) is a different matter (Fig. 8). This lesion is usually diagnosed by mammogram or physical exam and, untreated, will turn into cancer 30% of the time over 10 years.[11,12] The cancer inevitably occurs in the same area in the same breast as the DCIS and is almost always an infiltrating ductal carcinoma. The treatment goal is to prevent potentially invasive cancer. Preliminary information indicates that comedocarcinoma (comedo) DCIS is more likely to lead to invasive cancer than the noncomedo type.[13] Although not yet demonstrated in large studies, it has led us to treat comedo DCIS more aggressively. Comedo is defined as high nuclear grade. We currently approach DCIS with a variety of options. If the lesion is less than 2.5 cm and noncomedo and the reexcision is completely benign, we will follow the patient with mammograms and exams.[14] If there is residual disease but clean margins, or if the original lesion is comedo DCIS, we follow a wide excision with clean margins with radiation therapy.[15] If the margins are not clean, a mastectomy is recommended. Finally in those lesions over 5 cm, a mastectomy with or without immediate reconstruction is indicated. There is no indication for lymph node dissection in women with DCIS.

Local Control. Local control depends upon reducing the amount of cancer in the breast to a level at which radiation therapy can destroy it (Fig. 9). Clean margins are defined as normal breast tissue between the pathology and the ink. Close margins indicate pathology close to the ink in more than three focal areas. Dirty margins are defined as pathology at the ink in more than three focal areas. Margins are actually a surrogate for deciding how much cancer remains in the breast.[16] Pathology also plays a role in this determination.[17,18] The usual infiltrating ductal carcinoma will be easily excised with minimal residual disease. In this situation a close margin is acceptable. Infiltrating lobular carcinoma and infiltrating ductal carcinoma with an extensive intraductal component can be more insidious, and



[a]Bonadonna regimen: Ax4 doses followed by CMF x 8 cycles q3W
[b]Chemotherapy is the first choice for adjuvant therapy, and no tamoxifen co-therapy is given.

Figure 10 Adjuvant Therapy

both demand a reexcision and a clean margin before breast conservation with radiation therapy can be considered. A dirty margin after reexcision requires a mastectomy with or without immediate reconstruction. Our current policy is that all biopsies done elsewhere must be reexcised.[19] All resections must be inked and tissue sent for estrogen receptor (ER) and progesterone receptor (PR), DNA flow cytometry, and Her 2 neu evaluation. All women with invasive cancer over 5 mm in diameter will have levels one and two axillary dissection.[20] In some postmenopausal women with ER-positive tumors over 2 cm where the need for adjuvant tamoxifen has been predetermined, an axillary dissection may be foregone. All breast conservation patients are treated with 5000 CGy of external radiation followed by an electron boost.

Systemic Therapy. First and foremost, we encourage eligible patients to participate in established protocols. If patients are ineligible or refuse to participate in a trial, we recommend systemic treatment primarily on the basis of the stage of the breast cancer and the patient's overall physiologic status.

Lymph Node Negative. As many as 23% of breast cancer patients diagnosed with tumors measuring less than 2 cm and without lymph node involvement will ultimately die from recurrent disease.[21] Individual trials

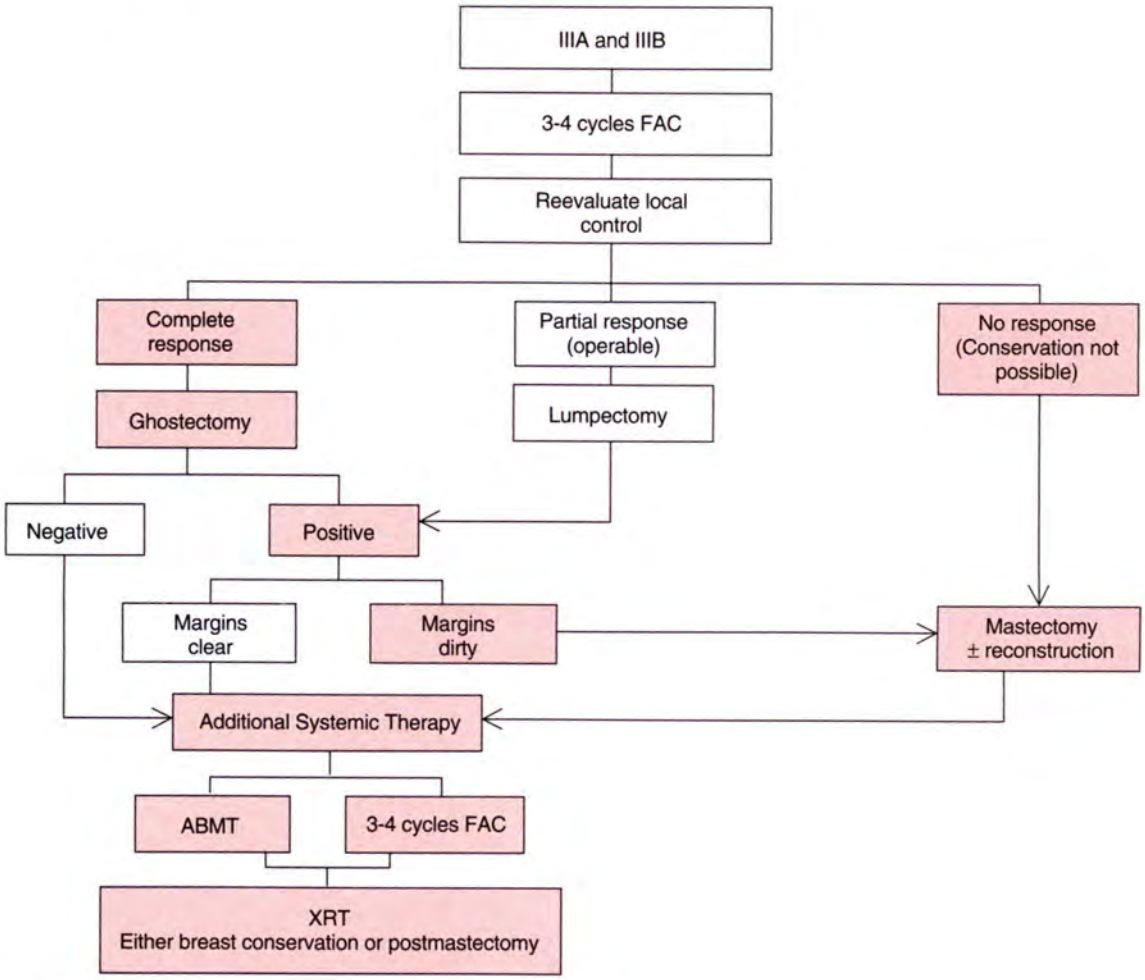


Figure 11 Locally Advanced Disease

of adjuvant systemic therapy have reported improvement in relapse-free and overall survival (OS) in subsets of treated patients with stage I disease.[22-24] The meta-analysis update by the Early Breast Cancer Trialists' Collaborative Group has also demonstrated a survival benefit in node-negative patients treated with systemic therapy.[25]

Available data have documented tumor size as being the most powerful prognostic indicator in this group for the risk of developing recurrent disease (Fig. 10).[26,27] Therefore, we primarily use tumor size as a guide for recommending adjuvant treatment in node-negative patients. Patients with tumors smaller than 1.0 cm have a favorable prognosis with a greater than 90% 10-year disease-free survival (DFS).[26,28,29] The 1990 National Institutes of Health Breast Cancer Consensus Conference recommended that these patients only rarely be treated with systemic adjuvant therapy.[30] These patients are generally not offered adjuvant therapy unless the tumor has a high histologic grade and high mitotic rate.[31] For patients with a primary tumor measuring between 1.0 and 2.0 cm, for whom a 28% 20-year recurrence rate has been reported,[21] a "balanced discussion" is held in which other potential prognostic variables are considered. The latter includes the hormone receptor status, flow cytometry (ploidy and S-phase), histologic subtype and grade, and presence and extent of lymphatic invasion. These factors offer predictive information regarding the risk for recurrence in stage I patients.[21,32-34] In general, patients exhibiting one or more unfavorable prognostic factors are offered systemic treatment.

Patients with stage II lymph node–negative breast cancer have an approximately 33% recurrence rate at 20 years for tumors measuring between 2.1 and 3.0 cm and 44% for tumors measuring between 3.1 and 5.0 cm.[35] These patients are generally offered adjuvant systemic therapy.

Once the decision has been made to use adjuvant therapy, the type (chemotherapy vs hormonal) is based on the tumor's hormone-receptor status and the patient's menopausal status. The overview meta-analysis reported the annual odds of recurrent breast cancer to be reduced by polychemotherapy by 28% and by tamoxifen chemotherapy by 25%, with the results relatively independent of nodal status. The results favored the use of chemotherapy in premenopausal patients and tamoxifen in postmenopausal women older than age 50.[25] The overview also observed that chemotherapy administered for a duration of 6 months versus a mean of 16 months

was equally effective; the benefit of tamoxifen improved with treatment duration beyond 2 years.

Premenopausal women are routinely treated with 6 months of cyclophosphamide, methotrexate, 5-fluorouracil (CMF),[36] regardless of hormone-receptor status. Postmenopausal women with hormone-receptor negative tumors are also treated with CMF and, if hormone-receptor positive, with tamoxifen (20 mg/day for 5 years).[37,38] Perimenopausal patients (within 2 years of their last menstrual period) are treated the same as premenopausal patients. To date, combination hormonal and chemotherapy has not been shown to offer a survival advantage in any of these subgroups and is therefore not recommended.

Lymph Node Positive. Lymph node involvement with breast cancer remains the most important prognostic variable for recurrence, with 10-year relapse rates of 30% to 90% and overall survival rates of 25% to 40%.[28,39,40] Multiple studies have demonstrated that adjuvant systemic therapy can reduce the recurrence rate and prolong survival in both premenopausal and postmenopausal patients with node-positive cancer.[41-43] At 10 years, the overview meta-analysis found that polychemotherapy for premenopausal women and tamoxifen for postmenopausal women resulted in an absolute difference in overall survival between treated and control patients of 10% and 8%, respectively.[25] It is our practice to treat all of these patients, providing their overall health permits (Fig. 10).

The benefit of combination chemotherapy in premenopausal patients with lymph node involvement has been well substantiated by investigators.[44,45] An ongoing controversy exists, however, as to whether or not doxorubicin-containing regimens offer any significant advantage. To date, most trials have been able to demonstrate equivalent but not superior results (both DFS and OS) with doxorubicin.[46-50] Only the ONCO-France study was able to demonstrate improved OS with a doxorubicin-containing regimen.[51] In a trial of sequential versus alternating administration of doxorubicin and CMF to women with more than three lymph nodes involved, the sequential arm was found to be superior.[52] Many oncologists interpreted this data to support the superiority of doxorubicin, but the lack of a CMF control arm makes this an unfounded conclusion. Current studies in lymph node–negative patients comparing CMF to a doxorubicin regimen with or without tamoxifen (NSABP B-23 and Intergroup-0102) should provide further insight into this issue, as well as to any additive benefit of hormonal therapy in this group. In the interim period, however, our practice is to treat premenopausal women with CMF, regardless of hormone-receptor status, given its efficacy and relatively favorable toxicity profile. Doxorubicin-containing regimens such as 5-fluorouracil, doxorubicin, cyclophosphamide (FAC) and doxorubicin with cyclophosphamide (AC) are acceptable alternatives.

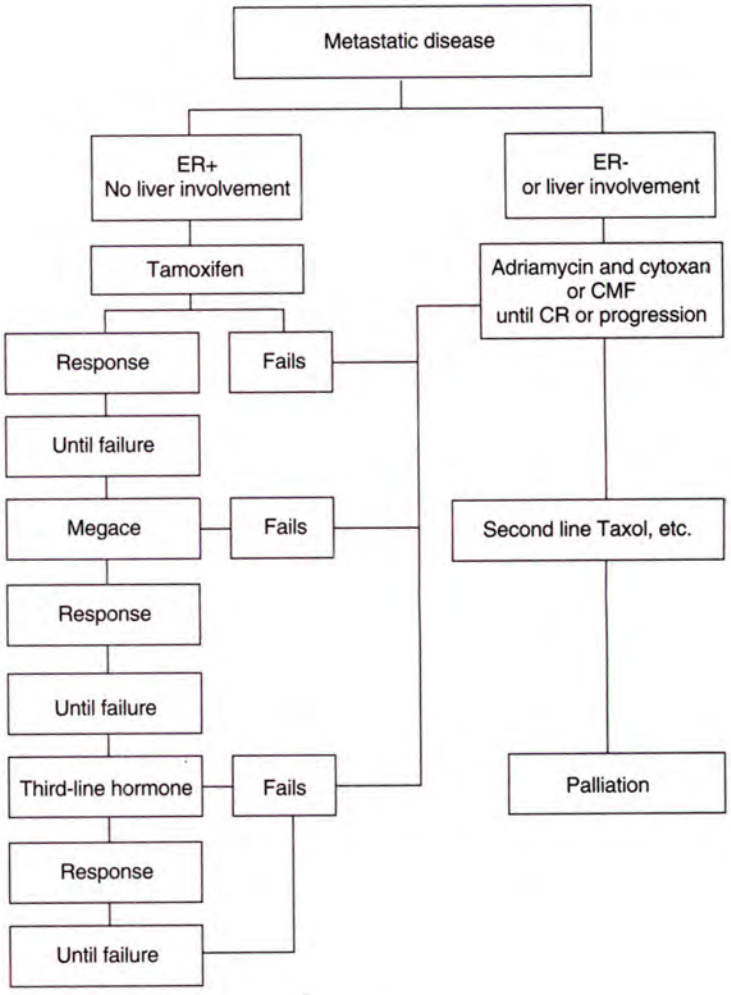


Figure 12 Guidelines for Metastatic Disease

For node-positive postmenopausal patients with hormone receptor–positive tumors, studies have demonstrated efficacy with tamoxifen as well as with combination chemotherapy.[25,45,53] The overview analysis,[25] as well as the NSABP B-16 trial (AC and tamoxifen vs tamoxifen)[54] suggested that chemotherapy plus tamoxifen may be more effective than either therapy given alone. In the latter study, however, approximately 20% of the patients were estrogen-receptor negative and an unknown number of premenopausal women older than 50 years were included. Other studies have demonstrated equivalent results when comparing both treatments (used alone or in combination) in this setting,[55,56] including the recently published results of the Southwest Oncology Group comparing CMFVP (CMF, vincristine, prednisone) to CMFVP plus tamoxifen to tamoxifen alone.[57] Therefore, patients with hormone receptor–positive disease are offered treatment with tamoxifen, 20 mg per day; hormone receptor–negative patients are treated with CMF.

For patients with 10 or more involved lymph nodes, standard therapy has had a minimal impact on the extremely high 10-year recurrence rate (of 70%–90%).[58] For patients younger than age 65 who

are otherwise healthy, we recommend high-dose chemotherapy with peripheral blood progenitor cell (PBPC) support as part of a clinical trial. Patients with hormone receptor–positive disease receive tamoxifen therapy afterward.

Stage III. Patients with stage III, locally advanced breast cancer (LABC), generally have a poor prognosis, with 5-year survival rates ranging from 12% to 38% when treated with primary radiotherapy.[59] The standard treatment for these patients, involving multimodal sequential therapy, has resulted in an improvement in survival when compared to historical controls.[60] Neoadjuvant chemotherapy has demonstrated response rates exceeding 80%[59,61,62] and may downstage the primary tumor size, allowing for breast conservation surgery.

Our practice is to treat LABC with three or more cycles of doxorubicin-based chemotherapy until maximal tumor response, after which the patient is evaluated for surgery (Fig. 11). Breast-conservation surgery or modified radical mastectomy is done based on the degree of the clinical response. Following surgery, healthy patients younger than age 65 who demonstrated a clinical response to the neoadjuvant chemotherapy are considered for high-dose chemotherapy with peripheral blood stem cell transplantation followed by radiation treatment. This recommendation is based on the continued high rate of metastatic disease in these patients. The remaining patients receive two to three further cycles of chemotherapy prior to radiation treatment.

Patients with inflammatory breast cancer undergo similar sequential treatment, except that radiation treatment may be done prior to surgery. For patients undergoing PBPC treatment, however, radiation is deferred until the end of high-dose chemotherapy due to the possible exacerbation of pulmonary toxicity associated with the nitrosourea-based conditioning regimen.[63]

For patients with hormone receptor–positive tumors and comorbid disease or physiologic status precluding chemotherapy, a 2 to 3 month trial of neoadjuvant tamoxifen is attempted for patients with IIIb disease.

Staging and Follow-Up Evaluation. In accordance with published data, our policy is to stage only women with clinical stage III disease.[64] These women receive a bone scan, chest x-ray examination, liver function tests, CEA, and CA 15-3 (Table 1). Follow-up evaluation after initial treatment with breast conservation with or without adjuvant systemic therapy consists of a mammogram prior to starting radiation therapy. A mammogram is then done at 6 months following therapy and every 6 months for 2 years and every year thereafter. History and physical exams are done every 6 months for 2 years and then once a year. No routine blood tests or scans are performed in asymptomatic patients.[65] Following mastectomy, a contralateral mammogram is done once a year. We do not recommend contralateral mastectomy since the risk to the second breast is limited and prophylactic mastecomy has never been shown to make a difference in its incidence.

Local Relapse Guidelines. Local relapse following mastectomy is generally treated with excision and radiation as well as adjuvant systemic therapy (Table 2).[66] Relapse after breast conservation is more problematic, because it can represent either residual disease (i.e., DCIS) or systemic disease.[67] Local therapy is a total mastectomy. If there has been no prior adjuvant therapy and the relapse is infiltrating carcinoma, we recommend systemic therapy. If, however, the relapse is DCIS or has a very good prognosis (diploid, low SPF) we would not recommend adjuvant therapy. Late relapses from BCT are treated like new primaries and adjuvant therapy is recommended according to the guidelines.

Stage IV. Patients with metastatic breast cancer are not thought to be curable with systemic therapy and have a median survival of 2 years when treated with standard systemic therapy.[68,69] Response rates of 40% to 80% have been reported with combination chemotherapy[70,71] with a median duration of response of 6 to 12 months.[72] Similar results (43%–62% response rate) have been reported with the use of hormone manipulation in hormone receptor–positive disease.[73] Autologous stem cell transplant studies have reported complete responses in 0% to 55% of patients, with overall response rates of 6% to 94%; the corresponding average weighted responses are 36% and 70%, respectively. This stands in contrast to the corresponding average weighted response rates of 8% and 39% with conventional chemotherapy.[74] In a review of 267 patients who underwent transplantation, 14% to 30% remained in continuous complete remission with follow-up times of 19 to 40 months from transplant.[75] The superior results of high-dose chemotherapy, however, have not yet demonstrated a definitive improvement in DFS or OS.

Treatment. For patients with hormone receptor–positive disease who lack visceral involvement, hormone therapy with tamoxifen is recommended as the first line of therapy (Fig. 13). For premenopausal patients, medical or surgical ovarian ablation are alternative options.[76,77] If the converse is present and the patient has hormone receptor–negative disease, visceral involvement, or rapid, symptomatic disease progression, chemotherapy is recommended. A doxorubicin-containing regimen is used unless the patient received it for prior adjuvant therapy, in which case tamoxifen is generally prescribed. CMF is an acceptable alternative first-line treatment for patients who are chemotherapy naive or who received prior CMF in the adjuvant setting with a disease-free interval of greater than 1 to 2 years.

For patients who are younger than age 65 with a partial or complete response to standard chemotherapy, protocol high-dose chemotherapy with PBPC support is recommended after maximal disease response.

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ERRATA

In the September/October 1995 issue of the journal, Dr Nathaniel I. Berlin's former affiliation was incorrectly listed as Director of the Division of Clinical Biology, National Cancer Institute. It should be listed as Director of the Division of Cancer Biology, National Cancer Institute. (Cancer J Sci Am 1995;1:187-190)

Due to a printing error, some of the data in Table 1 from the article by Schultz et al ("Iododeoxyuridine radiosensitization of human glioblastoma cells exposed to acute and chronic gamma irradiation: mechanistic implications and clinical relevance" Cancer J Sci Am 1995; 1:151-161) was placed in the wrong columns. The table is correctly reproduced below. In addition, one of the authors, Mary J. Lindstrom, is a PhD, not an MD as stated in the article. We regret both errors.

Table 1. Acute and Chronic Dose-Response Parameters With and Without IdUrd

	G18 Cell Line				U251 Cell LIne			
Dose Rate	IdUrd / % dThd Replacement ± SE	α ± SE (Gy^{-1})	β ± SE (Gy^{-2})	SER at 10% Survival	IdUrd / % dThd Replacement ± SE	α ± SE (Gy^{-1})	β ± SE (Gy^{-2})	SER at 10% Survival
Chronic[a]								
20 cGy/hr	0 μM/-	0.25 ± 0.03	-	1.90±0.19[d]	0 μM/-	0.17 ± 0.02	-	1.37±0.27[d]
	2 μM / 8.5% ± 2.6	0.51±0.08[c]	-		2 μM / 4.1% ± 0.8	0.24 ± 0.04[c]	-	-
40 cGy/hr	0 μM/-	0.37±0.02	-	1.32±0.23[d]	0 μM/-	0.36 ± 0.05	-	1.79±0.52[d]
	2 μM / 12.1% ± 1.6	0.55±0.05[c]	-		2μM /19% ± 3.2	0.67±0.05[c]	-	-
80 cGy/hr	0 μM/-	0.33±0.04	-	1.62±0.21[d]	0 μM/-	0.22 ± 0.02	-	1.37±0.52[d]
	2 μM / 20.4% ± 2.25	0.44±0.12[c]	-	-	2μM/5.9% ± 5.0	0.39±0.05[c]	-	-
Acute[b]								
1.41 Gy/min	0 μM/-	0.32±0.08	0.025±0.01	-	0 μM/-	0.15 ± 0.10	0.024 ± 0.01	-
	2 μM/6.7%±0.4	0.43±0.08	0.036±0.01	1.28±0.12	2 μM/8.6% ± 2.8	27± 0.10[c]	0.021 ± 0.01	1.25± 0.18
	10 μM/15.6%±0.5	0.76±0.08[c]	0.011±0.01	1.85±0.20[d]	10 μM/24% ± 1.1	0.29 ± 0.10[c]	0.060 ± 0.01	1.75 ± 0.26[d]

[a]Chronic irradiation data fit to linear model: Ln S = - α dose.
[b]Acute radiation data fit to linear quadratic model: Ln S = α dose - β $dose^2$.
[c]Significant enhancement with IdUrd vs. no (or lower concentration) IdUrd, $P \leq 0.05$ by global comparison.
[d]Significant enhancement with IdUrd vs. no (or lower concentration) IdUrd, $P \leq 0.05$ by SER analysis.
Abbreviation: SER, sensitizer enhancement ratio.

Recombinant Anticancer Vaccines

Nicholas P. Restifo, MD, *Bethesda, Maryland*

Immunization with viruses has proven its efficacy for more than two centuries. Beginning with the use of cowpox to prevent smallpox (the last reported case of which occurred in Somalia in 1977), viruses have been used to bring under control a number of other human diseases, including polio, measles, and rabies. Recent efforts have been made by a small but growing number of scientists to explore the potential uses of viruses as recombinant anticancer vaccines, useful not only in the prevention of cancer, but in its treatment as well.

A number of different strategies for using viruses in the immunotherapy of cancer are being developed. One particularly exciting strategy involves the use of recombinant viruses capable of expressing proteins not normally encoded in the virus. This has been made possible by a confluence of recent advances in the fields of tumor immunology and molecular virology.[1]

Creating some recombinant viruses, including adenoviruses and retroviruses, can involve the removal of genes critical to viral replication prior to the addition of new genetic material. Resulting viruses can then accommodate the new genetic material within the confines of a viral capsule of a particular and limited size.

Poxviruses like vaccinia can be made to produce heterologous protein through a process called homologous recombination. To achieve such a recombination, a plasmid is constructed that contains pieces of DNA, homologous to specific sequences in the viral genome, which flank the gene of interest. A poxviral gene promoter is placed in front of the desired gene, which is then transfected into a cell already infected by vaccinia. When the homologous sequences from the engineered plasmid align themselves with sequences in the vaccinia virus genome, and a double crossing-over event occurs from the viral genome to the plasmid then back to the viral genome again, the engineered molecule becomes stably integrated into the viral genome, and a recombinant virus results.

In this issue of the journal, Peplinski et al describe the use of vaccinia virus genetically engineered to express interleukin-1β (IL-1β), one of the most inflammatory cytokines known.[2] By exploiting vaccinia's tendency to preferentially replicate in tumor cells, these investigators hypothesize that they have delivered high concentrations of this cytokine locally to the tumor bed. IL-1β then acts like a warning flag to the immune system, apparently summoning immune cells to the site of the tumor deposit. The recombinant vaccinia virus is shown to prevent growth of the experimental tumor used in this study. The authors surmise that the tumor is destroyed through a combination of direct tumor lysis by the virus as well as immune activation due in large part to the cascade of events initiated by the effects of IL-1β.

ALTERNATIVE USES OF RECOMBINANT VIRUSES

Although every cancer that results in the death of its host represents a cancer that has escaped immune destruction, some viruses elicit immune responses of great intensity and duration. One strategy taken by investigators has been to turn these powerful antiviral immune responses against tumor cells. This is theoretically possible because antiviral and antitumor immune responses both involve elements of the cellular arm of the immune system, the specificity of which is provided by T lymphocytes.

Despite the observation that cancer cells do not generally elicit robust immune responses, scientists have managed to grow T lymphocytes with antitumor reactivities in some malignancies.[3,4] These antitumor T lymphocytes have been used to identify the genes encoding the antigens that are recognized by the immune system.[5] The genes encoding tumor-associated antigens can then be used to create recombinant viruses such as vaccinia, that can act as immunogens to elicit immune reactivities against recombinant proteins expressed by the viruses. These immune reactivities will then theoretically also recognize cancer cells, because they express antigens identical to those that have been cloned into the virus.

It has now been shown that mice bearing experimental tumors expressing model tumor antigens can be occasionally cured of their disease if they are infected with recombinant viruses expressing the same model antigens. Although the exact mechanisms remain unclear, it appears that the immune responses elicited by the viruses are far stronger than those elicited by the tumor cells.[6]

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No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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The National Breast Cancer Coalition
a grassroots advocacy effort

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March 15, 1995

To: Milanne Verveer
From: Fran Visco

You told me this could be a rough draft, and I took you at your word. If this is not what you want, or not enough info, just call me. I will be at home tonight 215 238 1353 and on the road tomorrow, but I check my voice mail often - 215 351 -2092.

BACKGROUND

The National Breast Cancer Coalition's vision for the National Action Plan on Breast Cancer has always been that of a public-private partnership in which scientists, government, industry, and consumer advocates, would be at the table, with equal voice, to design and implement a plan of action, a strategy, to address the breast cancer epidemic on every level, science, access, education, treatment, policy. This would avoid duplication of effort and waste of resources, and would bring all of the powerful forces working on breast cancer -- as well as new, untapped sources -- together, in a concerted effort.

This vision was articulated by NBCC at the While House in October 1993 and shared by the President and Secretary Shalala. In December, 1993, the Secretary hosted a conference to begin this process.

THE SECRETARY'S CONFERENCE.

The planning for the conference was done by government (through NIH, HHS, Congress) and consumers and the conference itself was extremely successful. Most of the players involved in the planning also shared the vision and understood what had to be done. The planning group invited leaders from all segments and ensured a diversity of opinion and background.

At the conference itself, we broke up into ten working groups - each group consisted of a cross section of the conference participants: representatives of the scientific community, consumers, government, and private industry. The groups were formed to address the following areas: Research: Basic, Applied, Epidemiology; Education: Consumers, Physicians, Scientists; Access to and Delivery of Health Care; Translation of Research into Practice; Information Dissemination and Coordination and Health Care Policy and Regulation.

The participants in the working groups were asked to brainstorm and strategize what actions in their areas should be proposed as part of a national breast cancer strategy.

At the end of the day, the co chairs of each group presented their conclusions to the entire group. The co chairs of the groups then met to synthesize the information.

A report of the proceedings - a summary of the proposals from each working group, has been published in what is now called the "green book", entitled Proceedings - the Secretary's Conference to Establish a National Action Plan on Breast Cancer.

It is important to note that this document IS NOT A PLAN, it is a compilation of proposals that came out of that conference in December.

SUBSEQUENT EVENTS

Nothing happened until June, when the co-chairs of the ten working groups were brought together with representatives from most of the federal agencies, to being to design a plan. The group insisted that someone co-chair the Plan with Susan Blumenthal and the group elected Fran Visco to do this.

The Secretary asked us to identify five priority items to begin the Plan.

The entire group - co chairs and government reps - identified about 19 or 20 priorities and these were then ranked by the group. Six priorities were deemed important to begin the process.

The June group then identified members of planning groups for each priority, who were to meet and identify proposed members of working groups for each of the priorities. The working groups were to begin the design of a plan of action within their priorities and implement those actions.

The nominees for the working groups were to be given to Susan Blumenthal and Fran Visco who would look at them as a whole to make certain that there was sufficient diversity, etc. The nominees were sent to Susan and Fran, who met several times, came up with a list and then held conference calls with the co-chairs of the planning groups to finalize the lists.

The co chairs of the working groups and certain others comprise a steering committee to oversee the plan.

WHERE WE ARE NOW

The six priorities chosen are:

Involvement of Consumers - goal is to place consumer advocates at all levels of decision making in breast cancer.

Etiology of Breast Cancer - goal is to identify gaps in research on the etiology of breast cancer and recommend strategies on how to fill those gaps.

Information Action - goal is to make certain that the information superhighway (including of course telephone, TV and radio) give out the right information on breast cancer to consumers, physicians and scientists

Clinical Trials - goal is to identify barriers to access to clinical trials and to develop strategies to overcome those barriers - increase accrual of women into breast cancer studies

National Resource Bank - goal is to develop best method to collect and distribute biological resources needed by the research community

Genetics - goal is to develop and implement a comprehensive plan to address the needs of individuals carrying a breast cancer susceptibility gene

PROBLEMS.

Problem: Vision

The major problem with the process so far is that it has been slow and, more important, lacks a coherent vision. We don't even have a plan to get a plan. There is no vision of what the National Action Plan comprises, no vision of what it is to accomplish and no articulated plan or timeline to accomplish it.

Example:

The federal agencies have been pulled together as a coordinated group to work on breast cancer issues. They were told they would be working on the national action plan for breast cancer. What happened is that they were given the green book and asked to identify what their agencies were doing that matched a priority listed in this book. They then met to identify their own priorities, with no private input.

Issue:

What is the Plan? Is it everything that has happened and is going on in breast cancer or is it what the public private partnership that is the steering committee prioritizes from the green book and then the working groups again reflecting public private membership plan and design?

- Is it everything going on even outside the government, eg., in ACS, in DOD at the Coalition that is the Plan and thus under NAPBC leadership? On March 13 the steering committee voted that the Plan is the process developed by the steering committee.

Issue:

On the issue of there being no real plan - through the steering committee process, we are beginning to design one through the six working groups, building the plan by taking the

proceedings from the conference, looking at the proceedings in an organized, inclusive way, developing an overall strategy by focusing on groups of priorities and making certain that this is all done by a private public partnership, both in t he design and implementation stages.

Solutions:
The National Breast Cancer Coalition will draft a proposed "plan to get a plan" for submission to SB's office and the steering committee. (Actually we are in the process of doing this).

Have a meeting of the Secretary, Hillary Clinton, Fran Visco, Susan Blumenthal, Susan Love, and agree to overall vision

Hire someone to do day to day management of plan and make it work

Problem: Funding

The issue of how this Plan is funded is another problem. The money as I mentioned is now in NCI, and this has created many problems. NCI process is slow and they have not been forthcoming on how to appropriately speed up that process.

Because of past history of plan, we are now faced with spending $10 million in five months. No one wants to spend that money inappropriately, yet the working groups are just now beginning. While they can come up with some short term goals, they must be driven by goals, rather than by the need to spend the money.

Solutions
Make certain that NCI is on board.

Establish a quasi public foundation so that we can attract private funds also - but the foundation must be solely for the National Action Plan on breast cancer and must be solely controlled by the steering committee.

Plan the best way to spend this money by the steering committee and make certain this never happens again.

Problem: Priorities

Work is just beginning on the six priorities and it is too soon to tell just what the obstacles and barriers are. We need a strict timeline for the work and a product that we can evaluate. Federal agencies must be encouraged to work in concert with the working groups and not in tangent. All decisions should go through the steering committee so that misunderstandings can be minimized. If this is truly to be a new way of doing things we need to continually monitor that we are fulfilling our mandate.

DEPARTMENT OF THE ARMY
U.S. ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
FORT DETRICK, MARYLAND 21702-5012

March 10, 1995

REPLY TO ATTENTION OF:

Office of the Commander

Ms. Frances M. Visco
President
National Breast Cancer Coalition
1707 L Street, NW, Suite 1060
Washington, DC 20036

Dear Ms. Visco:

Thank you for your letter to President Clinton concerning the appropriation of the Breast Cancer Research Program funds. It certainly is our desire to ensure that collaborative research efforts in this area continue. At this present time; however, a decision has not been made as to which organization will manage the $150 million dollars appropriated for Fiscal Year 1995.

Thank you for your keen interest in this most important matter.

Sincerely,

Russ Zajtchuk

Russ Zajtchuk
Brigadier General, Medical Corps
Commander

Milanne -
FYI

Clinton Presidential Records
Digital Records Marker

This is not a presidential record. This is used as an administrative marker by the William J. Clinton Presidential Library Staff.

This marker identifies the place of a publication.

Publications have not been scanned in their entirety for the purpose of digitization. To see the full publication please search online or visit the Clinton Presidential Library's Research Room.

fight breast cancer

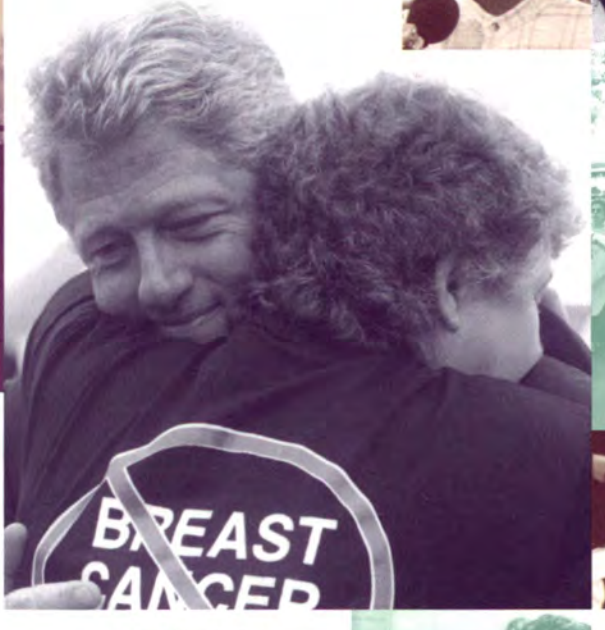
NBCC

National Breast Cancer Coalition

« a grassroots advocacy effort »

2.6 campaign

2.6 Million Signatures for 2.6 Billion Research Dollars



Each year,

more than 184,000 women are diagnosed with breast cancer and more than 44,000 women die of the disease.

File: Breast Cancer

SECURE, COMPREHENSIVE CARE:

BREAST CANCER COVERAGE UNDER THE HEALTH SECURITY PLAN

Women are increasingly the victims of life-threatening illness, yet still are at the bottom of our medical research agenda. Funding for research into breast and ovarian cancers, osteoporosis and other diseases remains inadequate. Of all the health problems American women face, however, breast cancer is the deadliest.

The Facts on Breast Cancer in America:

- One in nine women in the U.S. will develop breast cancer in her lifetime. (National Breast Cancer Coalition)
- 2.6 million women in the U.S. have breast cancer today, and this year another 182,000 American women will be diagnosed with the disease, approximately one women every three minutes. (National Breast Cancer Coalition)
- 46,000 women will die from breast cancer this year in the U.S., approximately one woman every 12 minutes. (National Breast Cancer Coalition)
- There is no known cause or cure for breast cancer.

The Health Security Act addresses women's health care seriously and comprehensively, guaranteeing coverage to all women, regardless of health status, marital status, employment status, or ability to pay. Specifically, the Health Security Plan will cover a schedule of preventive screenings, tests and checkups at no cost, protection available in only a few of today's insurance policies.

BREAST CANCER EARLY DETECTION AND CARE COVERAGE UNDER THE HEALTH SECURITY PLAN

Medically necessary or appropriate care: Women of any age can receive clinical services, including clinical breast exams, and mammograms at any time when they are medically necessary or appropriate with cost sharing as specified by their plan.

Care for women at risk: Women of any age who are defined to be at risk of breast cancer by the National Health Board will receive additional visits, including clinical breast exams, and mammograms at a schedule appropriate to their risk status *with no cost sharing.*

Care for all women: All women receive regular clinician visits, including clinical breast exams, every three years from age 20 - 39 and every two years from age 40 - 64 *with no cost-sharing.* All women will also receive routine screening mammograms every two years, beginning at age 50, *with no cost sharing.*

In addition, the following services are covered for pap smears:

Pap/pelvic exams are covered annually for women who have reached childbearing age and are at risk of cervical cancer as part of clinical preventative services *with no cost-sharing*. Once three negative smears are obtained, pap smears are covered every three years for women age 20 - 39 and every two years for women 40 and above. If the patient is at risk for fertility-related infectious illnesses, pap smears may be covered more frequently.

Additional pap smears: Additional, or more frequent pap smears may be done at any time they are medically necessary or appropriate. In these cases, the services are covered *with cost-sharing* as is any other medical procedure.

SUPPORTING WOMEN'S HEALTH RESEARCH UNDER THE HEALTH SECURITY PLAN

The clinical preventive services package will be supported by significant increases in investments in breast cancer research.

- This year the National Institute of Health's breast cancer research budget increased by 44 percent, from $208 million to almost $300 million.

Additional increased funding for early detection and preventive services is available through the following agencies, which have increased investment in their own breast cancer research programs:

• Centers for Disease Control	From $71 million to $78 million
• The Food and Drug Administration	From $3 million to $13 million
• The Department of Defense	This year earmarked $210 million for breast cancer research.

Under reform, new research initiatives will concentrate in prevention of many illnesses affecting large numbers of women, including mental health, reproductive health and osteoporosis.

# #

See page 3 for breast cancer re Health Security Act

President William Jefferson Clinton
Remarks to the National Breast Cancer Coalition
The White House
October 18, 1993

[Recognitions]

The White House has seen more than its share of unusual gatherings and important moments since we arrived here nine months ago. But today marks a special occasion for all of us. This morning, each of us is reminded of the despair that a terrible and frightening disease has brought to our lives. But we meet also to celebrate your courage and your commitment to making the lives of women all over our nation safer and more secure.

This is an audience that is all too familiar with the grim statistics that lie behind the ravages of breast cancer. In the three minutes since I stepped up to this microphone, another American woman has been diagnosed with breast cancer. Every twelve minutes, a woman in our nation dies from it. Recent surveys have found that one in every three women does not receive basic services like mammography that can help detect breast cancer. And breast cancer will cost our nation an estimated $6 billion this year in medical bills and lost productivity.

And yet despite the proportions of this epidemic, and the best efforts of some of this nation's best scientists and doctors, we don't know what causes breast cancer. We don't know how to prevent it. And we don't know how to cure it.

What we do know is what it does -- not only to women, but to all of us.

[option: story of your mother's illness and it's impact]

The devastating effects of this illness were brought home to me most recently on a July day when Sherry Kohlenberg came to visit Hillary and me in the Oval Office. Some of you in this room knew Sherry; she was a breast cancer victim who worked with your Coalition.

In the early part of this year, Sherry had been in remission but then, in the spring, she had a relapse. She contacted us and said that, before things got worse, she wanted to

have her son, Sam, meet the President. And so she brought Sam and her husband, Larry, to visit.

Sherry was in a wheelchair that day, her husband pushing it, and Sam clinging to her leg. We spent about a half-hour together. And as they left the Oval Office, Sherry turned to Hillary and me and said: "Don't ever let anyone forget what this disease does to those who are left behind."

We told her we would not. And I am pleased this morning to be able to say to Sam and Larry -- they are with us this morning and I salute them for their courage...Let me say to all of you this morning we have not forgotten Sherry's words. And we are working hard to make it possible for all of our mothers and daughters to live in a world where breast cancer no longer numbers among their fears.

Meeting that promise will require action on all fronts in the war against breast cancer. And I can report to you today that we are moving on each of those fronts -- research, detection, delivery, and outreach.

Because we recognize that future progress against breast cancer depends on our ability to tackle new frontiers in basic research, I proposed -- in my first budget submission -- the creation of the Office of Research on Women's Health and the largest increase in funding for breast cancer research in the history of the National Institutes of Health. We have also increased funding for detection and preventive services at the Centers for Disease Control, the Food and Drug Administration and the Department of Defense. Together, it adds up to some $600 million this year alone.

As one step in coordinating our research and delivery efforts, I am pleased to announce that -- in keeping with that commitment -- Secretary Shalala will bring together groups like yours, a broad range of health professionals, and government officials to develop a national action plan for the prevention, diagnosis and treatment of breast cancer. Developing and carrying that national strategy is what these petitions that you have

delivered are all about -- and with your help, I am convinced the Secretary will succeed, and that we will all be better off as a result.

But research, as you have consistently pointed out, is not enough. We need to do everything in our power to detect this disease early and to make mammography and medical treatment available to every American woman.

I believe that our Health Security plan is going to fundamentally change the fight against breast cancer. It is a plan that -- quite frankly -- shows the signs of several strong women at work. A plan that is based on the notion that, when it comes to health care research and delivery, women must no longer be treated as second class citizens. That we must invest in prenantal care, nutrition, maternals and child health. A plan that is based on the idea that we must try and detect and prevent disease -- not just try to heal people after they fall ill.

The Health Security plan guarantees every American a comprehensive package of benefits that can never be taken away. And at the core of those benefits are a wide range of preventive benefits provided at no cost to the patient, some of which will help us take great strides in the fight against breast cancer.

Among other things, the plan covers, at no cost to the patient, routine clinician visits, where women can receive appropriate clinical breast exams and other important preventive services -- things like immunizations and Pap smears. Because we know that we can reduce deaths by making mammography widely available, the plan covers mammograms every two years -- at no cost to the patient -- for all women over 50. And for those women who are at high risk of developing breast cancer, the plan provides more frequent mammograms at any age. Let me assure you that these benefits are based on the best available scientific evidence -- and can be updated to reflect new or better studies, or recommendations like those we will soon receive after two years of hard work by the President's Special Commission on Breast Cancer.

Finally, our Health Security plan recognizes a seemingly simple but critical fact: the best care in the world doesn't do anybody any good unless you can get to it. And so our plan will offer new help to our nation's public health system....it will spread the latest technology to doctors and nurses in the smallest rural communities and our nation's inner cities....and it will allow every health professional to contribute to the best of her or his ability and training.

As you know from your effort to gather these signatures, change requires that people work together. I believe that working together, we can develop a strategy to win the war on breast cancer and create an American health care system that is grounded in equality, compassion and security. Health care that says women's health care must be given equality -- in attitude and dollars. Health care that says it's better to keep people healthy -- not only treat them after they get sick. Health care that says every one of us deserves health security, health care that is always there.

Every American brings unique experiences, skills and weapons to the battle against illness and the battle for health security. Your weapons are not the dollars and deal-making talents of the lobbyists. They are not the stethoscopes or the syringes of the doctors and nurses. They are the pen and the petition -- and the knowledge that a chorus of voices is so much more powerful than even the strongest voice singing alone.

I urge you to continue your fight, and add your voices to ours in the months ahead.

[after applause]

Now I am going to sign a proclamation that declares tomorrow, Tuesday, October 19th, National Mammography Day.

NBCC

NATIONAL BREAST CANCER COALITION

grassroots advocacy in action

FOR IMMEDIATE RELEASE
August 14, 2000

CONTACT: Jennifer Levine
202-973-0593

NBCC HONORS CONGRESSWOMEN FOR ACTION ON SUBSTANTIVE BREAST CANCER ISSUES

The National Breast Cancer Coalition Hosts Breakfast to Salute Reps. Anna Eshoo and Nita Lowey

What: **Breakfast Reception to Honor Congresswomen**

Who: **Representative Anna Eshoo (D-CA)**
Representative Nita Lowey (D-NY)
NBCC President Frances Visco

Date: **Tuesday, August 15, 2000**

Time: **8:30 a.m. – 10:00 a.m.**

Where: **The Four Seasons Hotel**
The Ballroom
300 South Doheny Drive

(LOS ANGELES, CA – AUGUST 14, 2000) – As part of the Democratic National Convention, the National Breast Cancer Coalition (NBCC) will host a breakfast reception in Los Angeles to honor two Congressional members, Representatives Anna Eshoo (D-CA) and Nita Lowey (D-NY). Both women have been long-time supporters of NBCC's legislative priorities and strong breast cancer activists. This reception will celebrate their work on legislation to appropriate funds to substantive breast cancer research and to make treatment available to low-income women diagnosed with breast cancer. A similar reception was hosted by NBCC at the Republican National Convention.

Nearly 500 people are expected at the breakfast reception. Numerous celebrities and local breast cancer advocates, including Peri Gilpin and Sharon Lawrence, will join Fran Visco, NBCC President, to honor these extraordinary Congresswomen for their commitment to the eradication of breast cancer.

The National Breast Cancer Coalition is a grassroots advocacy organization dedicated to eradicating breast cancer through the power of action and advocacy. The goals of NBCC are to: increase research into the causes, optimal treatments and cure for breast cancer; improve access for all women to high quality screening, diagnosis and treatment; and increase the influence of breast cancer survivors and other activists in research, clinical trials and national policy.

# # #

Fran Visco Remarks from Award Presentation to Anna Eshoo on Tuesday, August 15th in Los Angeles, CA

Without Congresswoman Eshoo, the Breast and Cervical Treatment Act would not be where it is today. Congresswoman Eshoo has done everything in her power to move the Breast and Cervical Cancer Treatment Act forward. Her support was essential and was reflected in the 421-1 vote in favor of the bill when brought to the floor of the House of Representatives for a vote.

Led the Fight in Creating Enormous Bipartisan Support for this legislation. Congresswoman Eshoo worked tirelessly to increase the number of cosponsors on this legislation, working with a Mother's Day deadline, which led to more than 218 cosponsors in the first session of the 106tth Congress. This year, she set the goal for this legislation to pass the House of Representatives by Mother's Day and was relentless in securing passage of this bill out of committee to be voted on on the House Floor to meet this deadline.

Ensured that this bill moved through the House Commerce Committee so that it could be voted on in the Full House. She simply would not take No for an answer. She was the bill's champion in getting hearings held, relentless in scheduling markups after the hearings for bill to be passed out of sub and full committee and set the deadline for a full House vote. She was relentless in urging the Chairman of the House Commerce Committee, Representative Bliley, and the Chairman of the House Commerce Subcommittee on Health and Environment, Rep. Bilirakis, to schedule hearings on this bill, and to mark it up and pass it out of Committee in order to meet a deadline of Mother's Day for passage on the House floor.

Helped to Overcome obstacles at every step of the way. She helped move the bill through the Committee when it looked like there was going to be a delay and she worked to stave off amendments which could have undermined the effectiveness of the bill as written.

She took a back seat when the bill came to the floor, since it was renamed in honor of two breast cancer survivors. However, she was critical - at every stage in the process - to getting this bill passed on the House floor, and to ensuring that it wasn't weakened – for example, initially, the new H.R. 4386 (renamed for the breast cancer survivors) did not contain the essential enhanced match section - which is the philosophical underpinning of this bill since it closes the gap in the existing program which has an enhanced match, and ensures that states will have the incentive to opt for this new benefit.

She was a leader in the bipartisan effort to accomplish this goal.

Representative Eshoo has done more than pay lip service to this issue. She has shown us by her actions that she supports the Coalition's efforts and that she's committed to working with us to ensure an end to this dreaded disease.

She has been honored several times by the Coalition for her ongoing work on substantive breast cancer policy issues and for her commitment to women with breast cancer and all those impacted by this deadly disease. The Congresswoman has been critical to the success of the Breast and Cervical Cancer Treatment Act and continues to support all of NBCC's legislative priorities.

Anna Eshoo was willing to forgo getting credit for the work she did on the bill, and instead remained focused - through the whole process - on the end result - getting the Breast and Cervical Cancer Treatment Act enacted so that low-income women diagnosed through the BCCEDP can receive the lifesaving treatment they deserve.

It's easy to put a pink ribbon on your lapel but it's hard to make substantive change. I believe that Congresswoman Eshoo has and will continue to work with the National Breast Cancer Coalition to bring about true, meaningful change in the fight against breast cancer.

Congresswoman Eshoo is a true breast cancer advocate in every sense of the word.

I am proud to present her with an award from the National Breast Cancer Coalition for helping to "Make Breast Cancer History!"

HRC BREAST CANCER AWARDS

July 16, 1993 – **Iris Cantor Humanitarian Award**, which recognizes contributions to women's health. HRC was the first recipient of the award. The award luncheon supported the Iris Cantor Center for Breast Imaging at UCLA Medical Center.

October 2, 1995 – **Government Leadership Award from the National Breast Cancer Awareness Month Board of Sponsors and Zeneca Pharmaceuticals** for her "outstanding initiative in launching efforts to educate all women about mammography, especially women eligible for Medicare." (from press release)

October 20, 1997 – **SELF Magazine's Pink Ribbon Award**. Awarded to both the President and First Lady, the award is given to honor those who make a significant contribution to the fight against breast cancer.

September 28, 1999 – **Public Leadership Award from the National Breast Cancer Coalition** for work to eradicate breast cancer.

March 28, 2000 – **"Woman of Courage" Award from Cedars-Sinai Research for Women's Cancers and Saks Fifth**. The First Lady was honored for her commitment to eradicating women's cancers, including breast and ovarian.

August 2000 – **National Breast Cancer Coalition Honoree** at Democratic Convention Reception for her efforts to eradicate breast cancer.

Ruby – for you and Melanne –
FYI – I sent ltr
it up to Ann + Neera.

file Breast Cancer

Good Housekeeping

959 EIGHTH AVENUE, NEW YORK, NY 10019 * 212-649-2200 * FAX 212-265-3307

July 2, 1999

Ms. Melanne Verveer
Office of the First Lady
Old Executive Office Building
Room 100
Washington, D.C. 20502

Dear Melanne Verveer:

I believe Ellen Levine told you to expect a letter from me, since I'll be handling the Breast Cancer Awareness project here. You'll find the questions for Mrs. Clinton below, but let me first bring you up-to-date on my conversations with Paul McCartney's office.

Basically, it's all good news: He has agreed to let us offer two of Linda McCartney's photographs for sale; the proceeds will go to NABCO. (Ellen is particularly thrilled about this—as she's sure Lisa Caputo will be, since they sit together on NABCO's board.) It is also possible that we will interview Paul McCartney for the piece—as the fellow in his office told me, "When the request comes from 10 Downing Street, you pay attention!"

Now we need to make sure our *readers* pay attention, which is where we think Mrs. Clinton's involvement in the project will make all the difference. She, like so many in our audience, grew up in a time when breast cancer was never talked about. These days, however, it's discussed so openly that people who have not been directly touched by the disease may have stopped paying notice. But they will pay notice if Mrs. Clinton takes advantage of her leadership position and addresses the topic in a personal way. That personal connection is what makes a piece effective, as we learned so well last year when we worked with Katie Couric on our award-winning article on colon cancer.

Good Housekeeping

959 EIGHTH AVENUE, NEW YORK, NY 10019 * 212-649-2200 * FAX 212-265-3307

What I suggest is that we open the piece with a paragraph that covers the First Lady's public relationship with breast cancer. Questions that could be covered include:
1) Why are you getting involved in Breast Cancer Awareness month in this way?
2) What's the message you're trying to get across?
3) Is there any particular policy relating to breast cancer—research, prevention, or treatment—that you'd like to see changed and/or enacted?
4) Did you ever meet Linda McCartney? Have you met Sir Paul?
5) What's the reason for doing this "joint action" with Mrs. Blair?

Then we would move to Mrs. Clinton's private relationship with the disease, covering such topics as these:
1) Do you do breast self-exam? How often? Now, be honest...
2) Is there any breast or ovarian cancer on your side of the family?
3) Since the President's mother died of breast cancer, do you have any particular worries about Chelsea?
4) Have you discussed breast cancer—and its prevention—with her?
5) Could you imagine suggesting that she (or the President) get tested for the cancer gene?
6) Have you had any close friends who have had breast cancer?
7) If so: Other than your concern for them, did their disease arouse an emotional response in you?
8) If so: Was it more fear or anger?

I'll call you next week (or you can reach me at 212-649-2348), so we can talk about the piece. I have the highest hopes for it, as well as for the exhibit of Linda McCartney's photographs we're organizing for mid-September. The First Lady's attendance at that event would be another important boost for breast-cancer awareness.

Have a fabulous Fourth, and many thanks for all your help.

Best,

Susan Bolotin

Susan Bolotin
Executive Editor

THE WHITE HOUSE
WASHINGTON

DOMESTIC POLICY COUNCIL

Date: 10/25

To: Chris / Deborah
Ruby
Barbara W

Telephone: Fax: 65357
66244

From: Heather Howard

Telephone: 456-7263 Fax: 456-2878

Subject:

Pages: _____ (Including this cover sheet)

Comments: I don't know if you saw
This letter from Fran Visco

SECOND FLOOR WEST WING ❖ WASHINGTON, DC 20502
TELEPHONE (202) 456-7263 ❖ FACSIMILE 456-2878

FLI: Breast Cancer

NBCC
NATIONAL BREAST CANCER COALITION
« grassroots advocacy in action »

October 25, 2000

The Honorable William Jefferson Clinton
The White House
Washington, DC 20500

Dear Mr. President:

On behalf of the National Breast Cancer Coalition (NBCC) and the more than 2.6 million women living with this disease, I want to thank you for signing the Breast and Cervical Cancer Treatment Act into law yesterday. We are extremely grateful for the Administration's outstanding leadership in enacting this lifesaving bill.

Throughout your Presidency, the National Breast Cancer Coalition has valued the incredible partnership we have had with this Administration in working to eradicate breast cancer. Your understanding about the critical need to establish a treatment component to the Centers for Disease Control and Prevention's Breast and Cervical Cancer Early Detection Program is just one example of your commitment to moving substantive breast cancer policy forward. Your support for the Breast and Cervical Cancer Treatment Act ensures that low-income women screened and diagnosed through this federal screening program will no longer have to scramble for treatment in the fragile and deteriorating system of charity care that currently exists.

This Administration has understood that screening must be coupled with treatment to reduce mortality from breast and cervical cancer. We are grateful for your leadership on this issue, and for the thousands of lives that will be saved as a result of this bill's passage.

Sincerely,

Frances Visco

Fran Visco
President