"New Directions in Breast Cancer Research"

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Good morning Senator Specter and Members of the Subcommittee. I am Richard Klausner, M.D., Director of the National Cancer Institute (NCI). I am pleased to have this opportunity to speak with you today about breast cancer research.

Over the past two decades, intensive research sponsored by the NCI into all aspects of breast cancer has led to many important discoveries. We understand more than ever before how a healthy breast cell becomes cancerous, how breast cancer spreads, why some tumors are more aggressive than others, and why some women suffer more severely and are more likely to die of their disease. We are having increasing success in translating these discoveries into therapies that extend cancer-free survival and improve the quality of life for those continuing to live with the disease. Likewise, our discoveries are leading to more refined technologies for detecting and diagnosing breast cancer, better supportive care and improved outcomes for patients during and after treatment, and finally, we are getting closer to identifying effective strategies for preventing the disease altogether.

Though these advances have been significant and provide hope for the future, we still have far to go to remove the threat of breast cancer from women's lives. In 2001, it is estimated that 192,200 women will be diagnosed with breast cancer (another 1500 cases will occur in men), and 40,600 will die from breast cancer. It is the most common cancer among women in each of five major population groups (white, black, Asian and Pacific Islanders, American Indians and Alaska Natives, and Hispanics), and the second leading cause of cancer mortality for women in all major population groups with the exception of Hispanics, for whom it is ranked first.

The breast cancer incidence rate in women has increased substantially, going from 83 (per 100,000 women) in 1973 to 118 (per 100,000 women) in 1998. Analysis of more recent trends (1992-1998), indicate that incidence is increasing by slightly over 1% per year among white women and is relatively flat among black women. In contrast to incidence, breast cancer death rates have decreased by 3.4% per year since 1995,

including a significant decline in rates for white women and relatively stable rates for black women.

The increase in detection and diagnosis of breast cancer occurs for women of all ages but is greatest among those over 50 years of age, particularly women 50-64 years of age. Consistent with increasing utilization of mammography, the greatest increase in breast cancer incidence rates occurs in women diagnosed with early stage malignant disease as well as in women with premalignant tumors.

Risk and Prevention

Approximately one out of every eight American women will develop breast cancer in her lifetime. About half of the incidence can be explained on the basis of identified risk factors, including heritable gene mutations associated with breast cancer, and investigators continue to search for the elements of breast cancer causation and understand how they influence each other. Undoubtedly, changing childbearing practices are important, since studies have repeatedly shown large increases in risk among women who have remained childless or who have delayed childbirth until their later reproductive years. Breastfeeding may reduce risk, although probably not for the durations practiced by most American women. It is widely accepted that risk is increased among women who are heavier consumers of alcoholic beverages and who are overweight (this latter relationship being true only for postmenopausal breast cancer). Since both of these factors are modifiable, they are viewed as important means by which disease incidence could potentially be reduced.

A great deal of attention has focused on the role of exogenous hormones, given the widespread exposure of women to both oral contraceptives and menopausal hormones. For oral contraceptives, there appears to be a slight increase in risk for current users of the preparations, although risk dissipates five years after discontinuation. More concern relates to menopausal estrogen use, since long-term use (10+ years) appears to increase risk to a moderate extent. This risk may be even further increased if progestins are added to the regimen.

Other factors are under investigation, but the relationship of risk to most of these factors remains controversial. There has been great emphasis on identifying dietary means of reducing disease risk, although there is little consensus as to which constituents of diet might be important (enthusiasm over a potential role of dietary fat has been tempered by recent studies that have failed to show much evidence for an effect). The role of physical activity is also not clearly understood. Extensive attention has focused on understanding the role of environmental agents, including ones to which women have been increasingly exposed, although studies to date have provided inconsistent results.

Cancer susceptibility is a critical piece of the puzzle. We know that disruption of fundamental cellular processes contributes to the development and progression of the more common, non-hereditary forms of cancer. Even among individuals who have inherited cancer-predisposing genes, the risk of developing cancer appears to be modified

by other genetic and environmental factors. There is mounting evidence that a person's genetic make-up may influence susceptibility or even resistance to cancer-causing exposures. Opportunities now exist to determine how variations in these genes combine with environmental and other factors to induce cancer in the general population. There is great hope that controversies regarding many of the poorly understood risk factors may be resolved by assessing the interactions between genes and the environment.

Single mutations in major cancer-associated genes are thought to account for 5-10% of all breast cancer. Among the most important of these genes are BRCA 1 and BRCA 2 which are thought to account for nearly 80% of families with inherited predispositions to breast cancer. Women with these mutations are also at an increased risk for ovarian cancer. A variety of other much less common conditions caused by mutations in other genes contribute to an increased risk of breast and/or ovarian cancer in other families.

While these major breast cancer risk factor genes play an important role in determining who gets breast cancer in such families, not all who inherit such a mutation will get breast cancer. Though early studies suggested that the lifetime risk of breast cancer for those inheriting mutations in BRCA 1 and 2 might be as high as 80%, more recent studies suggest a much lower, though still quite elevated, risk in the range of 37-56% for breast cancer, and 16% for ovarian cancer. Whether these risks are the same for all of the more than 600 different identified mutations in BRCA 1 or more than 450 identified mutations in BRCA 2 is unknown. What is clear is that other modifier genes or environmental and lifestyle risk factors must play some important roles. In addition, current evidence suggests that the mechanisms that produce breast cancer linked to BRCA 1 & 2 mutations may differ in important ways from those that lead to other more common breast cancers. The evidence suggests that these genes have important roles in DNA repair and regulation of the cell cycle and therapeutic and preventive interventions should be tailored to these mechanisms in order to be effective.

The use of prophylactic surgery, such as mastectomy or oophorectomy, as a prevention method for high-risk mutation carriers has had extensive consideration and is sometimes offered to such women. However, the effectiveness of such treatment has been less clear. Recently, investigators sponsored by the NCI have produced significant evidence that such an approach can have real benefits. For instance, a 1999 study of women at high risk for breast cancer suggested a 90% reduction in risk of breast cancer after prophylactic mastectomy, and it has also been reported that BRCA 1 carriers who have bilateral prophylactic oophorectomy may have a reduction in breast cancer risk in the vicinity of 50%, even if they receive hormone replacement after surgery. Surgical approaches to prevention of cancer have significant adverse consequences and may not be acceptable to many women at-risk.

While tamoxifen has not been shown to reduce the risk of breast cancer specifically among high-risk mutation carriers, NCI's Breast Cancer Prevention Trial, including 13,000 women at increased risk for breast cancer, demonstrated that women taking the drug tamoxifen for an average of four years reduced their chance of developing breast cancer by 49 percent. Other health benefits were noted as well, but tamoxifen is not

without potential harm, particularly for postmenopausal women, who had an increased risk of developing life-threatening health problems: endometrial cancer, pulmonary embolism, and deep vein thrombosis.

It is now vital to find effective preventive agents that cause fewer or no side effects. For example, raloxifene has action similar to that of tamoxifen, and was originally studied in the treatment and prevention of osteoporosis. Scientists noted then that woman who took raloxifene developed fewer invasive breast cancers than those who were given placebo. Raloxifene is believed to have fewer side effects than tamoxifen; to date, studies have not shown an increased risk of endometrial cancer from the drug. NCI began the Study of Tamoxifen and Raloxifene (STAR) in 1999 to compare the two drugs. As of April 1, 2001, 9,359 postmenopausal women at high risk for developing breast cancer have joined STAR, which is seeking 22,000 women. Lessons learned from BCPT have improved outreach to minorities, and 500 minority women have joined STAR. This is more than five percent of the total number of women on the trial.

Both tamoxifen and raloxifene block estrogen receptors in breast tissue, dramatically reducing the development of breast tumors that exhibit estrogen receptors (ER+). But neither drug seems to affect estrogen receptor-negative (ER-) tumors, which are more prevalent in women under age 50, in black women, and in women at risk due to a mutation in their BRCA1 gene. About 20 percent to 30 percent of breast cancers are ER-. NCI is sponsoring new research to discover strategies for preventing ER- breast cancer. Preclinical studies using animal models are critical for identifying new agents to prevent cancer: creation of animal models of ER- breast cancer (using the Mouse Models for Human Cancer Consortium) allows the development of protocols aimed at finding specific and potent agents to prevent ER- breast cancer. Agents to be studied in clinical trials to prevent ER- breast cancers include kinase inhibitors, nonsteroid anti-inflammatory drugs such as COX-2 inhibitors, and retinoids.

Screening and Early Detection

Analysis of the data from the National Health Interview Surveys revealed that in the last decade, utilization trends for several cancer screening modalities, including mammography, Pap smears, fecal occult blood tests, sigmoidoscopy, and digital rectal examination, all increased. The most dramatic increase was seen in the use of mammography. Mammography was first monitored nationally in 1987, when less than thirty percent of all women 40 and older reported having a recent breast x-ray. Between 1987 and 1992, use of mammography almost doubled, and by 1998, 67 percent of women reported receiving mammography within the last two years. Utilization rates vary by age group. In 1998, 73 percent of women aged 50-64 reported recent mammography, while women in age groups 40-49 and those over age 65 received mammography at the rate of 63 percent.

For breast cancer screening, high-quality mammography, an X-ray technique to visualize the internal structure of the breast, is the most effective technology presently available. Randomized trials in women screened for breast cancer with conventional mammography

have shown reductions in mortality by 16% to 30%. We feel there is potential for improvement in the way screening is done. Problems with screen film conventional mammography include difficulty in detecting early lesions in women with dense breast tissue, false negatives with up to 10-20% of breast cancers detected by physical examination not being visible on screen-film, and false positives with only 5 - 40% of lesions detected by mammography being malignant on biopsy. The screen-film has limitations, based on the fact that film is the medium of imaging acquisition, storage, and display. Once the mammogram is obtained, the image cannot be altered or manipulated to obtain an improved view. These limitations pose a challenge for the technology developers to devise improved technologies for detection.

Digital mammography has potential advantages over conventional mammography, which include: improved detection and breast lesion characterization due to due to a more representative breast image; image acquisition and display are separated, and each component in this process can be optimized; image storage, transmission, and retrieval can be improved; and there is software to assist the radiologist in interpreting the images.

Over the past year, the NCI has been actively involved in facilitating the development of a rigorously designed trial with the American College of Radiology Imaging Network, four competing device manufacturers, the Center for Devices and Radiologic Health, Food and Drug Administration, and the Health Care Financing Administration (HCFA). The trial will start this summer, and will be conducted in women presenting for screening mammography at one of 20 participating sites. Approximately 49,500 women will be enrolled over 1.5 years and followed for an additional year. One fourth of the participants will be screened on each of the four digital mammography devices, and it is estimated that approximately 16% will be age 65 or older. Each woman will be screened with two mammograms - one will be a conventional screen-film, and the other will be a digital mammogram. Abnormalities on either screening test will be evaluated, and normal screens will be re-evaluated at one year with conventional mammograms.

The NCI continues to explore new ways to improve imaging methods for breast cancer screening. We are sponsoring research on non-X-ray based technologies such as magnetic resonance imaging (MRI), and breast-specific positron emission tomography (PET) to detect the disease. Scientists are also evaluating the use of several forms of non-ionizing radiation in the diagnosis of breast cancer. Promising areas of investigation include elastography, electrical impedence spectroscopy, and infrared spectroscopy. The possibility for the future of breast imaging is to use one or more of these technological approaches to enhance or even replace x-ray mammography as the screening study for breast cancer.

Molecular Approaches to Early Detection

As we understand more fully cancer's fundamental nature, our capacity to use a variety of tools to detect the molecular changes associated with a tumor cell promises to vastly improve our ability to detect and stage tumors, select treatments and monitor the effectiveness of a treatment, and determine progress. As the science advances, seeing

how the processes and pathways inside a cell change as the cell transforms from normal to cancerous will allow us to detect changes in people earlier, and eventually we expect to be able to visualize the actual molecular signatures of a cancer. We will be able to tell which genes are being expressed in a patient's cells, and we will be able to translate this information directly into better management of the disease.

The NCI is furthering early cancer detection by establishing a new national effort toward discovery and development of novel markers for all cancers: the Early Detection Research Network (EDRN). The objective of the EDRN is to develop and test molecular tools capable of detecting early cancer and assessing cancer risk. To do this, the EDRN is unveiling cellular anomalies of early cancers, known as a cell's signature, which are signposts of a cell's progression towards cancer. By harnessing the uniqueness of these molecular signatures, the EDRN is turning these signatures into molecular tools - biological markers for screening and detection efforts.

The EDRN was specifically formed to address the unique testing strategies required for early cancer or risk assessment biomarkers. Because of low tumor burden in individuals with early stages of cancer or at risk for developing cancer, the testing strategy for these biomarkers is necessarily stringent. Not only does the biomarker need to be clinically adaptable, it must be highly sensitive and specific, be capable of identifying few abnormal cells among billions of normal cells, and be available for minimally-invasive testing if it is to be used for screening. To help address the specific testing requirements of early cancer and risk biomarkers, the EDRN distributes cancer researchers into separate, yet coordinated, development, validation, and clinical laboratories.

The EDRN 's approach to biomarker research is also novel because it encourages leading cancer researchers to focus their research on highly prevalent cancers, like breast cancer. Of the 31 centers in the EDRN, nine are developing biomarkers to identify early breast cancer or an individual's risk of developing breast cancer. This comprehensive, collaborative approach to breast cancer research merges genetic pursuits with protein approaches, providing a systematic view of how the molecular signatures of breast cancer can be used as a unique, identifying mark.

Genetic approaches to breast cancer detection and risk assessment are currently underway in five EDRN developmental and clinical laboratories. Research encompasses biomarker discovery strategies, such as examining the patterns of active genes, known as gene expression, by comparing genes expressed in normal cells with cancerous or precancerous breast cells. Additionally, several laboratories are examining the gain, change, or loss of genetic material. Some studies involve genes whose levels are abnormally elevated in breast cancer, like BRCA-1 and Ki-ras oncogenes, and the p53 tumor suppressor gene. Others focus on genes that are inactivated by genetic changes, like the DNA repair gene XPD, and promising research of genetic loss on chromosome 4 in high-risk populations is underway. Hereditary studies are also proceeding to amass detailed information and biological samples from breast cancer prone families.

Complementary to gene-based research, protein-based efforts provide a view of how genetic gains, changes, and losses affect the proteins arising from such altered genes. State-of-the-art protein biomarker research for breast cancer is underway in four developmental and validation laboratories. Similar to gene expression pattern research, protein patterns are being explored in three developmental laboratories. In one laboratory, breast nipple fluid protein patterns are compared between normal and abnormal breast tissues.

Nipple aspirate fluid (NAF) is a substance that circulates in the breast ducts, the very structures where breast cancer originates. Because proteins associated with the biology of the breast are secreted into this fluid, examination of the fluid should provide a "snapshot" of the breast environment. The fluid can be extracted using a method similar to a breast milk pump, which is non-invasive and easily performed. The first goal of this research is to identify a protein signature in breast tumor tissue, then see if this signature can be reliably detected in NAF. Using the Surface-Enhanced Laser Diffraction Ionization (SELDI) Time-Of-Flight (TOF), with as little as one drop of NAF, investigators have demonstrated that different protein peaks could be identified in the samples from the cancerous breast compared to the normal breast in the same woman. Further studies are in progress to determine the validity of this approach with a large number of specimens.

A Revolution in Diagnosis

Future attempts to advance our understanding of the etiology of breast cancer will undoubtedly require a better understanding of the natural history of this complex and multifactorial disease. It will be important to consider breast cancer not as one disease but as a collection of possibly heterogeneous diseases. A number of biomarkers should be useful in advancing thinking regarding breast cancer. Efforts are underway to distinctly classify tumors by a variety of parameters, including hormone receptor status, histologic patterns, and presence of oncogenes. This approach challenges conventional thinking, but it conveys the opportunity to target common precursor cells as well as divergent targets later in the developmental pathway.

The most pressing diagnostic challenges for breast cancer relate to directing therapeutic choices. Earlier detection of breast cancer is resulting in a shift to smaller tumors, and in over 50% of cases, there is no apparent spread to the axillary lymph nodes. Clinical practice guidelines suggest that all breast cancer patients be considered for some sort of adjuvant therapy, often involving toxic chemotherapy regimens. About 70% of lymph node-negative patients will actually be cured by definitive surgery plus local/regional radiotherapy. We do not know how to separate, with sufficient certainty, the patients with a high risk for recurrence from those in whom their cancer will not recur.

When patients have metastatic disease, either at the time of their initial diagnosis or at the time of recurrence, choices must be made about which therapeutic regimens will be most effective. As new, targeted therapies, such as Herceptin, are developed, it is important to be able to identify the patients most likely to benefit.

Both the decisions regarding which patients should be treated and the choice of treatment require greater understanding of the underlying biology of breast cancer and of the specific lesion present in the patient. New comprehensive molecular technologies are allowing researchers to look at the full spectrum of alterations that have taken place in the formation of a given tumor. The NCI initiative "Director's Challenge: Toward a Molecular Classification of Tumors" is funding investigators to develop profiles of molecular alterations in human tumors using DNA, RNA, or protein-based comprehensive analysis technologies. These "molecular signatures" are intended to redefine tumor classification, moving from morphology-based to molecular-based classification schemes. Tumor classification, based on morphology, or the tumor's structure, does not always accurately predict the patient's clinical behavior. Molecular profiles are expected to provide more informative molecular classification schemes for human cancers by identifying clinically important tumor subsets within morphological classes. The goal of the Director's Challenge projects is to have these new molecular classification schemes developed and ready for clinical validation by the end of the initial five-year funding period.

A group of Director's Challenge investigators has developed molecular profiles that identify subsets of node negative breast cancer patients. Tumors in one subset appear to arise from luminal cells in breast glands. Tumors in the second subset appear to arise from basal cells. Patients with basal cell tumors appear to have a significantly worse outcome and may represent those node negative breast cancer patients at greater risk for recurrence. Studies are underway to confirm and extend these initial findings. Another group that was just funded under the Director's Challenge initiative is attempting to use a different comprehensive analysis technique to characterize early breast cancer lesions.

Other research teams are working on development of robust techniques for analysis and detection of alterations in tumors. It is likely that patients who do not appear to have involvement of their regional lymph nodes but later have a recurrence of breast cancer have, in fact, released cells from the primary tumor site. A number of investigators are assessing methods for detecting residual disease and evaluating the clinical significance of their findings. The NCI will be holding a meeting in the autumn of 2001 to assess the state of the science of detecting minimal disease and to determine what the research agenda should be.

Development of tests to identify patients who will respond to particular therapies or classes of drugs requires considerable coordination and generally large numbers of patients or specimens from patients. The NCI has just launched a new effort, the Program for the Assessment of Clinical Cancer Tests (PACCT), to ensure the translation of new knowledge about cancer and new technologies to clinical practice. The initial focus of PACCT is on breast and colon cancer. As part of the effort to evaluate new markers and to validate the utility of some known markers/tests, the NCI is putting together reference sets of specimens. These specimens will be made available to academic and industry researchers to facilitate the development process. The PACCT is also developing criteria to help determine the data that are needed to move a marker test forward to clinical practice.

NCI is accelerating discovery and development of imaging methods that use new technologies to identify biological and molecular properties of precancerous and cancerous cells in order to predict clinical course and response to interventions.

Scientists are studying women with estrogen receptor-positive (ER+) breast cancer before and just after initiation of tamoxifen therapy using PET, enhanced by the administration of a chemical agent that indicates estrogen receptor status, to evaluate whether this technique can be used to predict responsiveness to hormone therapy in this group of patients. Others are developing novel radiolabeled estrogen receptor binding molecules as potential tools for imaging and possible therapeutic applications. NCI-sponsored researchers are identifying a number of other molecules that can be conveniently labeled for imaging studies to target and characterize multi-drug resistance factors in tumors as well as other tumor-specific features.

New Strategies for Treatment

The convergence of scientific advances in the areas of cancer biology, synthetic and biosynthetic chemistry, and high throughput screening has resulted in the potential to exploit molecular targets for cancer treatment and the opportunity to revolutionize cancer drug discovery. We are developing a whole new generation of cancer treatments: "smart" drugs that target the molecular features characteristic of a particular type of cancer. Even within cancers, like breast cancer, that have been historically classified only on the basis of tumor site, we now know that significant heterogeneity exists in terms of molecular profile. For example, about 35% of breast cancers display higher than normal numbers of receptors for epidermal growth factor, whereas only 5% overexpress a protein called MDM-2. As many as 75% of breast cancers may have altered function of the p53 protein. Since in reality, multiple forms of breast cancer exist, the truly effective therapies of the future will be tailored to the molecular characteristics of the tumor being treated.

Every point of difference between premalignant or malignant cells and their normal counterparts is a potential target of opportunity for drug discovery. Targets may be revealed by understanding the consequences of fundamental molecular changes in cancer, such as those that spur blood vessel growth to nourish tumors or the means by which tumors spread by invading surrounding tissue and migrating from their site of origin. For breast cancer, more than 75 potential targets, representing over a dozen classes of targets, have already been identified. NCI is involved in testing over 50 new agents directed at these targets, and many others are being tested within the private sector. Scientists report new findings in cancer cell biology every day, giving us new targets to explore. The opportunities for discovery in this area are boundless.

As the most promising treatment strategies emerge from developmental testing, they progress to evaluation in clinical trials, the final crucial step in translating new discoveries into effective therapies for patients. In September 2000, the Early Breast Cancer Trialists' Collaborative Group, a world-wide collaboration of scientists studying breast cancer, reported that 5 years of tamoxifen therapy reduces the absolute death rate from breast cancer by 9% in women with hormone-sensitive cancers followed for as long

as 15 years after the start of treatment. A majority of the patients that form the database for this international overview participated via NCI-sponsored tamoxifen studies. These long-term survival results prove the principle that targeting a specific biologic feature of the breast tumor cell, the estrogen receptor in the case of tamoxifen, can lead to improved outcomes. Furthermore, development of this targeted treatment demonstrates a prime example of the incremental manner in which successive clinical trials can result in important improvement in outcomes. The approach tests new agents initially in advanced disease and then moves the successful agents into earlier stage treatment aimed at improving survival.

An even more recent example of this targeted therapeutic approach is presented by the agent Herceptin. Recently approved by the FDA for treatment of advanced breast cancer, Herceptin is a recombinant antibody that targets a specific receptor on the breast cancer cell membrane. This agent has been shown to improve survival by an average of 5 months in women with advanced cancer whose tumors express this receptor. Two definitive studies sponsored by NCI are now underway to test whether this agent will improve survival even more markedly in women with earlier stage disease. It is plausible that Herceptin might follow the same path as tamoxifen and be useful for prevention of breast cancer, especially in the case of the hormone-insensitive variety that doesn't respond to tamoxifen. We still have much to learn about the optimal use of Herceptin and are actively studying ways to combine it with other active drugs without enhancing side effects. The NCI is sponsoring ten trials currently with this agent, while Genentech, the maker of Herceptin, is sponsoring five trials, and there are 35 investigator-sponsored trials worldwide.

Based upon discoveries in the research lab, there is a plethora of breast cancer targets with active agents under development. Among the leading candidates that NCI is studying in clinical trials in advanced breast cancer at present is an agent that interferes with a prime growth pathway for breast cancer cells, the epidermal growth factor pathway. Phase II studies combining the agent with Herceptin and with chemotherapy will begin shortly. A humanized monoclonal antibody that interferes with the development of tumor blood supply (angiogenesis) by blocking vascular endothelial growth factor is also under investigation. A phase III study testing this agent in combination with standard chemotherapy has recently been approved by NCI. Another phase III trial is testing an inhibitor of an enzyme (matrix metallo-proteinase) that destroys the supporting tissue around tumors, administered after conventional chemotherapy in patients with advanced disease. Still another example of a promising new therapy under evaluation is one of the first selective estrogen receptor degradation (SERDS) agents. Early work has shown activity in patients whose tumors are resistant to tamoxifen and a large trial is planned by NCI to test this agent in early stage disease.

Clinical trials for breast cancer treatment have demonstrated remarkable success and are a vital component of the NCI's research program. Currently our clinical trials database contains descriptions of over 165 treatment trials for breast cancer, including 103 NCI-sponsored trials. Of these, 81 are Phase I and/or Phase II studies in which novel approaches to treating breast cancer are tested for safety and efficacy, and 22 are Phase

III trials representing interventions that are closest to general medical practice. The NCI Clinical Trials Cooperative Group program performs definitive, large-scale trials to determine whether new treatments actually improve upon results seen with current standard approaches. Presently, several new promising treatments are being evaluated in Phase II and III Cooperative Group trials. For breast cancer treatment, this effort is the largest single therapeutics development effort in the world.

While we are working steadily to find new and improved cancer therapies for breast cancer, we must be certain that the research results of our trials are communicated effectively to physicians and patients around the country. In November 2000, the NCI sponsored a Consensus Development Conference on Adjuvant Therapy For Breast Cancer that addressed major questions confronting physicians and their patients once a diagnosis of regionally advanced breast cancer has been made. An independent, non-governmental panel of breast cancer experts reviewed the results of clinical trials, and summarized what we have learned about breast cancer treatment and discussed promising research directions. Recommendations from this conference were widely disseminated in both the lay and professional media.

It is imperative that the questions we ask in breast cancer treatment studies reflect the needs of real people who are coping with breast cancer. The NCI has developed a new way to describe breast cancer as a series of clinical states that represent decision points confronted by patients and physicians. Each of the clinical states is characterized by tumor features and degree of disease progression, and lends itself to a tailored management plan based on its collection of defining traits. A woman who is faced with a diagnosis of breast cancer today has choices. As she consults with her physician she will learn about specific aspects of her own disease - the type of tumor she has, the number of affected lymph nodes, the presence or absence of estrogen receptors and tumor-specific antigens, and whether or not the disease has spread to other organs. She and her physician can make informed decisions about which treatments have potential benefits and which treatments have risks that outweigh their benefits in her particular case. And our clinical trials portfolio can be organized to correspond to the clinical states of breast cancer so we can ensure that our research is relevant and comprehensive.

Survivorship

Although cancer remains among the worst fears of Americans, it is becoming increasingly clear that cancer is not the "death sentence" it once was. More than 7 million Americans alive today have a history of cancer. The past ten years have seen an explosion of effective, well-tolerated treatments for cancer. Researchers continue to develop interventions that will help ameliorate the worst side effects of the treatment, and measurement of a patient's quality of life now is included routinely as a component of most NCI-supported clinical trials.

In one of the largest follow-up studies conducted to date, NCI funded researchers surveyed the quality of life of almost two thousand breast cancer survivors, looking at the woman's physical, social, emotional and sexual functioning post-cancer treatment.

Results of this study confirmed earlier findings that while most breast cancer survivors continue to do well, women who receive adjuvant treatment experience poorer functioning long term. Fatigue, though not a significant problem for the majority of breast cancer survivors in this study, was closely linked with depression, bodily pain and sleep disturbance in those who did report fatigue. Lymphedema subsequent to surgery was found to be more of a problem than previously acknowledged clinically. Problems with arm swelling were reported by 46 percent of women undergoing mastectomy alone, 24 percent of women with lumpectomy and 26 percent of women with mastectomy plus reconstruction.

A descriptive profile of the demographic, clinical, and survival characteristics of breast cancer survivors diagnosed over a 24-year period in nine SEER areas in the U.S. was developed by NCI. An improvement in the relative survival by decade of diagnosis was confirmed, and additional analysis was done to compare married and unmarried survivors. Findings indicated improved survival rates for married survivors for each decade, reflecting the possible role of social support or economic advantage in better outcomes.

There are deficits in memory and concentration associated with breast cancer treatment. NCI funded a study to look at breast cancer survivor's intellectual ability, quality of life, and normal activities and roles following breast cancer treatment. Breast cancer survivors treated with systemic chemotherapy in addition to standard local treatment, were compared with age-matched breast cancer survivors who had received local treatment alone. Results of the study showed significant differences across a variety of neuropsychological tests between the two groups.

As more cancer patients are successfully treated, we must learn more from the experiences of long-term cancer survivors. The NCI will continue to support research covering the entire spectrum of challenges facing cancer survivors as this need continues to rise.

Conclusion

Last year, NCI invested $439 million in breast cancer research, including $3.5 million in proceeds from the sale of the breast cancer semi-postal stamp. We expect this to grow to $464 million in 2001 and $510 million in 2002 in accordance with the President's 2002 budget request for NCI as part of the National Institutes of Health. Illustrating our commitment to accelerate progress against breast cancer, the NCI convened a Progress Review Group (PRG) in 1998 to conduct an intensive review of our research portfolio in breast cancer. This initiative, the first of a highly beneficial series of PRG's fitting within NCI's new disease-specific planning framework, featured expert panels who provided a comprehensive view of the state of our current knowledge, and many of our research priorities reflect their recommendations. We have learned the value of including as broad a constituency as possible in our review, advisory, and planning activities, and we have forged new relationships with patients, practitioners, scientists in different fields of research and medicine, other government agencies, private sector companies, innovators

in technology, and many other partners where such alliances were rare or non-existent only a few years ago.

We are making progress against breast cancer. The diligence of all the people of the breast cancer community is fulfilling the long awaited promise of science. We have reached an exciting point where we have a molecular window on cancer and our new strategy of looking at all aspects of breast cancer from a molecular point of view is bearing fruit. The pace of discovery is rapid. Our challenge is to translate this new knowledge into useful and effective screening, preventive, diagnostic, and treatment tools as quickly as possible to ease the suffering caused by breast cancer and relieve families of this terrible burden.

Thank you, Mr. Chairman, for inviting me to appear before the Committee today and to share with you the progress we have made against breast cancer. I will be pleased to answer any questions the Committee may have.