REVIEW ARTICLE

MEDICAL PROGRESS

BREAST CANCER

(Third of Three Parts)

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ADJUVANT THERAPY OF BREAST CANCER

The demonstration that adjuvant systemic therapy (i.e., systemic therapy given at the time of primary local treatment in the absence of demonstrated metastases) can prolong the disease-free interval and improve overall survival has been a major advance in the management of breast cancer. Randomized clinical trials of systemic adjuvant therapy were pioneered by the Istituto Nazionale per lo Studio e la Cura dei Tumori[176] and the National Surgical Adjuvant Breast and Bowel Project[177] and provided the first evidence of the benefit of cytotoxic chemotherapy in women with involvement of axillary lymph nodes, particularly younger women. The Nolvadex Adjuvant Trial Organization[178] and Scottish trials[179] demonstrated a similar benefit for the anti-estrogen tamoxifen in older women. These early studies fostered a large number of national and international multi-institutional cooperative clinical trials. Most of these trials have had relatively simple designs, comparing multidrug regimens (often cyclophosphamide, methotrexate, and fluorouracil with or without other drugs) with no treatment or comparing tamoxifen with placebo. In addition, there have been numerous trials testing the value of combining tamoxifen and chemotherapy.

On the basis of available information, discussed in detail below, a number of general conclusions regarding the effects of adjuvant systemic therapy appear reasonable. The effect on the disease-free interval has generally been larger than the effect on overall survival. The effect of polychemotherapy has been larger than the effect of monochemotherapy. Polychemotherapy has a greater effect in premenopausal patients, and tamoxifen has a greater effect in postmenopausal women. The administration of full doses of chemotherapy is associated with improved results. Chemotherapy lasting more than six months has not generally been associated with greater benefit, whereas several years of tamoxifen therapy have provided more advantages than a single year of use. No reproducible evidence supports a favorable role for any nonspecific immune adjuvant. No consistent evidence supports the addition of tamoxifen to chemotherapy in younger women; in older women, there is some inconsistent evidence that the addition of chemotherapy to tamoxifen results in improved overall survival. The benefit of tamoxifen is greater in patients with estrogen-receptor–positive tumors than in those with estrogen-receptor–negative tumors.

The demonstrated benefit of adjuvant systemic therapy has prompted intense interest in identifying clinical and laboratory factors that can be used to select patients who do not need further therapy because their prognosis is so favorable ("prognostic" factors). In addition, there is interest in identifying factors for use in selecting patients who are likely to respond to a particular form of adjuvant systemic therapy ("predictive" or "responsive" factors). As noted above, the presence and extent of axillary-node metastases is the best-established prognostic factor.[132,133] The following are of prognostic importance in specific series of patients: the status of estrogen and progesterone receptors[180]; the growth rate, measured by flow-cytometric determinations of the S-phase fraction[181]; DNA ploidy[182]; the occurrence of oncogene amplification or overexpression of the epidermal growth-factor receptor[183] or *erbB2* (*HER2* or *neu*)[184]; the extent of cell-surface proteolysis, determined by measuring cathepsin D[185]; the amount of urinary plasminogen activator[186]; or histologic features, such as the histologic or nuclear grade.[187,188] Some of these prognostic variables may also be specific predictors of the response to therapy. For example, the work of Silvestrini et al.[189] suggests that adjuvant chemotherapy is of far more value in patients without involvement of lymph nodes whose tumors have a high S-phase fraction than in those with a low S-phase fraction. Estrogen-receptor status is known to be an important predictive factor for endocrine therapy. Other newer, promising prognostic factors, such as heat-shock proteins,[190] nm23,[191] collagenase type IV,[192] and *erbB3*,[193] will require more study. In addition, there is evidence to suggest that the presence of micrometastases in bone marrow detected by monoclonal antibodies[194] and the presence of new blood vessels in the vicinity of the tumor detected by factor VIII immunohistochemical staining[195] may be useful in assessing prognosis. Unfortunately, the studies to date have been too small to evaluate all these prognostic variables simultaneously, leaving clinicians and patients confused about the

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tests on which they should rely. Ideally, a measurable product of cancer cells that is shed in blood or urine would permit objective assessment of residual microscopic tumor deposits and simplify decisions about adjuvant therapy.

Because the overall effects of most individual trials, particularly on survival, have been small and because of the great interest in analyses of subgroups (classified, for example, according to menopausal status and nodal status), relatively large numbers of patients are required to observe small but clinically important effects. This has led to the use of a combined analysis, or meta-analysis, of all breast-cancer trials. This effort, organized by the Early Breast Cancer Trialists' Collaborative Group,[196] is based on a worldwide collaboration involving 133 randomized trials with 31,000 recurrences of disease and 24,000 deaths among 75,000 women. Table 4 lists the reduction in the annual odds of either recurrence or death after treatment, as compared with the annual odds for the control group, as a function of therapy and age, as determined by the most recent meta-analysis.[196] This reduction is an approximation of the relative decrease in the rate of recurrence or death in the treated group as compared with the control group. The absolute benefit of adjuvant therapy will depend on the patient's risk of dying from the disease. For example, if adjuvant therapy reduces the relative risk of death by 30 percent, then the absolute benefit (the additional percentage of patients alive at 10 years) will be about 4 percent for patients with stage 1 disease and good prognostic factors, who have a 10 to 20 percent risk of death from breast cancer; 8 percent for patients with stage 1 disease and poor prognostic factors, who have a 20 to 40 percent risk of death; and 12 percent for patients with stage 2 disease, who have a 40 to 80 percent risk of death. If adjuvant therapy reduces the relative risk by 15 percent, the corresponding absolute benefit will be half as great. In the recent meta-analysis,[196] there was a small but statistically significant gain in overall survival among older women who received chemotherapy.

Although meta-analyses can detect small benefits of treatment, they usually do not identify differences between trials in such variables as dose intensity, drug sequencing and selection, or population differences that may be important in the outcome. In addition, the large statistical power of these analyses should not obscure the fact that on an absolute scale, the survival benefits of these therapies are small. These small effects may, however, be important from a population point of view in that the collective benefit may accrue to many thousands of patients with this common disease.

Table 4. Percent Reduction in the Annual Odds of Either Recurrence of Breast Cancer or Death from Any Cause as a Function of the Type of Therapy and Age.*

Type of Therapy	Comparison Group	Recurrence		Death	
		<50 yr of age	≥50 yr of age	<50 yr of age	≥50 yr of age
Polychemotherapy	No chemotherapy	36±5	24±3	24±5	13±4
Tamoxifen therapy	No tamoxifen therapy	12±4	29±2	6±5	20±2

*Data are from the Early Breast Cancer Trialists' Collaborative Group.[196] Plus–minus values are means ±SD.

The short-term toxic effects of chemotherapy used in the adjuvant setting are generally well tolerated. Most patients are able to maintain a reasonable quality of life during treatment. Newer antiemetics and more supportive environments as well as the trend toward shorter treatment periods have improved patients' tolerance. Nonetheless, alopecia, weight gain, and fatigue remain the most burdensome toxic effects for most patients. Febrile neutropenia is uncommon, and life-threatening hemorrhagic complications are even less common. Longer-term toxic effects are also of substantial concern. Some patients, particularly those who are 40 years of age or older, experience premature menopause, with its resulting symptoms and loss of fertility. An increase in the long-term risk of cardiovascular disease and osteoporosis in patients with premature menopause has not been demonstrated, but is likely. Induced leukemias are rare, except with regimens including high cumulative doses of melphalan. A recent study estimated that about 5 of 10,000 patients treated for six months with a cyclophosphamide-based regimen might be expected to have leukemia within 10 years of the diagnosis of breast cancer. This risk is increased by the addition of radiation to the chest wall and regional lymph nodes.[197] The rates of other types of cancer have not been found to be increased. Cardiomyopathy induced by doxorubicin is a devastating result, but occurs less than 1 percent of the time in women whose total dose is less than 320 mg per square meter of body-surface area.[198]

There has been renewed interest in the use of ovarian ablation as a form of systemic adjuvant therapy in premenopausal women on the basis of a meta-analysis showing a reduction in annual mortality of 25 percent.[196] The size of this reduction is similar to that seen in younger women using polychemotherapy, according to an indirect comparison of the results of meta-analysis. These data again raise the possibility that some of the benefit of cytotoxic chemotherapy in younger women may be attributable to endocrine effects on ovarian follicles. Trials are currently under way to assess the relative contributions of direct cytotoxicity and hormonal manipulation associated with adjuvant chemotherapy.

One of the most controversial aspects of the use of adjuvant therapy is its role in patients whose axillary nodes are free of metastases. The rate of recurrence in these patients is approximately 10 to 40 percent, and a series of recent trials has established that adjuvant therapy is of value for at least some of these women.[199-202] Tamoxifen is increasingly being used among older women with tumors that are estrogen-receptor positive, because the relative improvement in the dis-

ease-free interval and overall survival is approximately equal in patients with node-negative cancer and those with node-positive cancer. In addition, this agent is relatively nontoxic, and there is evidence that tamoxifen may have beneficial effects on bone density[203] and blood lipid levels.[204] It also appears to reduce the risk of contralateral breast cancers.[205] For many physicians and patients, this information justifies its use even in patients at low risk of relapse.

Guidelines for the use of adjuvant chemotherapy in patients with node-negative cancer have not been established. Most oncologists would agree about which patients with node-negative cancer would be placed in the subgroup with a very good prognosis and which ones would be placed in the subgroup with a very poor prognosis. For example, patients with tumors measuring less than 1 cm in diameter, who have an average relapse rate at 10 years of about 10 percent,[206] would often not be treated. Patients with tumors that are larger than 3 cm, particularly ones associated with another unfavorable prognostic factor (e.g., lack of estrogen receptor, poor nuclear grade, high S-phase fraction), clearly have a sufficiently high risk of recurrence to be offered adjuvant therapy. The use of systemic treatment in patients with node-negative cancer whose prognoses fall somewhere between these extremes is more controversial. In current practice, the patient's age is often an important factor in choosing adjuvant chemotherapy. Younger women with tumors that exceed 1 cm in diameter are typically offered treatment with adjuvant chemotherapy.

A major area of clinical investigation is the use of more intensive chemotherapy regimens as adjuvant therapy. Since bone marrow is the dose-limiting tissue for most chemotherapeutic agents, more intensive chemotherapy regimens followed by transplantation of autologous bone marrow have recently been developed. Trials to define the specific usefulness of autologous bone marrow transplantation in conjunction with high-dose chemotherapy appear justified given the encouraging results of this approach in advanced disease.[207,208] In patients with previously treated recurrent metastatic disease, autologous bone marrow transplantation has induced objective response rates of 50 to 80 percent, about one third of which have been complete.[209] A minority of patients with a complete response have remissions that last longer than a year. The toxicity of such treatment, however, is considerable, with most patients requiring a month of hospitalization and mortality rates of up to 15 percent. The use of autologous bone marrow transplantation in previously untreated patients and the addition of treatment with bone marrow growth factors have lowered the mortality rate. On the basis of these improvements, there has been a recent trend toward performing transplantation in patients with stage 4 disease after successful primary systemic induction therapy, in patients with stage 3 disease who have no evidence of disease, and in patients with stage 2 disease and a poor prognosis (those with 10 or more positive axillary nodes) after standard multidrug adjuvant regimens. Large controlled trials testing the value of this approach are under way.

The most important overall recommendation that can be made with respect to adjuvant chemotherapy is to encourage women to participate in clinical trials. Referring physicians should make every possible effort to help women find and enroll in such trials. Even if the next generation of trials is restricted to known agents, many critical questions will only be answered by well-designed clinical protocols. Among the most important issues currently under study are the role of dose intensity with and without cytokine support, the effect of the combined use of chemotherapy with various endocrine therapies, the role of preoperative chemotherapy, and the efficacy of therapy in relation to various prognostic and predictive factors.

Finally, a variety of new agents and approaches to drug modulation are showing promise in initial phase I and II clinical trials. Among the most exciting of the new agents is taxol, an antimicrotubule agent isolated from the bark of the western (Pacific) yew, which has shown substantial activity against breast cancer.[210] A series of new anthracyclines (the anthrapyrazoles)[211] and topoisomerase inhibitors (camptothecin derivatives) have also shown activity in early clinical trials. In addition, modulation of fluorouracil activity with leucovorin has produced responses even in patients in whom previous treatment with fluorouracil has been unsuccessful, and this approach is being investigated further.

Chemoprevention

Earlier in this article, we described the increasing incidence of breast cancer, summarized the available information regarding its associated risk factors, and indicated the difficulties in modifying these factors to reduce the incidence of the disease. On the basis of these considerations, there has been increasing interest in the development of "chemoprevention" or "chemosuppression" — that is, interventions directed at inhibiting neoplastic development through pharmacologic measures.

Two important agents being studied in research on breast-cancer chemoprevention are retinoids and tamoxifen. The term "retinoids" applies to vitamin A (retinol) and its isomers, derivatives, and synthetic analogues. Since retinoids are biologic regulators of orderly epithelial-cell development, they are potentially ideal agents for controlling abnormal epithelial proliferation, such as occurs in carcinogenesis. Retinoids can control cellular proliferation in vitro[212] and have reduced the incidence of mammary tumors in animal models.[213] The chief obstacle to the long-term use of retinoids for prevention is their toxicity; most accumulate in the liver and can cause hepatic failure. Recently, a relatively nontoxic retinoid (fenretinide) has been synthesized, and a long-term clinical trial evaluating

its role in the prevention of second primary breast cancers is in progress.[214]

Tamoxifen, as previously described, is useful as an adjuvant after the treatment of primary breast cancer, especially in postmenopausal women. In randomized trials of tamoxifen as an adjuvant treatment for breast cancer, women who received tamoxifen were also found to have a reduced incidence of contralateral primary breast carcinomas.[196,200,205,215] Tamoxifen has also been reported to reduce the incidence of both 7,12-dimethylbenzanthracene-induced[216] and spontaneously occurring[217] mammary carcinomas in rats. On the basis of these findings,[218,219] randomized trials have been started in several countries (including the United States) to evaluate the potential of tamoxifen for preventing breast cancer in high-risk women.

The association of early childbirth and menopause and a reduced risk of breast cancer suggests that pharmacologic hormonal interventions during the reproductive years should be considered. Although such an approach may seem radical, many women already use pharmacologic doses of sex hormones for years to prevent conception. The use of currently available oral contraceptives for five years reduces the incidence of endometrial and ovarian cancer by approximately half.[220] The possibility that some combination of sex hormones would produce similar benefits for breast cancer has been suggested by Pike et al. in the form of a gonadotropin-releasing–hormone agonist that would reversibly eliminate ovarian function.[221] By combining this agent with a low-dose estrogen and progestogen supplement to minimize bone loss and atherogenesis, these workers envision that the incidence of breast cancer could be reduced by 50 percent after 10 years of use. Another theoretical approach would be to use an oral contraceptive during the teenage years that would simulate pregnancy. Epidemiologic studies (reviewed earlier) and investigations in animals[75] suggest that this could potentially reduce the incidence of breast cancer.

The pursuit of effective chemopreventive agents for breast cancer will require unusually long and costly research commitments, but seems warranted because of the magnitude of the incidence of breast cancer and its unremitting increase.

Prophylactic Mastectomy

Some women have a high risk of breast cancer; however, prophylactic bilateral mastectomy is a drastic solution to this problem. Only very few women have a lifetime risk of breast cancer that exceeds 50 percent. In addition, it is useful to understand that a woman's risk of breast cancer over a more limited time span (e.g., from the age of 35 to the age of 70) or of dying of the disease may be considerably smaller than her lifetime risk of having the disease. There are currently no absolute indications for prophylactic bilateral mastectomy. This surgery is considered for a woman at very high risk for the development of breast cancer, particularly if the woman's breasts are difficult to evaluate by both physical examination and mammography and she has persistent disabling fears that she will have the disease.

In patients selected for prophylactic bilateral mastectomy, the optimal type of mastectomy is controversial. Some have advocated subcutaneous mastectomy with preservation of the nipple–areolar complex.[222] This procedure, however, does not remove all the breast tissue[223] and does not prevent the development of breast cancer.[224,225] The risk of breast cancer after this surgery has not been established, since follow-up in treated patients has not been complete. Because of these concerns, most surgeons prefer total mastectomy, with consideration of immediate or delayed reconstruction if prophylactic mastectomy is to be performed.

New Opportunities for Therapy Based on an Increased Biologic Understanding

Perhaps one of the most hopeful aspects of breast-cancer research is the possibility that an increased understanding of the biology of the disease will lead to earlier diagnosis, an improved ability to assess prognosis, and advances in therapy. One important element in this research involves the central role of steroid hormones in promoting the disease, as indicated by epidemiologic evidence (summarized earlier in this article) as well as experimental findings.[226] Much work has focused on identifying the products induced by these hormones that contribute to the development of the malignant phenotype characterized by mitogenesis, invasion, and metastasis. On the basis of this research, it now appears highly likely that a series of growth factors are responsible, at least in part, for the evolution of normal breast epithelium to breast cancer and that breast-cancer cells maintain their malignant phenotype as a result of the effects of these growth factors.[227,228] These factors include the insulin-like growth factors,[229] transforming growth factor-alpha,[230] epidermal growth factor,[231] transforming growth factor-beta,[232] mammastatin,[233] platelet-derived growth factor,[234] members of the fibroblast-growth-factor family,[235] and ligands for *erbB2*[236] and *erbB3*.[193] These growth factors can contribute to the progression to and maintenance of cancer growth through a number of mechanisms involving stimulation of epithelial cells or the surrounding cells in the stroma.

Therapies directed against these growth factors (ligands) and their receptors have been developed in vitro and in a variety of experimental breast-cancer systems. The assumption underlying these investigations is that there is sufficient specificity between tumors and their normal adult-cell counterparts to permit safe therapy directed against the cellular products of the cancer that contribute to the malignant phenotype. A variety of different strategies have been suggested (for a review, see Lippman[237]), including the use of the following: (1) high concentrations of exogenous normal growth factor, which binds to the cognate receptors and inhibits the growth of tumor cells; (2) monoclonal antibodies against an individual growth factor

to block its action; (3) monoclonal antibodies against an individual growth-factor receptor, either alone or conjugated with a variety of toxins, radionuclides, or drugs[238]; (4) growth-inhibiting factors to counteract the effects of growth factors; (5) growth-factor fragments to inhibit the effects of growth factors or such fragments combined with toxic moieties to target the latter to cancer cells; (6) agents, such as antisense oligodeoxynucleotides, which can be incorporated into the DNA of tumor cells to down-regulate the production of a growth factor or its receptor[239]; (7) soluble extracellular domains of growth-factor receptors to block the binding of growth factors to their receptors on cell surfaces; (8) agents capable of interacting with growth factors and inactivating them or blocking their access to growth-factor receptors (for example, suramin[240] and pentosan polysulfate sodium[241]); and (9) tyrosine kinase inhibitors to interfere with signal-transduction cascades after growth factor is bound to its receptor.[242] These various strategies are illustrated in Figure 4.

It may also be possible to base the treatment of breast cancer on the inhibition of angiogenesis. Neovascularization, or tumor-induced angiogenesis, is a mandatory component of tumor progression beyond 1 or 2 mm.[195,243] New agents derived from naturally occurring inhibitors of angiogenesis are now being assessed in clinical trials.[241]

In contrast with earlier chemotherapeutic agents, these newer therapeutic approaches have developed from studies of fundamental cellular and molecular biologic properties of breast cancer rather than empirical observations. Many of these approaches are not mutually exclusive, and it may also be possible to combine biologic therapies (e.g., blocking a specific growth-factor receptor while simultaneously attempting to lower biologically available concentrations of that growth factor).

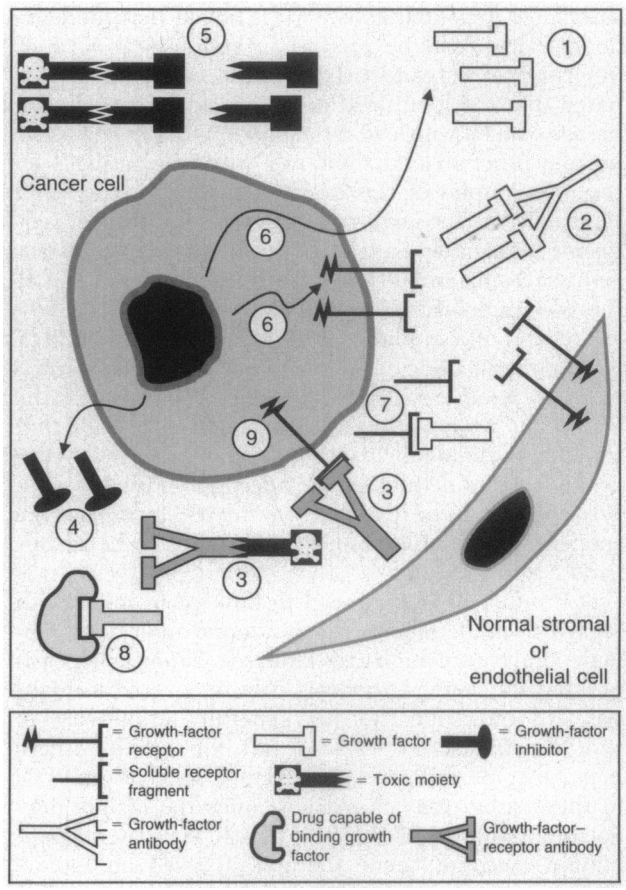

Figure 4. Potential Sites of Therapeutic Interventions in Pathways Mediated by Growth Factor.

The anti–growth-factor strategies involve the following: inhibition by high concentrations of ligand (1); antibodies against growth factor (2); antibodies against growth-factor receptor (alone or conjugated to toxins) (3); growth-inhibiting growth factors (4); growth-inhibiting fragments of growth factor (alone or conjugated to toxins) (5); inhibition of the synthesis of growth factor or its receptor (6); soluble extracellular domains that bind growth factor (7); drugs that sequester growth factors outside cells (8); and blockade of signal transduction (9).

DNA Mutations in Breast Cancer

Breast cancer, like other types of cancer that are better understood, probably results from a series of molecular genetic events involving the activation of oncogenes and the inactivation of tumor-suppressor genes. The progression from the proliferation of breast epithelium to a localized invasive tumor to metastatic disease probably depends on accumulated genetic alterations, but may also involve the failure of host mechanisms. It is not known, however, whether these events must occur in any particular order, nor do we know how many separate pathways involving different genetic events may eventually lead to the phenotype of breast cancer. For so-called sporadic breast cancer (the occurrence of the disease in a woman with no apparent family history of breast cancer), a variety of genetic changes have been described in the tumor tissue, although their pathogenetic importance has not been fully elucidated. These include amplification (i.e., an increase in the number of copies of a gene in the DNA), with or without overexpression, of the oncogenes *erbB*, *erbB*2, and *erbB*3 (amplification of one of these oncogenes occurs in about two thirds of cases)[193]; amplification, with or without overexpression, of the oncogenes of c-*myc* and H-*ras*[244,245]; amplification (generally without overexpression) of the oncogenes *hst* and *int*2[246]; overexpression of the tumor-suppressor gene p53 protein (apparently commonly associated with the loss of one allele and a point mutation of the other, leading to stabilization of the protein product)[247,248]; loss of Rb (the retinoblastoma tumor-suppressor gene); and loss of heterozygosity at numerous other chromosomal locations of unknown importance at this time. Other contributory genetic elements will undoubtedly be identified.

One important avenue for research is the study of high-risk kindreds. Studies of these kindreds can identify inherited genetic lesions associated with the development of the disease. It is now possible to perform linkage analysis of families with a history of breast cancer to identify the chromosomal location of these

associated genetic lesions.[249] It is hoped that these genetic lesions will be present in sporadic as well as inherited breast cancer. In addition, it may be anticipated that the identification of genes associated with breast cancer will lead to an understanding of their normal function and their role in oncogenesis. Two recent examples of this exciting approach have been reported. In the extremely rare Li–Fraumeni syndrome (associated with breast cancer as well as osteogenic sarcoma and other cancers), a point mutation of the p53 tumor-suppressor gene leading to the overexpression of a mutated form of the protein or inactivation of one allele of this gene has been demonstrated.[250] In another study, a chromosomal locus for the loss of heterozygosity (17q21) has been identified that is highly correlated with the appearance of breast cancer in a series of high-risk kindreds.[251] This locus on 17q is known to be distinct from the p53 locus, but the specific putative repressor gene remains to be identified.[252]

A number of things need to be kept in mind with regard to epidemiologic, genetic, and molecular biologic analyses of high-risk kindreds. First, it is possible that the genetic abnormalities uncovered in high-risk kindreds may not be generally applicable to sporadic disease.[253,254] As a result, for example, there may be some danger in restricting prevention trials to these subgroups of women, since the results may not be predictive of the outcome in the general population. Second, "gene therapies" based on repairing an identified defect do not appear close to clinical reality. Third, although the identification of specific genetic abnormalities will undoubtedly be of value in counseling and will improve the specificity of screening and the rate of early detection, it may also present new psychological, ethical, and legal problems.[255]

Conclusions

The incidence of breast cancer is increasing in the United States, and the factors responsible for this increase remain uncertain. In particular, risk factors whose modification would be culturally acceptable have not been established, although efforts to identify them continue. The mortality rate of breast cancer, in contrast to its incidence, has been stable, and this is most likely due to an improved ability to diagnose the disease in an early stage and to improvements in treatment. Nearly all women in the United States are at a substantial risk for the development of breast cancer. However, the majority of women in whom breast cancer is diagnosed will live out their lives without a recurrence of the disease. Randomized trials have clearly established the effectiveness of screening, breast-conserving treatment, and adjuvant systemic therapy. Screening, particularly with mammography, can detect very small breast cancers, and its use can reduce breast-cancer mortality by approximately 25 percent. Breast-conserving treatment, which provides important benefits related to body image and quality of life, is appropriate for the majority of patients and is associated with survival rates that are equal to those following mastectomy. Adjuvant systemic therapy, particularly chemotherapy in younger women and tamoxifen in older women, decreases the odds of dying within 10 years after diagnosis by approximately 20 to 25 percent. Although the benefits of these strategies demonstrate the substantial progress that has been made, they are, overall, small in relation to the magnitude of the problem of breast cancer. New strategies include prevention of the disease and the development of more specific treatments based on evolving knowledge of the biology of breast cancer. The development of effective chemoprevention, however, will be a long and costly process. Phase III clinical trials are under way to assess the value of retinoids and tamoxifen for the prevention (or suppression) of the disease. Phase I and II studies are under way to assess the potential of more specific treatments to inhibit growth factors important in maintaining the malignant phenotype. More long-term studies are needed to address this major public health problem.

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