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# Charting the Course: Priorities for Breast Cancer Research

Report of the Breast Cancer  
Progress Review Group

*August 1998*

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## **From the Chairpersons:**

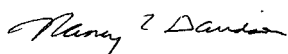
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More than one year ago, the Breast Cancer Progress Review Group (BC-PRG), comprised of basic and clinical researchers from academia, industry, and government, and representatives of the patient advocacy community, accepted the charge of the National Cancer Institute (NCI) to develop a national plan for the next decade of breast cancer research. In carrying out this charge, the BC-PRG assessed the status of basic, translational, and clinical breast cancer research, employing the broad expertise of its members, input from the scientific community, and a comprehensive report on the NCI's breast cancer research portfolio. Based on this assessment, the PRG identified and prioritized the scientific research opportunities and needs that must be addressed to continue and accelerate progress in treating breast cancer, and ultimately, to prevent this disease. The BC-PRG's recommendations related to these identified opportunities and needs, provide, we believe, a blueprint for addressing the crucial questions that must be answered to eliminate the threat of breast cancer.

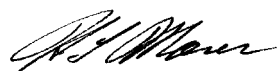
Therefore, on behalf of the Breast Cancer Progress Review Group, we are pleased to submit the attached report to the Advisory Committee to the Director of the NCI. It is our hope that these recommendations, reflecting the extensive and diligent work of the members, will prove to be valuable in our shared quest to further reduce the toll of human suffering and death due to breast cancer.

We look forward to discussing our findings with you and the leadership of the National Cancer Institute.

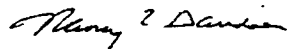
Respectfully,



Nancy Davidson, M.D.  
Co-Chairperson  
Breast Cancer Progress Review Group



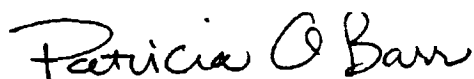
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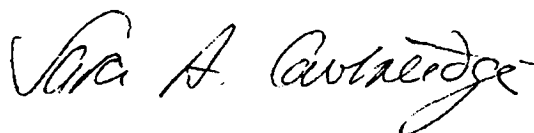
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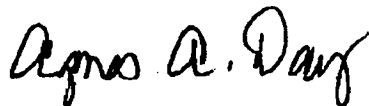
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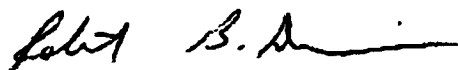
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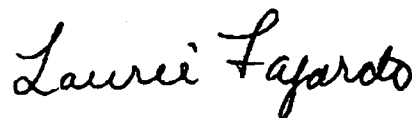
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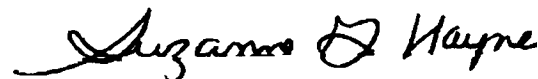
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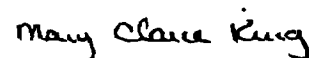
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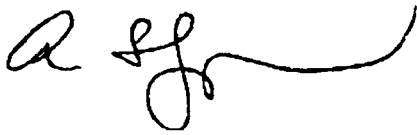
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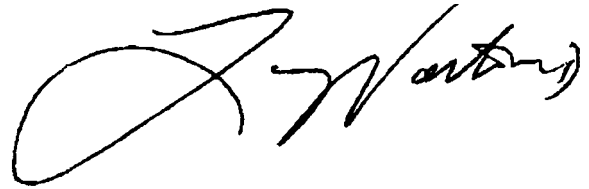
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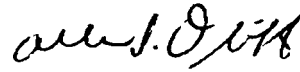
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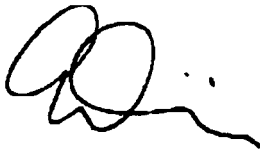
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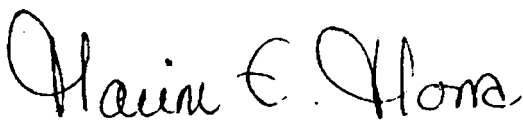
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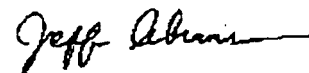
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## **Acknowledgements**

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The work of the Breast Cancer Progress Review Group (BC-PRG) that led to this report involved nearly a year's worth of deliberations, meetings, and conference calls. Dr. Jeff Abrams served as the Executive Director of the BC-PRG and the NCI Task Force. His expertise and experience in the field of breast cancer research, along with his adeptness in working with the diverse interests of both groups, made him indispensable to the process.

Coordination of this major effort was assured by the dedicated staff of NCI's Office of Science Planning and Assessment (OSPA) in the Office of Science Policy. Leading the OSPA team was Anna Levy, whose managerial skills and broad-based scientific understanding helped the Group to overcome the many obstacles posed by multi-disciplinary collaboration. She was ably assisted by Susan Rossi, Jason Nichols, Grace Ault, Marilyn Duncan, and Annabelle Uy. Cherie Nichols, the Assistant Director of OSPA, merits special thanks for contributing her organizational skills and experience to this new NCI endeavor.

An essential part of the PRG's charge was dependent on a review of the current status of NCI's breast cancer research. The PRG wishes to thank all of the members of NCI's Breast Cancer Task Force who contributed to the portfolio review, "The Breast Cancer Research Portfolio of the NCI - A Survey of Research and Resources, 1997."

Finally, Suzanne Reuben of Progressive Health Systems deserves special recognition as the PRG science writer. Suzanne's talents helped the PRG co-chairs meld a unified report from a multiple-authored series of scientific reviews and recommendations.



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# **Executive Summary**

# Executive Summary

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Breast cancer continues to rob women of their health, their productivity, and their very lives. It robs families of mothers, grandmothers, sisters, aunts, wives, and partners. In 1998 alone, an estimated 178,700 women will be diagnosed with invasive breast cancer, and more than 43,000 women will be lost to this disease. Breast cancer strikes women of all ages, races, ethnicities, socioeconomic strata, and geographic locales; however, older women, African Americans, the poor, and others with limited health care access are disproportionately affected. Male breast cancer, because of its rarity (an estimated 1,600 new cases in 1998), is most often treated according to the lessons learned from studying the disease in women.

Over the past two decades, intensive research sponsored by the National Cancer Institute (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. To help chart the next crucial steps toward this ultimate goal, the Advisory Committee to the Director of the NCI requested that a multidisciplinary Breast Cancer Progress Review Group (BC-PRG) analyze the NCI's current breast cancer research portfolio and develop recommendations for achieving the next decade of progress.

The BC-PRG believes that by applying and expanding our foundation of knowledge, and with ample measures of teamwork, technology, and tenacity, major progress against breast cancer can and will be made in the next five to ten years. At this gateway to the next era in breast cancer research, the BC-PRG has identified 13 critical areas of equal priority spanning the continuum of breast cancer research and care in which greater emphasis is now imperative. These are presented below not in priority order, but in a manner that addresses issues from the bench to the bedside:

1. ***Our limited understanding of the biology and developmental genetics of the normal mammary gland is a barrier to progress.*** Much of our biological research in breast cancer has focused on understanding the initiation and development of the disease. This research has been fruitful, but it is now clear that a more complete understanding of the normal mammary gland at each stage of development--from infancy through adulthood--will be a critical underpinning of continued advances in

detecting, preventing, and treating breast cancer. This focus represents a major shift in breast biology research and requires increased support for these studies and the materials needed to conduct them.

2. ***Better model systems for human premalignant breast disease and breast cancer are needed.*** Appropriate animal models and models of human mammary cell and organ culture are urgently needed to accelerate progress in breast cancer research. We need these models to conduct experimental human genetics, to identify biological markers that indicate if preventive and therapeutic agents are working, and to test potential new agents for prevention and treatment. The models that currently exist are not sufficiently varied and do not reliably predict human experience. In addition to transgenic and knock-out mouse models, breast cancer research across the spectrum of investigation requires organ culture systems, cell strains, and cell lines from normal, premalignant, and cancerous human breast tissues.
3. ***Our current knowledge of the genetics and biology of precancerous lesions and their progression to invasive, metastatic cancers is incomplete.*** We need a fuller understanding of gene mutations and gene expression in breast epithelial cells through all stages of cancer development and progression, including metastasis. These genetic changes and gene expression differences must then be correlated with known cellular, tissue, and clinical characteristics. With this knowledge, we can identify target molecules to be used as agents of prevention, detection, and therapy. This work will require access to carefully collected and catalogued human breast tissues.
4. ***Key biomarkers and surrogate endpoints for epidemiologic studies and prevention and therapy trials need to be identified.*** Current and future advances in basic biology and genetics should be used to identify and validate markers that detect breast cancer far earlier than is currently possible. It is hoped that such markers also could serve as indicators of risk and surrogates for actual cancer development. The markers could be used to develop and test prevention and therapeutic strategies, and significantly expedite the lengthy clinical trials process. Among the important activities in this research will be to achieve a consensus on criteria for accepting specific biomarkers as study endpoints, resolving issues relating to technology transfer, and finding ways to develop and improve access to extensive biorepositories.
5. ***Pivotal research cannot be conducted without the appropriate tools and technologies.*** Funding is seriously deficient for developing and disseminating new technologies and for purchasing expensive equipment

for breast cancer prevention, diagnosis, and treatment research. Though costly, these tools are now indispensable to progress in breast cancer research and strategies must be implemented to increase access to them. Shared resource and technology transfer mechanisms should be fully explored to make these tools more accessible and affordable, and NCI should take the lead in standardizing and disseminating key technologies, software, and information sources.

6. ***The capacity for developing new treatment approaches at academic health centers is being underutilized.*** Advances in the cellular and molecular biology of breast cancer have identified more promising targets for drug development and other treatment approaches than can be exploited by current mechanisms. The academic health centers have ample intellectual resources to pursue this important work, but require resources for drug screening, genomics, and chemistry infrastructure. It is critical that the NCI lead the effort to forge academic/industry/NCI partnerships for drug development. Effective collaboration between these parties with their unique and complementary strengths could greatly facilitate development of new drugs for breast cancer prevention and treatment.
7. ***Existing mechanisms must be modified to facilitate translational, prevention, and therapy clinical trials.*** It is imperative that we develop faster mechanisms for designing and conducting innovative clinical and translational trials at single academic health centers or consortia of academic health centers. Moreover, since the majority of breast cancer patients are treated in the community, the cooperative groups must be more strongly supported and should strive for enhanced minority participation in clinical trials. Translational research must also receive heightened emphasis in the cooperative groups if major progress is to take place. Finally, reimbursement of the health care costs of clinical trials by insurers (e.g., health maintenance organizations, Medicare, and other payers) is essential to the success of this entire effort. Although research grants should cover the research costs, it is legitimate and in the interest of society to require that clinical care costs be borne by health insurers for patients on approved clinical trials.
8. ***Breast cancer basic and clinical research and communications efforts need to embrace patient and survivor needs and concerns.*** Breast cancer research efforts of all types should reflect the values of those most directly affected by the disease--high risk or recently diagnosed patients, long-term survivors, and their families. Effective and understandable education and communication about risk, detection, and treatment must take into account the differing motivations, concerns, and characteristics of diverse groups

of women, including those typically underserved. Interventions are needed to improve quality of life across the full continuum from risk assessment to treatment at the end of life. The expertise and collaboration of patient advocates representing our ethnic diversity must continue to be sought in developing research priorities and in designing and implementing programs.

9. ***We do not adequately understand biobehavioral mechanisms and decision-making relevant to cancer prevention, detection, and treatment.*** There is little understanding of the processes and mechanisms underlying behavior related to diverse cancer issues from genetic testing to prevention, screening utilization, treatment, and preferences for palliative care when disease is advanced. In addition, decision-making about all aspects of cancer prevention and care is highly complex and is influenced by myriad demographic, cognitive, personality, and cultural differences among people, and by the help they receive in making cancer-related decisions. We also do not know how people use both traditional and new media to process information and make decisions. A focused program of research is needed in basic behavioral change, decision-making, and communicating research findings and their health implications to the individual.
10. ***Strategies must be implemented to attract new investigators to breast cancer research and to provide the multidisciplinary training required to translate laboratory discoveries into better breast cancer prevention and care.*** Increasingly, new investigators whose talents are needed to achieve the next generation of progress against breast cancer are choosing careers in industry or private practice over academia because they do not perceive the likelihood of a viable career in academic breast cancer research. This situation grows more dire with each passing year. We believe incentives for academic researchers are needed if both academia and private industry are to make optimal contributions to progress against breast cancer. It is also critical that multidisciplinary training take place so that individuals can participate effectively in multi-investigator collaborations that bring basic research discoveries to the bedside.
11. ***Breast cancer research is increasingly becoming a multidisciplinary endeavor that requires better communication among investigators.*** To promote communication across the breast cancer research continuum, a breast cancer task force should be established with representation from all of the major disciplines and with oversight and fiscal resources to address critical areas of breast cancer research not covered by other mechanisms. Tools are needed to improve the sharing of resources, databases, and other

information. Informatics development for all types of research will be essential throughout the next decade. There is an overarching need to expand NCI's communications outreach to address the diverse needs for disseminating cancer research results discussed in all areas of this report.

12. ***Current review and funding mechanisms do not encourage innovation or accommodate longitudinal studies and other special research needs.*** The existing peer-reviewed, investigator-initiated research project grant mechanism has served us very well over the years and should be continued and enhanced such that funding is available for at least 40 percent of high quality applications. Other options are needed, however, to support important research not currently well served by existing mechanisms. Seed money should be provided for innovative, higher risk ideas, and peer review of these "idea" grants should be through a mechanism other than the current NIH Center for Scientific Review and NCI Division of Extramural Activities study sections. Special study sections, non-governmental review and funding groups, contract mechanisms, and targeted funding all offer possible approaches to fostering innovation and meeting specialized research needs. There is a critical need for more reasonable review and funding of multidisciplinary grant applications, and for longer term funding for tissue resource development, longitudinal epidemiologic studies, and prevention and therapeutic trials.
13. ***Current approaches to informed consent and confidentiality protection are a major barrier to breast cancer research.*** The need to protect the rights and confidentiality of breast cancer patients and those at risk is recognized fully; however, current consent procedures are so cumbersome that they impede crucial research on the disease and may discourage participation by clinicians and patients. Ways to streamline and standardize the informed consent process for clinical trials and strategies to simplify protocol review, such as empowering regional or national Institutional Review Boards, must be addressed. Methods to encourage women of all races and ethnicities to donate tissues for research purposes while simultaneously protecting them from harm must be developed.

In addition to intensive discussions on how best to address breast cancer issues that cross-cut the research and care continuum, the BC-PRG worked in eight subgroups representing the major disciplines engaged in breast cancer research. These subgroups identified, distilled, and prioritized in concert with the full BC-PRG, the most important key scientific questions and research opportunities for the

next five to ten years specific to each discipline. While all of the scientific questions and opportunities identified are important emphases for the next decade of breast cancer research, those judged to be of the most immediate or central importance are highlighted below.

**Biology:** Most of the research to date in breast cancer biology has focused on changes in the basic biologic processes that enable breast cancer to grow, particularly the role of hormones, gene alterations, and biochemical communication within and between cells. This research has been extraordinarily valuable, however, at this time *we need to refocus breast cancer biology research to expand our knowledge in three key areas: (1) normal breast development, (2) the earliest breast lesions leading to invasive cancer, and (3) how breast cancer spreads throughout the body.* This represents a major shift in emphasis in this realm of research and will require resources for necessary training, the development of animal models, access to human tissues and essential compounds, technology development and access, and collaboration between diverse disciplines and between industry, academia, and government.

**Etiology:** Although a substantial number of factors have been associated with breast cancer development, most breast cancer cases cannot be attributed to any of the known risk factors. To devise effective methods for preventing breast cancer, we must understand which factors--alone or in combination--raise the risk of triggering a tumor, and which factors protect against the disease. Goals for the next decade of etiologic research are to: (1) *identify and validate the risk factors that can be modified to reduce breast cancer risk,* and (2) *achieve a better understanding of how various genetic and environmental factors interact to affect the risk of breast cancer.* To reach these goals, we need model systems that better mimic human breast disease; greater collaboration among investigators from diverse disciplines; new technologies for “high throughput” testing of DNA, RNA, and proteins; targeted funding for innovative, high

risk studies; and clinical trials to assess the effects of environmental and other variables.

**Genetics:** We know that all breast cancer is genetic, although only a small fraction of cases result from inherited genetic predisposition. Most breast cancers are due to non-inherited gene alterations that occur in breast epithelial cells; many of these remain undiscovered. Major goals for genetics research in the next decade will be to: (1) *identify all of the genetic alterations that occur at each stage of normal breast development and progression of breast epithelial cancers,* (2) *identify targets of therapeutic intervention based on genes that go awry,* and (3) *create an informed and experienced workforce to provide medical and genetic counseling and clinical care for women with inherited predisposition to breast cancer.* Achieving these goals will require that new technologies such as arrayed DNA and expression libraries be made more available to public sector investigators. Similarly, human tissues and cell lines must be made more available so that gene and gene expression profiles can be generated. Transgenic mouse models are critically needed to accelerate progress in breast cancer genetics research.

**Prevention:** Prevention strategies aim to delay or prevent the initiation, promotion, and progression of breast tumors in women. Crucial steps over the next decade toward achieving this central goal will be to: (1) *develop better animal and human models of precancerous breast biology* so that targets for preventive interventions can be identified, and (2) *develop and validate biologic indicators (surrogate endpoint biomarkers) that can replace the development or lack of development of cancer as a measure of a preventive intervention’s success.* The current



research structure does not provide for the unique needs of research in this area. Strategies must be implemented so that indispensable long-term biomarker studies can be conducted, and precancerous models can be developed. A multidisciplinary Prevention Research Working Group should be created to work with the NCI and members of the scientific community to prioritize drug development and guide preclinical and early clinical trials design.

**Early Detection, Diagnosis, and Prognosis:**

The ultimate goal of detection, diagnosis, and prognosis research is to develop noninvasive methods for detecting and characterizing precancerous and cancerous breast lesions with certainty when they are small and more easily treatable. Among the most important areas for investigation in the next five to ten years will be: (1) *determining the potential of the newer imaging technologies to detect and diagnose breast disease better than physical examination and conventional mammography*, and (2) *developing new serum and tissue-related methods to diagnose clinically significant breast disease and predict clinical outcome better than is possible with conventional tissue examination and currently available biomarker tests*. Progress in these areas will require a wide range of translational studies, and will depend in part on the results of basic biologic studies and the use of basic biologic tools including animal models. Investments must be made in new technology development and technology upgrades for the aging academic research infrastructure.

**Treatment:** Continued breast cancer treatment research is needed to achieve longer disease-free survival, longer overall survival and genuine cure, less toxic treatments with fewer side effects including second cancers, better quality of life for patients during and

following treatment, and improved access to the highest quality treatment for all women. Among the most important avenues of investigation for the next decade will be: (1) *developing innovative approaches to breast cancer treatment in the laboratory and through pilot clinical trials*, and (2) *testing the most promising therapies in large clinical trials* focused on better survival, lower toxicity, reduced breast cancer incidence, and ease of delivery. Treatment research progress will be aided substantially by fostering multidisciplinary, multi-investigator translational studies; establishing a study section with funding authority for clinical investigation; achieving better coordination among the cooperative groups, cancer centers, and Specialized Programs of Research Excellence (SPOREs); and ensuring that routine care costs of patients in clinical trials are reimbursed. To encourage private industry to permit academic research using proprietary compounds, reasonable ways must be found to protect corporate investment in their development.

**Control:** A major focus of cancer control is finding the best ways to apply current knowledge about cancer to diverse populations as a means of reducing the national cancer burden. In the next decade, two of the most important areas of cancer control research will be to: (1) *gain a better understanding of the fundamental mechanisms underlying basic behavioral change*, and (2) *identify how psychosocial factors influence disease-related outcomes such as disease response and survival*. Actions needed to facilitate this research include creating a unit focused on basic behavioral and social research within NCI's Division of Cancer Control and Population Sciences, attracting investigators to this area by stimulating graduate and postgraduate training in basic

behavioral research as applied to cancer, sponsoring a consensus conference on the state of knowledge concerning psychosocial factors' impact on disease, and forging partnerships with health care organizations to conduct studies of psychosocial interventions. This research should be facilitated through more effective use of the existing cooperative group structure, and through targeted funding for basic behavioral research.

**Outcomes:** Little is known about patient-oriented outcomes for women following the diagnosis and treatment of breast cancer. These diverse outcomes, such as quality of life, treatment side effects, and the economic impact of cancer, must be identified so that better interventions can be designed and tested, and so that the interaction of biological and psychosocial variables can be understood to improve patient care and outcomes. Better methods and processes for studying outcomes are urgently needed. Among the most challenges for important outcomes research over the next decade are to: (1) *understand the short- and long-term effects of multimodal treatment for breast cancer*, (2) *develop ways to study patient-focused outcomes across the continuum of age and across diverse racial/ethnic backgrounds*, and (3) *integrate patient-focused data with biological prognostic information to improve treatment decisions*. This research will benefit greatly from more effective use of the NCI clinical trials groups and cancer registries; this will require greater focus within these mechanisms on patient-oriented outcomes, expansion of their capacity, and accompanying support for outcomes-related data and activities.

The attached full report of the Breast Cancer Progress Review Group presents in detail the recommendations both for overarching areas of research emphasis and for achieving

progress in each of the major disciplines engaged in breast cancer research. In addition, key breast cancer statistics and a listing of on-line resources for breast cancer information are included as appendices to the report.

# **I. Purpose and Activities of the Breast Cancer Progress Review Group**

# **Purpose and Activities of the Breast Cancer Progress Review Group**

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Breast cancer is the leading site of new cancer cases in women, and the second leading cause (after lung cancer) of cancer death among women. In 1998, an estimated 178,700 new cases of breast cancer will be diagnosed, and 43,500 women will die of this disease in the United States. Approximately two million women have been diagnosed with breast cancer at some point in their lives. Breast cancer also occurs among men, though far more rarely (approximately 1,600 new cases will be diagnosed in 1998); treatment for male breast cancer treatment is guided by our understanding of the disease in women.

## **Rationale for the Breast Cancer Progress Review Group (BC-PRG)**

NCI has supported a wide variety of basic, clinical, and population-based research projects to elucidate the causes and biology of breast cancer, and to develop strategies and technologies for detecting, diagnosing, treating, and preventing breast cancer. This research effort has contributed greatly to our knowledge base about breast cancer, and new data indicate that the application of research results is saving lives, as evidenced by the declining mortality rate for breast cancer among some, though not yet all, populations.

The fruit of the research effort also has provided a wealth of new scientific opportunities that, if pursued, should further advance our knowledge and our ability to care for women with breast cancer and those at risk. Yet this growing number of research needs and scientific opportunities requires that limited resources be used optimally. It was

deemed timely to undertake a review of NCI's breast cancer research portfolio and plan a research agenda for this disease that will guide the breast cancer research field into the next century of progress.

The BC-PRG is one of several Progress Review Groups being established to help NCI assess the state of our knowledge and identify scientific opportunity and need in its large, site-specific research programs. The Progress Review Groups fit within NCI's new overall planning framework, which embraces the use of expert panels and includes the establishment of Working Groups focused on specific aspects of scientific discovery and technology and more broadly focused Program Review Groups.

## **Charge of the Breast Cancer Progress Review Group**

The overall goal of the BC-PRG was to provide recommendations for a national breast cancer research agenda, consisting of a description of ongoing scientific activities and investigations and an enumeration of additional, unaddressed scientific opportunities that should be undertaken in priority order in light of the current activities.

Therefore, the BC-PRG was charged to:

- P Identify and prioritize scientific needs and opportunities that are critical to hasten progress against the disease.
- P Compare and contrast these priorities with an NCI-prepared portfolio analysis of the current NCI research program.
- P Review recommendations from the research and advocacy communities.
- P Define and prioritize the research agenda.
- P Develop an action plan, using the current research program as the baseline for recommended actions.

## **Breast Cancer Progress Review Group Membership**

Members of the BC-PRG were selected from among prominent members of the scientific, medical, and advocacy communities, and from industry, to represent the full spectrum of scientific expertise required to make comprehensive recommendations for the breast cancer research agenda. The membership (see roster, Appendix A) was also selected for its ability to take a broad view in identifying and prioritizing scientific needs and opportunities that are critical to advancing the field of breast cancer research.

## **Activities of the Breast Cancer Progress Review Group**

The BC-PRG met eight times between May 1997 and June 1998. Their principal activities were to:

- a. Plan, convene, and analyze input from the Breast Cancer Research Roundtable.
- b. Analyze the current NCI breast cancer research portfolio and information on breast cancer research conducted by other agencies and organizations.
- c. Develop a report for presentation to the Advisory Committee to the Director, NCI

These activities are summarized below.

### ***Breast Cancer Research Roundtable***

The Breast Cancer Research Roundtable, held on September 14-16, 1997, brought together approximately 250 leading members of the breast cancer research and advocacy communities in an open forum designed to formulate key scientific questions for the next five to ten years in breast cancer research and inform the deliberations of the BC-PRG. Attendees, nominated by the PRG members,

participated in an opening plenary session followed by two sets of breakout groups. The first of these explored knowledge and infrastructure needs, barriers, and opportunities for progress within the major disciplines comprising the scope of breast cancer research. In the second set of breakout discussions, interdisciplinary groups considered a range of potentially cross-cutting issues in breast cancer research. Finally, breakout group Co-Chairs reported highlights of the discussions in a closing plenary session. Input from the Roundtable was used by the BC-PRG in delineating and prioritizing recommendations for research directions, related scientific questions, and resource and infrastructure needs.

### ***Portfolio Analysis***

An internal NCI Task Force on Breast Cancer (see roster, Appendix B), led by the BC-PRG Executive Director, reviewed the current portfolio of NCI-funded breast cancer research with the aim of describing the ongoing NCI research effort for the BC-PRG to use as a baseline for formulating its recommendations. The task force included NCI scientific staff from the intramural and extramural programs and offices. Each Division designated at least one representative to the task force, and these representatives had a major role in presenting their Division's scientific goals and future research opportunities. The task force was charged to plan and conduct the portfolio review, prepare a handbook of cancer research and resources, and present this information to the BC-PRG. The BC-PRG used this information, along with descriptions of breast cancer research being conducted by other Federal agencies and major non-governmental breast cancer research sponsors (see Appendix E), in its analysis of the breadth of research on the disease and in developing its recommendations.

### ***Report Development Process***

Following the March 1998 meeting of the BC-PRG, at which key scientific questions within each of the major breast cancer research disciplines were prioritized by the full group through a voting process, the BC-PRG members prepared narratives on these scientific questions and recommended actions for inclusion in the report. Other sections of the document were prepared in collaboration with NCI staff under the direction of the BC-PRG Co-Chairs and Executive Director.

### **About This Report**

The remainder of this report is presented in two major sections. **Section II** details priority scientific questions and related recommendations in the eight major areas of breast cancer research, as defined by the Breast Cancer Progress Review Group:

- Biology
- Early Detection, Diagnosis and Prognosis
- Etiology
- Treatment
- Genetics
- Cancer Control
- Prevention
- Outcomes

**Section III** discusses the current status of breast cancer research--our successes and remaining gaps in breast cancer prevention, care, and outcomes--and presents overarching recommendations for breast cancer research over the next five to ten years. This section describes broad research directions, infrastructure needs, and actions that cross-cut the major areas of breast cancer research and are crucial to continued progress in preventing, detecting, and treating this disease.

In addition, the report includes several appendices. **Appendix A** provides a roster of the BC-PRG membership. A roster of the Task Force on Breast Cancer is provided as **Appendix B**. **Appendix C** presents key data on trends in breast cancer incidence and mortality. **Appendix D** is a directory of NCI and several other Federal on-line resources related to breast cancer, and **Appendix E** provides a listing of Federal and non-governmental breast cancer research sponsors that provided information on their programs to the BC-PRG.

## **II. Subgroup Reports and Recommendations**

# Chapter 1:

## Biology

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### I. The Status of Breast Cancer Biology Research

The past two decades have seen unprecedented advances in our understanding of what makes breast cancer grow; in particular, the central roles of hormones (e.g., estrogen and progesterone, insulin-like growth factors) and their signaling pathways; and of important genes involved in the genesis and progression of breast cancers (e.g., HER-2/neu, p53, PTEN, BRCA-1, and BRCA-2). Research during this period has been focused on in-depth analysis of these known modulators of breast cancer biology which has led to important tools for clinical care. These include therapeutic antibodies to HER-2/neu, refinements in our understanding of the structure and function of the estrogen and progesterone receptors that have permitted the development of the selective estrogen receptor modulators (SERMs), and the use of BRCA1 and BRCA2 in the diagnosis of carriers at risk for the disease. The detailed development of one target (HER-2/neu), for example, started with the identification of the importance of HER-2/neu as a prognostic factor and later led to the surprising observations that HER-2/neu functions primarily as a heterodimer with related receptor tyrosine kinases and can act as both a differentiation factor and an oncogene. The role of HER-2/neu in determining optimal chemotherapy, the use of HER-2/neu as a target for cancer vaccines, and the development of a therapeutic antibody against HER-2/neu were the clinical manifestations of this knowledge.

Discoveries in fundamental biological processes such as apoptosis, signaling, gene expression, DNA repair, and morphogenesis have contributed significantly to our overall understanding of breast cancer biology, though the direct clinical application of this understanding has yet to be fully appreciated. Transforming growth factors (TGF)  $\alpha$  and  $\beta$ , the retinoic acid receptors (RARs), estrogen receptors (ER)  $\alpha$  and  $\beta$ , the MET protooncogene, the notch genes, myc, and the fibroblast growth factors all have been implicated in some aspect of breast development and mammary cancer development, but their function relative to one another, and their impact on human breast cancer development remain obscure. Other advances in the field have been the development of mouse transgenic models for breast cancer, and of *in vitro* models of mammary gland development that are beginning to elucidate the interactions between ligands and receptors, and between epithelium and stroma. The promise of these approaches is to permit the precise genetic reconstruction of cancer progression in physiologic systems. Recently, improvements in molecular technology that permit the analysis of early breast lesions have shown that somatic mutations that are signatures of malignant disease exist in morphologically normal breast. Taken together, the current status of breast biology provides cause for optimism--we have the fundamental building blocks in place (e.g., advanced technologies to interrogate microscopic lesions, genetic models for mammary disease) and the knowledge of many genes important in breast



cancer behavior. The challenge, however, is to integrate this knowledge to better understand what we already know to be a complex network that controls normal breast development and breast cancer behavior.

Review of the current breast cancer biology portfolio shows that approximately 80 percent of grant funding is devoted to mammary gland carcinogenesis, while less than 10 percent is devoted to mammary development, and slightly more than 10 percent focuses on breast cancer metastasis.

## II. Goals for Breast Cancer Biology Research

Given that the two clinical challenges in breast cancer research are to prevent the onset of disease and to effectively treat metastatic disease, the overarching basic biological questions that need to be answered involve understanding the normal and early malignant biology of the mammary gland, and identifying factors responsible for metastatic disease. The key strategic concepts are comprehensiveness and integrated knowledge.

### *Normal and Early Malignant Biology of the Mammary Gland*

In the area of breast cancer prevention and tumorigenesis, several important goals should be pursued:

P **Identify the stem cells of the mammary gland.** The understanding of stem cell biology has greatly aided the development of diagnostic and therapeutic tools in leukemias and in cancer immunology; it is reasonable to anticipate that this knowledge will likewise be valuable for improving breast cancer diagnosis and treatment.

P **Define the role of recently identified transcriptional regulators (coactivators and corepressors) of ovarian hormone receptors.** Modulation of these transcriptional cofactors may explain population heterogeneity in breast cancer development and may lead to the identification of highly specific breast cancer prevention agents.

P **Improve our understanding of normal mammary development.** To have a realistic hope of improving attempts at breast cancer prevention, we must significantly shift research priorities to more comprehensively and effectively study normal mammary gland development. Specifically:

- a. A detailed understanding of the genes involved in normal breast development is needed.
- b. Detailed knowledge of the role of hormones, growth factors, and signaling molecules involved in breast development is required.
- c. A better understanding of epithelial-stromal interactions in normal breast biology is necessary.
- d. The triggers for apoptosis in normal breast development should be explored.

Considerable progress has been made to develop transgenic mouse models for study of the mammary gland, but these models have not been sufficiently exploited to study the stages of normal mammary development. In addition, these models have not been fully utilized to examine the roles of stem cells and steroid

receptors, coactivators, and corepressors in development, or to elucidate mechanisms of epithelial-stromal communication. Though some laboratories are intensively studying each of these topics, the field would benefit from increasing the number and variety of investigators using transgenics to attack these fundamental developmental questions.

**P Pursue the comprehensive analysis of the earliest forms of breast cancer and of breast epithelium at risk.**

Specifically:

- a. The exact nature of the earliest genetic steps in breast cancer should be carefully mapped in both human and mouse tumors. New technologies in genomics, molecular pathology, and expression arrays should be applied as appropriate.
- b. Elucidation of the hormonal, growth factor, and adhesion signals operative in early malignancy is needed; use of murine models of breast cancer should be emphasized.
- c. The role of interactions between the extracellular matrix and stromal cells in the induction of early breast cancer must be understood.
- d. Understanding the timing and role of angiogenesis in the progression of established cancers would provide valuable information.

As in the study of normal mammary development, transgenic mouse models of breast cancer have been underutilized by

the larger research community to investigate the transition from normal to malignant breast.

**P Improve understanding of mechanisms underlying the failure of the cell cycle to arrest and repair DNA damage at cell cycle checkpoints and the resultant genetic and genomic instability.**

Understanding the basis of failure of these control mechanisms is critical for further improvements in diagnosing and treating breast cancer.

***Breast Cancer Metastasis***

It has become increasingly clear that understanding the biology of the controls on growth, death, and genetic/genomic instability of a cancer cell will not be all that is required to eradicate the disease. Understanding these processes will be essential to develop new doses of drugs to treat breast cancer and to develop diagnostic and prognostic tools. More is required, however, if we are to prevent the disease from initially taking hold, and a major unknown feature of breast cancer is the mechanism of its spread and colonization of the bone, brain, lungs, and other sites. No therapy is known today that prevents the disease from becoming systemic, and researchers have little understanding of even how to design and test such drugs; yet metastases ultimately are responsible for much of the suffering and mortality from breast cancer.

In the area of metastasis, therefore, several important goals should be pursued:

**P Pursue the detailed study of the protein and genetic factors involved in the angiogenic process of metastatic breast**

**cancer deposits in both human and murine models.** Blood supply is a key factor in the growth of metastatic cell deposits. Though angiogenesis is thought to be a generalized process, the triggers of angiogenesis may differ from one tumor type to another.

- P **Integrate the role of genetic and biochemical pathways involved in motility and invasion in an experimentally tractable system.** The exact mechanisms whereby breast cancer begins to invade the local area of the breast remain unknown.
- P **Investigate the role of stromal influences in the metastatic process.** Epithelial-stromal interactions in the genesis of primary cancers are being studied, however, the role of stromal influences in the metastatic process is unknown.
- P **Facilitate discovery of the genetic profiles of metastasis-prone cells by coupling newer molecular technologies with transgenic systems.** Standard molecular methods have been used to pursue the identification of genes involved in the metastatic phenotype. The results have only been modest in terms of discovery, partly because of the burdensome technology, but also because a simple biological read-out is lacking.
- P **Improve understanding of breast tumor physiology.** Specifically, blood and lymph flow, permeability, diffusion of solutes/chemicals/cells, and intratumoral pressures all may contribute to the relative resistance of metastases to potentially curative therapies.  
Transgenic and knock-out mouse systems

also have been underutilized in the study of metastasis. Because each cancer has its own pattern of metastatic sites, the assumption that any experimental metastasis system can be generalized to breast cancer metastasis may not be true. Therefore, specific study of metastasis in breast cancer is necessary.

### III. Barriers to Progress in Breast Cancer Biology Research

#### *Mammary Gland Development*

The study of mammary carcinogenesis cannot move forward unless the fundamentals of normal mammary development are better understood. Progress in this field has been hampered by several significant barriers. To date, the study of mammary gland development has not been a field that has attracted large numbers of investigators. In addition, the field has been limited largely to the study of the rat and the mouse, with studies in human gland development significantly lagging, principally due to the lack of human material for study and to the lack of suitable *in vitro* systems. Funding has been insufficient for training new investigators and for multi-investigator and multidisciplinary grants that cross-fertilize basic studies in mammary gland development with studies in tumorigenesis and metastasis. The interface between academic investigators and the biotechnology and pharmaceutical industries, where compound repositories reside, has also been insufficient. Similarly, support has been insufficient for maintaining mouse colonies for development of new transgenic and knock-out models and for developing models in lower organisms, particularly those with an exploitable genetic component. Another major deficit has been insufficient support for obtaining human material (both fresh and archival), especially

early from breast lesions, for developmental studies. Finally, the lack of access to and application of new technologies (e.g., cDNA chip array, microdissection techniques, imaging, development of novel transgenic systems) to mammary gland development has been a major barrier to progress.

#### ***Tumorigenesis of the Mammary Gland: the Earliest Changes***

Study of the molecular, genetic, and biologic bases of the earliest breast lesions progressing to invasive disease has been plagued by insufficient archival and fresh human pathologic material and insufficient linked information retrieval systems. In addition, cell culture, primary tissue, xenograft, and transgenic/knock-out models have so far provided critical insights into only limited aspects and specific windows in tumorigenesis. Study of breast tumorigenesis, like that of breast development, is also limited by insufficient support for mouse colonies. Finally, and also similar to the problems with mammary developmental studies, there have been insufficient multi-investigator, multidisciplinary research and training grants. This is especially true in the training of individuals capable of manipulating the mammary gland either in organ culture or transgenic mouse model systems.

#### ***Metastasis of Breast Cancer***

Studies of metastasis have faced more barriers than any other aspect of basic biological research in the disease. First, there are very few cell culture, primary tissue xenograft, and transgenic mouse models of this process. In addition, very few investigators are funded in this area specific to breast cancer. Of particular importance is the scarcity of fresh and archival human material from metastatic sites with insufficient information retrieval systems. Finally, these studies have also been

limited by too few multi-investigator, multidisciplinary research grants and an insufficient interface between academia and the biotechnology and pharmaceutical industries. Extraordinary opportunities exist in identifying compounds that inhibit cell motility and primary invasiveness, and those that block homing to specific organ sites. The key is to link the compound repositories in pharmaceutical companies with the cell biological expertise in academia.

#### ***Resources and Training***

A key barrier crossing all programmatic boundaries has been the difficulty encountered by investigators in acquiring both technical and conceptual expertise in mammary development and biology. This is due to the complexity and cost of the experimental systems for studying mammary gland biology, the lack of funding for cross-training in this area, and the paucity of interdisciplinary programs that mingle animal and human pathologists, cell biologists, and molecular geneticists. Whereas these interactions have proven very fruitful in hematopoiesis, immunology, and the neurosciences, they are not occurring with the same frequency in breast cancer biology. Specifically, access to transgenic strains for investigators new to mammary biology is limited because of inadequate resources for sharing and housing animals; acquiring technical expertise in manipulating the mammary gland of both human and non-human systems remains daunting; the limited availability of early breast lesions and normal breast tissue from women at risk for breast cancer is a significant barrier to future progress; and the lack of standardized pathologic nomenclature for the murine mammary gland that parallels human breast pathology is problematic.

## **IV. Key Scientific Questions and Opportunities for Biology Research**

The BC-PRG identified important scientific questions and areas of opportunity for making significant advances in our understanding of breast cancer biology. These fall into the three major areas discussed above: mammary gland development, breast cancer tumorigenesis, and breast cancer metastasis. Certain areas of investigation appear to be well funded in the current portfolio, especially in the area of breast carcinogenesis. Though this area is of interest, further expansion is not recommended. Recognizing that resources are limited, the BC-PRG has prioritized these questions and opportunities within the three major areas to provide guidance to the NCI on funding specific areas of investigation over the next five to ten years. Resources and recommendations that cross-cut these three areas are reiterated at the end of this section.

### ***Mammary gland development***

The priority of support for the entire field of study in mammary gland development must be elevated significantly. Currently, less than 10 percent of NCI-funded research in biologic studies of breast cancer has this focus; this must change for more progress to be made in laying groundwork for the field of prevention. Important research questions to be addressed include the following:

#### **A. What are the genetic and biological bases of mammary gland development?**

##### **1. What is the nature of mammary gland stem cells?**

A high priority area of research is the developmental isolation, characterization, and propagation of the cells that initially

grow into the gland itself. These same cells or their immediate descendants are also involved in generating the secretory, lobuloalveolar structures of lactation and they are probably targets of the various etiologic agents that cause breast cancer. For example, it is reasonable to expect that the key metastatic cell would harbor some stem cell properties that can be identified by genetic or protein markers. Finding such a marker would facilitate breast cancer diagnosis and treatment.

***Current Support:*** There appears to be only one intramural project that supports this area of research.

##### **2. What are the principal cell types involved in mammary development, and what are the mechanisms of their interactions?**

A second high priority should be a full developmental description of the rodent and human mammary glands. This type of research should involve not only identifying cell types and characterizing their patterns of gene expression, but also elucidating the diverse mechanisms whereby different cell types communicate, and the genes/proteins expressed at each junction. These studies are critical for our understanding of how developmental pathways become perturbed in tumorigenesis.

***Current Support:*** NCI sponsors only about five projects in this area.

### **3. How are growth, death, and differentiation controlled in mammary development?**

Another high priority question involves study of these three critical processes in the normal gland. These are the processes that undergo selective perturbation in tumorigenesis; they must be understood in the context of the normal gland for comparison to cancer. Specifically, identifying genes involved in each process of the normal gland and how they interact should be the critical goals. To this end, we will need to couple transgenic systems with mouse pathology and gene discovery technologies, including the development of a genetic atlas of mouse mammary development.

**Current Support:** NCI now funds about five projects in this area.

### **4. What steroid receptor coactivator/corepressor and other transcriptional regulatory mechanisms are critical in mammary development?**

Transcriptional regulators of mammary development need to be fully elucidated. The steroid receptors and their coactivators and corepressors are excellent examples of these molecules; their study is essential to understanding of the regulation of breast cell growth, survival, and differentiation.

**Current Support:** NCI funds about five projects in this area; however, studies in this area are believed to be funded more substantially through other Institutes, such as the National Institute of General Medical Sciences (NIGMS).

### **5. What are the principal signaling molecules and pathways in mammary gland development?**

Research in this area involves full characterization of the growth factor, adhesion, and other signaling molecules and the pathways by which they modulate mammary development.

**Current Support:** NCI currently funds about 20 projects in this area.

### **6. What are the principal cell cycle checkpoints and their controls in mammary development?**

Hormones, growth factors, and other growth regulatory influences modulate the cell cycle. Very early alterations leading to breast cancer, however, are thought to involve overstimulation of the cell cycle or stimulation of aberrant cycles yielding improper DNA synthesis and/or cell division. Such damage is normally detected at specific points termed “checkpoints” in the cell cycle.

Regulation of these checkpoints must be understood in the mammary gland. This area of inquiry is in fact a subset of question A.3. discussed above concerning how growth, death, and differentiation are controlled in mammary development, but was deemed to be of sufficient importance for cancer prevention to warrant separate mention.

**Current Support:** Only about five NCI grants currently address this problem.

#### **Barriers to Progress:**

- P Barriers to identifying breast stem cells include inadequate cell culture and fractionation methodologies and inadequate support for the application of

nano-scale analytic technologies. Since there are only a few investigators in this field, expanding their numbers and encouraging cross-talk between individuals involved in the stem cell biology of other organ systems (e.g., brain) may be warranted.

P Understanding of the growth, death, and differentiation processes in the normal gland has been inhibited by the limited involvement of investigators from basic fields of growth, apoptosis, and differentiation in the study of mammary development. The complexity of the experimental system and the absence of funds to support investigators' transition to this field have been major stumbling blocks. The incomplete nature of the mouse expressed sequence tag (EST) database and the mouse genetic map, as

well as the unavailability of expression array technology to the scientific community are all problematic.

P Progress in understanding mammary gland development is being slowed by insufficient cell culture and immunohistochemical methodologies, insufficient numbers of investigators with this focus, insufficient support for transgenic mouse colonies for studies of relevant mammary developmental abnormalities, and insufficient access to fresh and archival normal human mammary tissue.

P Though basic investigation into general coactivators/corepressors of transcription is currently being pursued vigorously, those pertinent to breast biology are not yet fully defined.

### ***Recommended Actions:***

1. Increase funding for transgenic/knock-out models, mammary gland transplantation models, human mammary culture models, tissue microdissection technology, and the development of a mammary developmental atlas of gene expression.
2. Invest in support mechanisms for mouse colonies and human tissue shared resources with associated information retrieval.
3. Provide support for new gene analytic technologies including gene expression arrays and genomic tools such as comparative genomic hybridization (CGH) and spectral karyotyping (SKY).
4. Establish greater bioinformatics support and training related to the use of new gene analytic tools.
5. Support multi-investigator, multidisciplinary research grants in mammary gland development to facilitate the interaction between engineers, geneticists, and mammary physiologists needed to move the field forward.

6. Encourage basic investigators in the fields of growth, apoptosis, and differentiation to become involved in the study of mammary gland development.

### ***Mammary Gland Tumorigenesis***

This field of study currently receives more than 80 percent of the NCI funding awarded for breast cancer biology research, with the majority centered on human tissues and on stages of established cancer. The principal scientific need in this field now is to focus studies on the early transitions from the normal to the malignant state in human and rodent model systems. Future research in tumorigenesis could appropriately focus on a more limited array of questions, consistent with a shift in emphasis to mammary gland development, early forms of mammary cancer, and metastasis. The most crucial research questions to be addressed in tumorigenesis are the following:

#### **B. What are the genetic and epigenetic bases of pathologic lesions that occur during the progression of breast cancer from the earliest hyperplasias to invasive disease; can we develop appropriate diagnostic markers based on these studies?**

##### **1. What signaling pathways are most critical during tumor progression?**

A primary priority is to delineate in detail the dominant signaling pathways operant in breast tumorigenesis. These pathways regulate proliferation, survival, differentiation, and local invasion.

Studies that ask how individual pathways modulate susceptibility to hormonal and chemical carcinogens and how multiple pathways interact to alter normal and malignant breast biology should be

encouraged. Examples of such questions include: how the various ligands for the epidermal growth factor (EGFR) family of receptors coordinate biologically in modulating mammary cancer susceptibility in transgenic mouse systems; and whether the conditional expression of an oncogene during a window of mammary development would engender fixed genetic mutations leading to mammary cancers. Lastly, the use of expression array technology coupled with effective microdissection has great potential for elucidating the subtle differences between biological states and the early stages of transformation. Greater support for access to these technologies would be helpful.

**Current Support:** NCI supports about 180 grants in this broad research area, but only a small part of this portfolio is devoted to investigations of the early transition points and cancer induction.

##### **2. How are genetic and genomic instabilities triggered in tumor progression?**

Another primary priority in tumorigenesis research is to better understand how different types of genetic mutations and genomic instability are triggered in breast cancer. Assessing this instability, however, is problematic. In both the human and rodent models, identifying the earliest genetic lesions would lead to better understanding of cancer induction and may provide a unique molecular marker for



early breast cancer. Improvements in mapping the mouse genome and a better understanding of comparative genomics will be important tools for this endeavor. Applying spectral karyotyping (SKY) and comparative genomic hybridization (CGH) to both mouse and human models of breast tumor progression has significant promise. These technologies also have promise for improving diagnosis and prognosis and for designing new therapies to suppress the genetic mutations and genomic instability associated with tumor progression. Thus, collaboration among mammary biologists, breast pathologists, and experts in genomics should be a priority.

**Current Support:** NCI now supports about 70 grants in this important research area. More emphasis on these genetic processes in the earliest forms of breast cancer and in metastases is warranted.

### **3. What steroid receptor-coactivator/corepressor and other transcriptional regulatory mechanisms are important in tumor progression?**

This research area concerns the detailed characterization of mechanisms whereby transcriptional regulators such as the estrogen receptor regulate the onset and progression of breast cancer.

**Current Support:** Only about five NCI grants address this problem.

### **4. What are the bases of stem cell-carcinogen interactions?**

This question concerns the nature of DNA damage sustained by mammary stem cells after carcinogen exposure.

**Current Support:** NCI supports about 110 grants that address the types of genetic

damage induced by a wide variety of agents in mammary cells. This area of research is relatively well-represented in the current portfolio. However, studies to date have not directly assessed genetic damage in defined stem cell lineages.

### **5. What epithelial and stromal cell interactions are important in tumor cell progression?**

This research area explores how stromal cells such as fibroblasts and adipocytes promote tumorigenesis in the mammary gland epithelial cells.

**Current Support:** NCI supports about five projects in this area.

### **6. What is the nature of checkpoint abrogation mechanisms in tumor progression?**

Genetic and genomic damage accumulates as a function of cell cycle checkpoint abrogation. Understanding the mechanisms operant in checkpoint abrogation is another area of research that will contribute to better diagnosis and prognosis and the development of new therapies.

**Current Support:** NCI funds approximately 20 grants in this area.

### **7. What are the relative roles of ER $\beta$ and ER $\alpha$ in tumor progression?**

A new estrogen receptor has been recently discovered. The role of this receptor, compared to the classical estrogen receptor, must be understood in the context of tumor onset and progression. The narrower nature of this current, potentially promising question, however, makes it a research area of secondary

priority. These studies have obvious implications for tumor diagnosis, prognosis, and the development of new anti-hormonal therapies.

**Current Support:** NCI currently funds no grants in this area.

### **8. How important is immune tolerance and how is it mediated in tumor progression?**

We need to understand more precisely the role of the immune system in breast tumor progression. Specific questions include: why immune response to breast cancers is so poor, whether transgenic model systems can be exploited to address immune modulation to suppress mammary cancer development, and whether antigenic peptides are presented on the surface of breast cancers. These are important issues that have been studied in the past with less refined immunologic tools than are now available.

**Current Support:** Though NCI supports approximately 30 grants in this area of research, many are devoted to the clinical development of vaccines and only six appear to examine these fundamental immunologic questions.

#### **Barriers to Progress:**

- P Review of the portfolio shows that currently funded studies of signaling pathways appropriately tend to be in-depth investigations of one pathway or one molecule in a narrowly defined culture system. Given the current knowledge base, there appears to be a need to integrate this understanding of the

individual signaling pathways into the whole tissue biology of the mammary gland. Moreover, more emphasis in understanding pathways involved in the earliest forms of mammary cancers, in heightened cancer susceptibility, and in the metastatic process is needed.

- P Access to technologies that can analyze small amounts of tissue, and that can multiplex analyses (such as arrays), is currently inadequate.
- P Access to archival and fresh human pathologic material, especially for early malignant lesions and normal breast tissues, coupled with associated clinical and pathologic information, is insufficient.
- P Cell culture, primary tissue xenograft, and transgenic/knock-out models are inadequate at present. Specifically, there is insufficient support for disseminating mouse models pertinent to mammary carcinogenesis. It appears that established investigators working with transgenic mice have good access to these models, but qualified investigators peripheral to this community wishing to initiate transgenic experiments have access problems.
- P Important barriers between academia and industry are impeding progress. For example, once model systems for breast cancer induction are developed in academic institutions, the accessibility of pertinent compounds that may attenuate the development process is limited. Furthermore, the Oncomouse patent and the industrial conditions for its use significantly dampen academic interactions.

P Studies to date have not addressed DNA damage mechanisms directly within cells of proliferative potential that are known to give rise to mammary cancer.

P The investigations, to date, into a breast cancer vaccine prior to understanding the basic mechanisms of immunologic recognition/surveillance of mammary epithelia appear to be premature.

### ***Recommended Actions:***

1. Increase funding for projects that integrate knowledge of cell signaling with whole organ biology for the development *in vitro* models of breast differentiation, experimental xenograft systems, and transgenic/knock-out mouse models.
2. Improve mouse model access for new investigators in the field and provide appropriate training relative to their use.
3. Increase support for human tissue acquisition and disbursement and for collaborating pathologists.
4. Increase support for the dissemination of new technologies pertinent to mammary gland biology.
5. Increase access to compound repositories found in pharmaceutical companies that can be used to interrogate the carcinogenic process.

### ***Breast Cancer Metastasis***

The priority of support for research on breast cancer metastasis must be increased significantly. Currently, slightly more than 10 percent of NCI research funding in breast cancer biology supports studies of metastasis. Improved understanding of the metastatic process is essential to further progress in breast cancer diagnosis, prognosis, and therapy. The most important research questions to be addressed are:

**C. What are the molecular, genetic, and cell biologic bases of the biological processes involved in metastasis; can we develop appropriate diagnostic markers based on these studies?**

### **1. What cell survival pathways are operant in metastasis?**

A primary priority in the study of breast cancer metastasis is to understand what mechanisms allow survival of disseminated tumor cells in the hostile environments of distant viscera, bone, and brain. If therapies can be directed against these pathways, the morbidity and mortality of the disease could be drastically reduced.

***Current Support:*** NCI supports only about five projects in this area of research.

## **2. How is tumor angiogenesis regulated?**

Another primary priority is to attain a better understanding of tumor angiogenesis regulation, a process that promotes both primary tumor growth and its metastatic dissemination.

*Current Support:* Approximately two projects in this area specific to breast cancer were identified.

## **3. How does bone interact with the metastatic cell?**

Metastasis of breast cancer to the bone is of special significance to patient morbidity and pain. Tumor cell-bone interactions represent a secondary priority area for study.

*Current Support:* NCI supports about three projects in this area.

## **4. How is proteolysis controlled in metastasis?**

Synthesis, activation, and presentation of extracellular matrix-degrading proteases are thought to be critical in enabling metastatic breast cancer cells to cross multiple barriers to spread through distant tissue. Studies to identify and determine the functional signature of proteolytic mechanisms, however, are in their early stages.

*Current Support:* NCI currently supports approximately 10 projects in this area.

## **5. What tumor cell motility mechanisms are operant in metastasis?**

These metastasis studies focus on understanding of how tumor cell motility

is controlled. The metastatic process can be divided into invasion, evasion of immune surveillance, implantation/motility, survival, and growth. The genetic components of these processes have not been identified; however, the genes and biochemical pathways involved in motility and invasion are now being uncovered and may represent targets for intervention as well as providing markers of metastatic virulence. Integrating the role of these factors in an experimentally tractable system centered on breast cancer should be pursued.

*Current Support:* NCI now supports approximately three projects in tumor motility mechanisms in metastasis.

## **6. How are epithelial-stromal interactions important in metastasis?**

The nature of epithelial-stromal interactions is another secondary priority for the study metastatic breast cancer cell regulation. It is suspected these epithelial-stromal interactions are involved in the survival and growth of metastatic cells after implantation. The use of genetically-marked primary and metastatic tumor cells from genetically engineered animals holds promise as a new foundation for this research.

*Current Support:* The current portfolio includes approximately three projects in this area.

### **7. What signaling pathways are important in metastasis?**

The nature of the signaling pathways whereby hormones, growth factors, and adhesion molecules modulate metastatic mechanisms is another study area of secondary priority. For example, nm23, HER-2/neu, and p53 are several non-protease genes associated with metastases, but despite intense study, the exact mechanism for their association with increased metastatic potential remains obscure. Comprehensive analysis of genetic changes occurring between primary tumor and metastases and the development of a tractable system to study metastases are needed. The movement of ideas to and from experimental models to the human situation is also encouraged.

*Current Support:* NCI supports approximately seven projects on signaling pathways in breast cancer metastasis.

### **8. What cell cycle checkpoint abrogation mechanisms are operant in metastatic cancers that render them more refractory to systemic treatment?**

The metastatic cell is known to be especially refractory to a variety of therapies. Improving understanding of the mechanisms of cell cycle checkpoint abrogation in metastatic deposits of breast cancer is another secondary priority question.

*Current Support:* No NCI projects appear to directly address this problem at the present time; however, it is anticipated that investments in cell cycle checkpoint abrogation mechanisms in general will have positive effects on understanding their impact in metastasis.

### **9. What aspects of tumor cell physiology of established and metastatic cancers render them more refractory to systemic treatments?**

Recent studies have demonstrated significant barriers prevent systemic treatments from effectively reaching established solid tumors. These barriers include high intratumoral pressures, poor diffusion rates, and inadequate blood flow. Research to quantitate the extent of these problems and to find means of overcoming these physical barriers would be important. Technologies necessary to facilitate this research include optical imaging, confocal microscopy, and tracer (e.g., positron emission tomography) imaging in experimental animals.

*Current Support:* No support specific to breast cancer was identified.

#### *Barriers to Progress:*

- P Insufficient cell culture, primary tissue xenograft, and transgenic/knockout models are currently available.
- P Too few investigators are working on issues related to metastasis.
- P Funding for breast cancer metastasis research is insufficient.

Investigators have insufficient access to archival and fresh human pathologic material with appropriate information retrieval systems and collaborating pathologists.

- P Support for mouse colonies, for appropriate pathologic resources, and for new gene expression analytic technologies is inadequate.

- P A major unanswered question is whether metastatically competent cells grow differently in stroma from a variety of tissue sources compared with primary tumors.
- P No investigators are currently studying, with a focus specific to breast cancer, characteristics of tumor physiology that render solid tumors resistant to treatment; further, few investigators are working in this field relative to cancer in general. Sources of support (e.g., RFAs, program announcements) for this research are lacking. Moreover, the cost of the equipment and the necessary training in engineering and physics are limiting factors.

***Recommended Actions:***

1. Increase funding for development of better experimental animal models of metastasis.
2. Use existing program project, SPORE, and core grant mechanisms for increased support of mouse colonies, for human tissue shared resources with associated information retrieval, for new technologies, and for bioinformatics support.
3. Increase funding for other multi-investigator, multidisciplinary research and training grants. For example, support cross-training and the engagement of engineering students in investigations of treatment barriers posed by tumor cell physiology of established and metastatic cancers.
4. Provide support for equipment and training in engineering and physics needed to quantitate physiologic properties of solid tumors that render them resistant to treatment.
5. Educate the scientific community about the capabilities of the biotechnology and pharmaceutical industries.

***Refocusing Breast Cancer Biology Research:  
Cross-Cutting Resources and Recommendations***

Significant progress has been made in the past decade to uncover the genes and the biologic processes involved in the onset and progression of breast cancer. At this time, however, a redirection of future research is necessary in order that more progress be made in prevention and therapy. Specifically, more resources need to be invested in:

- P The study of normal breast biology.
- P Studies focusing on the process of metastasis and characteristics of metastatic cells.

- P The integration of human and mouse genomics and mammary biology.
- P Studies elucidating the roles of coactivators/corepressors of the estrogen receptor.

To conduct this research most effectively and expeditiously, the BC-PRG urges that the following cross-cutting resources and infrastructure needs should be the prime focus for future NCI initiatives in breast cancer biology research:

- 1. Training programs and training support are needed. Specifically:**
  - a. Provide training programs directed at non-mammary biologists who wish to enter the field. These programs may include instruction in the accession of animal models, mammary gland manipulations, pathology of experimental systems, and normal mammary gland biology. Such training might employ the format of a Cold Spring Harbor course.
  - b. Provide resources for mid-level academicians to redirect their research into mammary gland biology through special “sabbaticals.”
  - c. Increase access to training in new technologies.
- 2. Greater resources and support related to mouse models is essential:**
  - a. Enhance the development of more mammary-specific knock-out systems and the discovery of mammary-specific promoters. Consider the development of a national repository of these promoters and other related molecular reagents through the American Type Culture Collection (ATCC).
  - b. Improve access to transgenic mouse models of human breast cancer.
  - c. Provide adequate funding through a separate support mechanism other than the R01 for maintenance of mouse colonies and for the cost of transporting transgenic animals.
- 3. Improved access to compounds and human tissues is critical:**
  - a. Arrange for consortia with industry to release a portion of their compound repositories for experimentation in the academic community.
  - b. Provide adequate funding through support mechanisms separate from the R01 for the acquisition and distribution of human breast tissue from normal, primary tumor, and metastatic sites coupled with appropriate patient information and follow-up, and appropriate collaboration with breast cancer pathologists.

**4. Collaborative efforts and partnerships must be fostered:**

- a. Increase investment in multi-investigator, multidisciplinary grants.
- b. Develop virtual centers of mammary biology comprised of investigators in mouse genomics, molecular biology, bioengineering, and mammary biology by providing adequate travel funds in addition to research funds. These investigators may be from different institutions since a critical mass of multidisciplinary investigators in this field is rarely concentrated in one institution. In this manner, smaller and less developed institutions can raise their standards of experimentation in mammary biology.
- c. Create scholar exchange programs between industry, academia, and government.
- d. Encourage partnership between industry, academia and government to move compounds forward for breast cancer treatment and to provide reagents to interrogate critical signaling pathways in breast biology.
- e. Facilitate better use of websites by NIH, industry, and academic institutions for technology transfer, company information, and investigator patents.
- f. Sponsor and organize joint academia and industrial conferences to cross-fertilize research efforts in mammary gland development, tumorigenesis, and metastasis.

**5. New technology development should be facilitated:**

- a. Using the Small Business Innovation Research and Small Business Technology Research (SBIR/SBTR) mechanisms, encourage industry to develop and disseminate technologies pertinent to mammary biology such as expression array, micro dissection, and imaging technologies.
- b. Improve access to new technologies.



## Chapter 2: Etiology

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### I. The Status of Breast Cancer Etiology Research

The role of endogenous ovarian hormones as major etiologic agents of breast cancer is firmly established. The epidemiological evidence for this includes the observed increased risk of breast cancer that is associated with an earlier age at menarche, a later age at menopause, increased postmenopausal weight, extended use of hormone replacement therapy, and a marked decrease in breast cancer risk for women who have had an early bilateral oophorectomy and for women taking tamoxifen. Recent prospective cohort studies have also shown associations between estradiol concentrations and breast cancer risk. The evidence implicating progesterone is weaker but includes the observed increase in breast cell mitotic activity in the luteal phase of the normal menstrual cycle.

In the past five years, exercise has been promoted as a significant protective factor against breast cancer in premenopausal women, although controversy remains concerning this finding. Women who have exercised four or more hours a week since their teenage years appear to have an approximately 50 percent lower breast cancer rate than women who have exercised very little. The effect of such exercise may be explained by noting that this level of exercise has been found to be associated with an increased frequency of anovular cycles, and with decreased serum estrogen and serum progesterone levels in the cycles in which ovulation does occur. Lower amounts of

exercise may also be associated with a decreased risk; the mechanism of such an effect is not known, although even moderate amounts of exercise have been found to be associated with an increase in anovular cycles in teenaged girls.

The possibility that specific dietary factors may be associated with breast cancer risk, over and above their association with menarche and postmenopausal weight, has been and remains an area of active research. The hypothesis that has been most extensively investigated has been the role of dietary fat in breast cancer risk. The main support for a role of dietary fat has come from the observed strong association of breast cancer rates in different countries with an indirect measure of *per capita* fat consumption. Cohort studies of the association between dietary fat and breast cancer, however, have not supported the hypothesis. It has been argued that these studies are fundamentally flawed by the large error rates associated with measuring diet by questionnaire history or 24-hour recall. These methods, nevertheless, have been able to show relationships of diet with other diseases. The large ongoing NCI-supported randomized clinical trial of lowering the percent of calories from fat (Women's Health Initiative) should provide valuable information on this important topic.

High phytoestrogen (mainly soy) consumption has been suggested as an alternative explanation of the particularly low breast cancer rates observed in Asia until very recent times. Epidemiologic studies of this hypothesis have produced inconsistent

answers, and experiments to test whether increasing soy consumption would reduce ovarian hormone production (approaching the "traditional" low values observed in Asia) have not found such an effect. A few experiments to test whether increasing soy consumption would affect some aspect of breast biology directly in a protective direction have found no evidence of such an effect.

Increased fruit and vegetable consumption has been found to be associated with decreased risk at most cancer sites. There is little evidence for such an effect for fruit consumption in breast cancer, however, and the evidence for such an effect for vegetable consumption is weak.

In studies over the last decade, alcohol consumption has been consistently found to increase the risk of breast cancer to a moderate but significant extent. The mechanism underlying this effect remains unclear. Importantly, more research is needed to clarify how the amount of alcohol consumed affects risk.

It has been proposed that exposure to various environmental estrogens may increase breast cancer risk. Organochlorine compounds exposure has been investigated in multiple studies. Recent studies have not confirmed earlier reports of an increased risk with higher serum concentrations or adipose concentrations of 1,1-dichloro-2,2-bis(p-dichlorodiphenyl)ethylene (DDE), the major metabolite of dichloro-diphenyl-trichloroethane (DDT), or of polychlorinated biphenyls (PCBs).

Ionizing radiation is known to increase breast cancer risk, and there have been suggestions that electromagnetic fields (EMF) may also increase risk. The association between EMF

and breast cancer remains an open issue with a number of substantial ongoing studies due to report their findings in the next few years.

Whether the risk factors that have been identified for breast cancer in general apply to specific high risk subsets of the population such as carriers of a BRCA1 or BRCA2 mutation is currently not known. This is a high priority area since establishing risk factors for such populations is an essential component of designing appropriate preventive regimens for these women.

Despite this long list of factors associated with the development of breast cancer, a large proportion of breast cancer cases cannot be attributed to known risk factors. Additional insight into understanding the etiology of breast cancer, leading to avenues for prevention, may come from identifying susceptibility factors that predispose individuals to breast cancer if they are exposed to particular environmental agents. For example, inherited differences in the activities of enzymes involved in carcinogen metabolism may predispose some women to the effects of specific environmental factors. A recent report suggests that low activity N-acetyltransferase genotypes may predispose women to breast cancer induced by cigarette smoking. Other studies have linked inherited differences in activity levels of the glutathione S-transferases with subsequent breast cancer development. The risk of cancer is likely to be observed only among individuals with both the susceptibility factor and a history of exposure to a relevant environmental factor. Research into both the most relevant environmental factors underlying breast cancer and the potential inherited susceptibility factors offers a new opportunity for understanding breast cancer risk.

## II. Goals for Breast Cancer Etiology Research

### *Validation of Modifiable Risk Factors*

An overarching goal for breast cancer etiological research is to identify the risk factors that are in the causal pathway of disease and that if changed (modified) will alter the risk of developing breast cancer. For example, postmenopausal weight is a well-established breast cancer risk factor from both case-control and cohort studies, with increasing weight being associated with increasing disease risk. Validating postmenopausal weight as an underlying causal factor may be accomplished through clinical trials demonstrating that if a woman reduces her postmenopausal weight she will reduce her risk of breast cancer.

The unquestioned method of establishing the validity of a risk factor is to conduct randomized intervention trials with breast cancer incidence or mortality as the endpoint. Such trials are very difficult and very expensive to conduct because of the large sample sizes needed and long duration of the trials. Using intermediate endpoints rather than breast cancer incidence can lead to shorter trials with much smaller sample size requirements. To accomplish such trials, validated intermediate biomarkers of all stages of disease initiation, promotion, and progression are required.

This identification of biomarkers is critical to the validation of such important modifiable risk factors as exercise. For exercise it will be important to establish not only the relationships of type and duration of exercise to breast cancer risk, but also the possibly different effects that can be achieved at different ages. Without a validated biomarker

of risk such questions will likely remain unanswered.

### *Gene-Environment Interactions*

The genetic characterization of subpopulations at particularly high risk of breast cancer (e.g., with mutations in the BRCA1 gene) has raised questions as to the extent to which the known breast cancer risk factors apply to such specific high-risk populations and whether there are risk factors specific to these subpopulations. The studies of polymorphisms of hormonal and environmental carcinogen metabolism also may identify subpopulations at risk of breast cancer, albeit at a lower risk than associated with mutations in BRCA1 or BRCA2 genes. Because polymorphisms potentially associated with an increased risk of breast cancer occur quite commonly, however, the population breast cancer risk attributable to the common polymorphisms may be quite high even with moderate magnitudes of associated risks especially if the relevant environmental exposures are also common. Identifying and understanding such gene-environment interactions is an actively supported area, and holds great promise both for providing the essential data needed to design rational preventive strategies for these subpopulations and for furthering our fundamental understanding of breast cancer etiology. The studies of the relevant genetic contributions must go hand in hand with the studies of relevant environmental factors.

Successful studies in this area of gene-environment and gene-gene interactions require multidisciplinary efforts of geneticists, epidemiologists, and molecular and cell biologists. There is a great need to make these collaborations easier by providing cross-training and encouraging special funding for such collaborative efforts.

Many aspects of hormone production, metabolism, tissue localization and concentration, and interaction with receptors of direct relevance to breast cancer remain to be understood. Given the recognized hormonal nature of breast cancer, further understanding of these factors holds the promise of providing novel insights into breast cancer etiology and possibilities for prevention. The study of the role of different polymorphisms of genes involved in hormone production and action has only recently begun. Although the technology (e.g., sequencing) for identifying genetic polymorphisms still needs improvement, the pace at which polymorphisms are being identified is outstripping our understanding of their epidemiological (etiological) and functional significance. Strong support for studies of the functional significance of polymorphisms is essential. The identification of functional polymorphisms in hormone production raises important questions in feedback control; investigating these questions has the potential for fundamental advances in endocrinology and eventually in our understanding of hormonal carcinogenesis.

Studies of polymorphisms in ethnically diverse populations may be especially fruitful. These studies may lead to a much deeper understanding of puzzling observations; for example, African American women have higher breast cancer incidence rates at young ages but lower postmenopausal incidence rates than white American women. In addition, African Americans' breast cancer mortality rate is consistently higher than that of white women.

Effective epidemiological studies in this area require large sample sizes, since the relative risks associated with these genetic polymorphisms are usually small (<2)

although they may make a substantial contribution to the risk of breast cancer in the population. Establishing networks of collaborating investigators to facilitate recruiting sufficiently large samples of study subjects for either case-control or cohort studies should be encouraged.

A significant challenge to performing these studies involves confidentiality issues. Research on metabolism genes involves privacy and confidentiality issues that can impede Institutional Review Board (IRB) clearance.

### **III. Barriers to Progress in Breast Cancer Etiology Research**

Etiology and pathogenesis are closely related. Exposure to various environmental factors can lead to subcellular changes that may in turn develop into precancerous lesions, and eventually into invasive cancers. The complex interplay of human genes and exposure to environmental factors challenges biologists and epidemiologists to forge a coherent link between their two approaches. The opportunity now exists as never before to explore these relationships at the molecular level, and to use effects discovered and replicated in large populations to provide clues to the cause of breast cancer. Similarly, biological models are needed to guide the development of etiologic hypotheses and proposed interventions.

How can we achieve this dynamic dialogue between different disciplines? A good place to start may be with epidemiologic observations for which there is limited understanding of the underlying mechanism. For example, how are the protective effects of early first pregnancy and exercise achieved? Answers to these questions might be

facilitated by the development of animal tumor models that mimic human breast cancer development.

There is widespread agreement that traditional boundaries between population epidemiologists and basic biologists must be bridged if a deeper molecular understanding of breast cancer is to be achieved. Cross-training of scientists would help greatly to achieve this goal. In addition, technological innovations that permit simultaneous multiplexing of DNA, RNA and proteins for characterizing protein interactions are needed, as are statistical models capable of analyzing the large amounts of data produced. Finally, large data banks with clinical information linked to

tissue and blood specimens are required to confirm observations made in animal systems or in small epidemiologic studies.

If progress against breast cancer is to proceed rapidly, research must result in the establishment of validated biomarkers. Developing such intermediate biomarkers will enable researchers to test multiple new and different approaches simultaneously. In contrast to the large, sequential studies that characterize current preventive research, the availability of intermediate biomarkers should enable investigators to accelerate the development and testing of new prevention strategies.

#### **IV. Key Scientific Questions and Opportunities for Breast Cancer Etiology Research**

##### **A. What types of intermediate markers would be useful in order to advance our understanding of mechanisms involved in breast carcinogenesis?**

At the present time, the state of our knowledge requires interventional trials to use invasive breast cancer incidence as the endpoint, resulting in large trials of long duration. More work is needed so that more readily measured intermediate endpoints (e.g., hormone trends, mammographic density, genetic and biochemical alterations) can be substituted as endpoints in future prevention trials. The eventual development of serologic and/or tissue markers would greatly accelerate research.

*Current Support:* Current support for biomarker research is quite limited.

*Barriers to Progress:* Understanding of the mechanisms responsible for the progression of precancerous lesions to invasive lesions is incomplete. Therefore, it is unclear which markers can be used to forecast this progression. Biochemical epidemiology must be integrated into the understanding of the underlying biochemical and cellular processes. Further, few long-term studies have been conducted to provide information on useful biomarkers. This is due in part to the difficulties encountered in studying biomarkers in healthy women and also to the lack of adequate tissue banks.

***Resources Needed:***

Improved collaboration between epidemiologists and individuals trained in basic and clinical sciences, specifically endocrinology, immunology, and histopathology is needed. In addition, studies to identify precursor lesions in normal-appearing breast tissue and to understand the events that characterize them at the molecular level are essential.

***Recommended Actions:***

1. Develop model system(s) that mimic major aspects of human breast disease and identify serologic or tissue biomarkers that correlate with the development of breast cancer in these systems. Markers detected in these systems should then be tested in human trials.
2. Establish networks of clinical investigators with the appropriate technical support for developing markers in early clinical trials.

**B. What are the best approaches to understanding gene-environment interactions?**

The study of gene-environment interactions remains a key area for breast cancer research, although our current tools and methods are insufficient. Achieving progress will require emphasis on expanding knowledge of environmental factors relevant to breast cancer etiology and emphasis on genetic factors leading to an increased susceptibility to breast cancer development. Several areas require further study. For instance, to what degree do genes determine behavior that in turn increases breast cancer risk? What role do genes play in the differences between individuals and their ability to repair genetic damage caused by the environment? What are the relevant environmental factors and susceptible genotypes involved in breast carcinogenesis? To what extent do genetic and environmental exposures and their interaction explain the heterogeneity of breast cancer risk among diverse populations? The study of gene-environment interactions in large populations is attractive and is now potentially feasible.

***Current Support:*** This research receives fairly active support in the current NCI portfolio, especially support for BRCA1/2 studies. It is unclear, however, whether some studies can realize their goals given their limited sample sizes.

***Barriers to Progress:*** We do not adequately understand the function associated with most genetic polymorphisms, or the environmental factors most relevant to breast cancer risk and putative high risk genotypes. This lack of knowledge makes it difficult to predict likely gene-environment interactions. Increased emphasis on exposure assessment is essential to the study of environmental factors and would be aided by increased interdisciplinary collaboration. Further, effective studies in this area require large sample sizes with precise exposure information and study replication in diverse populations. These studies tend to be

costly, and the necessary funds are not often available. Confidentiality issues related to genetic testing can impede institutional review board clearance.

***Resources Needed:***

Further interdisciplinary collaboration is required. This must be coupled with support for the development of new technologies for high throughput testing of DNA, RNA, and proteins. Finally, statistical models are needed that can analyze large data sets.

***Recommended Actions:***

1. Sponsor an interdisciplinary workshop to stimulate useful approaches to studying gene-environment relationships, including better study designs and investigations that are biologically driven.
2. Encourage projects that develop better genotype-phenotype relationships for candidate polymorphisms so a better understanding of their possible functional role can be acquired.
3. Mount a concerted effort to generate data to determine convincingly which factors (genetic and environmental) explain the heterogeneity of breast cancer risk in diverse populations.
4. Establish research networks with existing cohort and case-control study populations to facilitate the rapid conduct and replication of genetic and environmental factors and to ensure adequate and sufficiently representative sample sizes to investigate potential interactions.

**C. What factors influence disease progression?**

***Current Support:*** The risk of second primary cancers is an active area of investigation, however, the effects of exposures occurring after the onset of disease is not adequately addressed presently.

***Barriers to Progress:*** It is unclear whether immunologic or psychologic factors are involved in disease progression. In addition, it is difficult to obtain access to underserved populations for necessary studies.

***Resources Needed:***

More clinical trials are needed to assess the effects of intervening variables.

***Recommended Actions:***

1. Conduct interdisciplinary workshops to stimulate useful approaches to studying disease progression, including better study designs and investigations that are biologically driven.
2. Encourage projects to develop better markers for assessing disease progression.

**D. What might be a useful approach to expanding our knowledge regarding breast cancer etiology?**

***Current Support:*** Some studies are currently funded, but high risk ventures are very limited.

***Barriers to Progress:*** Our understanding of the biologic processes underlying many of the identified risk factors (e.g., first full-term pregnancy) is incomplete. Most clinical studies lack innovation and animal models that sufficiently mimic the human situation do not exist.

***Resources Needed:***

Funding for high risk, novel investigations should be encouraged. Studies are needed to address the biologic correlates of identified risk factors. Animal models that mimic human disease and that can be used to develop new hypotheses are needed.

***Recommended Actions:***

1. Establish specific funding initiatives to determine the basis for the breast cancer protective effect of having a first pregnancy at an early age.
2. Institute a mechanism for funding high risk "idea" grants that provide adequate funding without the requirement for substantial preliminary data.

**E. Are there etiologically distinct components of breast cancer that would be useful to consider?**

***Current Support:*** Epidemiologic research in this area is limited, particularly with respect to the etiology of premalignant breast diseases.

***Barriers to Progress:*** The lack of understanding of the natural history of breast carcinogenesis hinders our ability to study etiologically distinct subsets of disease. There is a lack of epidemiologic studies on molecularly characterized tumors from



diverse populations. In addition, collaboration between clinicians, pathologists, molecular biologists, and epidemiologists is limited.

***Resources Needed:***

The widespread availability of tissue samples from diverse populations and resources to characterize tumors at the molecular level is needed. These activities require further interdisciplinary collaboration.

***Recommended Actions:***

1. Sponsor a workshop to explore how breast cancer may be subdivided into etiologically distinct components and how research can proceed on a multidisciplinary level.
2. Foster funding initiatives to focus attention on early stages of breast neoplasia that would also aid the development of intermediate biomarkers.

**F. What types of studies should be pursued to advance our understanding of the role of dietary factors in breast carcinogenesis?**

***Current Support:*** Most of the currently funded projects focus on expanding our knowledge of previously suggested risk factors rather than on identifying new dietary relationships.

***Barriers to Progress:*** We need to better understand the role of diet--nutrients, special foods (e.g., soy)-- in populations with low breast cancer rates and the effects of these dietary elements on breast carcinogenesis. Relatively few studies have been completed with useful biomarker information. It has been very difficult to study the role of food/diet in early life exposures. It also has been difficult to disentangle correlated factors, such as fat, total calories, exercise, and energy balance. The validity of dietary histories is questionable, particularly total caloric intake, obtained by interview.

***Resources Needed:***

Mechanistic studies of dietary effects on sex steroid production and metabolism are needed. It is also necessary to do studies in ethnically diverse populations.

***Recommended Action:***

1. Conduct studies to examine the possible affects of dietary components on breast cancer risk and their effects on potential intermediate biomarkers such as endogenous hormone concentrations.

## Chapter 3: Genetics

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### I. The Status of Breast Cancer Genetics Research

In the past five years, the integration of genetic approaches into breast cancer research has been extraordinary. This integration has occurred at all levels. Evaluations of families at high risk of breast cancer have led to the identification of four genes in which inherited mutations predispose to breast cancer: p53, BRCA1, BRCA2, and PTEN. Since then, population genetic and epidemiologic studies have revealed the impact of these inherited mutations on the public health burden of breast cancer in the United States and in other parts of the world. In parallel, clinical studies have begun to evaluate the appropriate management of patients with inherited predisposition to the disease. At the same time, inherited predisposition to breast cancer has been the catalyst for scrutiny of social, legal, psychological, and ethical issues in genetic testing and provision of genetic services to adults at risk of later-onset disease.

All breast cancer is genetic, although only a small fraction of cases are attributable to inherited genetic predisposition. Most breast cancer is due to genetic alterations that are specific to breast epithelial cells (i.e., somatic alterations), many of which are probably still unknown. Identifying and characterizing somatic genetic alterations that are rate-limiting steps to carcinogenesis relies increasingly on genetic approaches, including genomic comparison of tumor and normal tissues and differential expression of genes (both known and unknown) at each stage of tumor development. We expect these areas of

research to accelerate with the development of new tools for genetic analysis.

Very recently, new molecular therapeutic approaches for breast cancer have become possible. These therapies have derived from genetic analysis of breast tumors. The most fully developed model thus far is treatment of some advanced breast cancer with an antibody to the protein product of the HER-2/neu gene expressed on the surface of some breast tumors. The HER-2/neu model exemplifies a large class of future translational research: identifying a gene differentially expressed in breast cancer vs. normal breast epithelial cells; characterizing the gene and its product; identifying the biological role of the gene in tumorigenesis; developing an antibody (or in principle another molecule) to block the activity of the protein; and evaluating the approach in the clinical setting. This process is complex, long, and expensive. Only by involving both NCI and private resources can we move quickly to develop and evaluate the most promising therapeutics.

As this brief introduction suggests, results of research in breast cancer genetics are not separable from results in biology, prevention, diagnosis, or treatment research. In formulating recommendations, therefore, the BC-PRG focused on questions and opportunities that exploit genetic approaches and that may affect any of the substantive areas of breast cancer research.

## II. Goals for Breast Cancer Genetics Research

Although genetics research encompasses a broad range of scientific pursuits, the following key goals should be of the highest priority:

- P Identify all the genetic alterations--both germline and somatic-- that occur at each stage of normal breast development and progression of breast epithelial cancers. The central goal of this effort is to understand biological pathways that are the consequences of genetic changes. Successful outcomes would ultimately be the identification of target molecules to be used as agents of prevention, detection, and therapy.
- P Identify targets of therapeutic intervention based on genes that go awry. Most such therapies will be gene- inspired biochemistry and pharmacology rather than gene therapy per se.
- P Create an informed and experienced workforce in order to provide appropriate clinical management and medical and genetic counseling for women with inherited predisposition to breast cancer.

## III. Barriers to Progress in Breast Cancer Genetics Research

At present, the field suffers from a shortage of human and scientific resources. There are too few trained people who understand both biology and genomics. More must be done to stimulate career development in this area.

As for scientific resources, families at high risk, both with known predisposing alleles and

those not yet identified, need to be recruited into studies. Additional critical scientific resources that are required include:

- P Tissues, from biopsies and surgeries and from normal breast epithelium are scarce.
- P Amplification schemes and other techniques for obtaining more DNA from tiny amounts of primary material are needed.
- P More cell lines from normal breast epithelium and from a variety of pathologies need to be established.
- P Mouse strains, in particular transgenic mice for critical genes, against different genetic backgrounds, need to be developed to support a wide range of cancer genetics investigations.
- P Arrays of genes and genomic sequences need to be available--at affordable cost--to public investigators.
- P As clones for genes and genomic segments appear in vastly greater numbers, the challenge to make this information publicly available will become even greater.
- P Enhanced efforts in informatics will be required to comprehend this genomic information, and to integrate these efforts with breast cancer biology. This problem will make the inclusion of molecular genetics in clinical trials even more complicated and will require new trial designs and analyses.

## IV. Key Scientific Questions and Opportunities in Breast Cancer Genetics Research

### A. Identify and clone the remaining major predisposing genes.

*Current Support:* The model for this work has been well defined and the area is now recognized with several grants from NCI.

*Barriers to Progress:* The principal barriers are epidemiologic; that is, the relatively few very large high risk families with unknown predisposing genes. NCI is sponsoring or co-sponsoring efforts to identify and characterize such families, as well as statistical approaches feasible for other study designs.

#### *Resource Needs and Recommendations:*

The NCI should continue to support these projects with an emphasis on stimulating collaborative efforts when feasible.

### B. Identify somatic mutations and epigenetic alterations that are due to exogenous factors or to chance. As these are detected, it will be important to know which ones are rate-limiting. Once rate-limiting changes are identified, specific pathways altered by these genetic events can provide clues for possible targets for:

- P Identifying very small lesions (diagnosis)
- P Treatment (by reversing the altered phenotype)
- P Identifying tumor cells (in order to individualize therapy based on genotype of the tumor)
- P Prevention (by systemic treatment of women before critical changes occur)

*Current Support:* Many grants at NCI include these questions as a goal.

*Barriers to Progress:* This area will be facilitated enormously by new technologies, such as arrayed DNA and expression libraries. A major barrier, however, is the unavailability of these materials to the public research community at a feasible cost. At present, these critical materials are either proprietary or available only for such high prices (many thousands of dollars for each experiment) that they are effectively unavailable.

#### *Resource Needs and Recommended Actions:*

It is essential that NCI/NIH work with private industry to move these resources into the public domain in more than a nominal fashion. NCI must more effectively involve itself in ensuring timely use of new technologies by public sector investigators.

**C. Characterize genetic and expression profiles for normal breast epithelium at birth, puberty, adult, pregnancy, lactation, regression, and menopause.**

*Barriers to Progress:* This aim has been a goal of biologists attempting to understand breast cancer for more than 100 years. A primary constraint has always been availability of tissues from females at each stage of development.

*Resource Needs and Recommended Actions:*

NCI should develop a mechanism for obtaining such specimens, arrange for their clinical, pathologic, and histologic characterization, and make them available to public sector investigators.

**D. Characterize genetic and expression profiles of breast abnormalities at progressive stages of development from normal to invasive disease.**

*Barriers to Progress:* Ideally, this analysis would occur in tissue from the same individual over time, but we recognize this is not generally feasible. How are genetic changes and expression differences correlated with cellular, histologic, and clinical phenotypes? Goals of this effort are both to understand biology of tumorigenesis and to determine whether different treatment regimens are most effective given different genetic profiles.

*Resource Needs And Recommended Actions:*

NCI should facilitate the creation of new cell lines and develop a mechanism for acquiring and characterizing tissues with clinical and follow-up data that are made available to researchers. Furthermore, the expense of evaluating tissues is enormous. Technology is rapidly being developed that will enable this evaluation, but this technology is so expensive as to be effectively proprietary. NCI should create an infrastructure for screening tissues and providing results in the public sector for further analysis.

**E. Carry out experimental human genetics in mice, by generating mice with both wild-type and mutant human genes. Determine the effects of these genes on mammary gland, ovary, and endometrium (recognizing mouse-human differences). Determine the effects of mutations against different genetic backgrounds, with the goal of identifying genetic modifiers of mutant alleles.**

*Barriers to Progress:* This is expensive work, because multiple transgenic mice must be generated and bred.

***Resource Needs And Recommended Actions:***

Cooperative agreements across public and private sector laboratories are needed if this type of work is to be successful. NCI could provide the impetus for these collaborative efforts.

**F. Discussion and resolution of social and legal issues of informed consent and privacy of medical information in the context of genetic testing and genetic predisposition.**

***Barriers to Progress:*** Impediments to this work are educational and social. First, education of physicians in the community is extremely difficult, particularly given the pace at which new information is obtained, and the complexity of that information. Second, and more fundamentally, no level of genetic analysis or epidemiologic evaluation will suffice if health care is not available to persons with cancer- predisposing alleles revealed by these analyses. This problem is fundamental to all concerns about privacy, informed consent, and clinical research.

***Resource Needs And Recommended Actions:***

NCI should promote the importance and inter-relatedness of health care and health research and their reliance on each other.

The BC-PRG reviewed several additional questions. These are currently being addressed by research sponsored by NCI or by others, and/or are discussed elsewhere in this report:

- G. Do any life experiences, behaviors, or environmental exposures influence breast cancer risk among women with inherited mutations in major predisposing genes?**
- H. What is the efficacy of chemopreventive drugs in reducing breast cancer risk among women with inherited predisposition?**
- I. Are different recommendations for extent of surgery or reconstruction appropriate for women with inherited predisposition?**
- J. What is the efficacy of prophylactic mastectomy and prophylactic oophorectomy?**

## Chapter 4: Prevention

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### I. The Status of Breast Cancer Prevention Research

Prevention strategies aim to decrease morbidity and mortality from breast cancer by preventing or delaying the clinical onset of invasive disease. The emphasis in prevention studies over the past two decades has been (1) to describe behaviors or risk factors that appear to be associated with an altered risk of breast cancer development, (2) to identify natural or synthetic compounds that appear to be associated with altered risk or inhibit carcinogen- or virally-induced breast cancer in rodent model systems, or (3) to utilize drugs originally found to be effective as secondary preventive agents in established invasive cancers as preventive agents in high risk groups.

Advances in biology, genetics and epidemiology have led to identification of cohorts at increased risk for breast cancer development and as such likely candidates for prevention trials. However, as breast cancer frequently occurs in women without established major risk factors and is one of the most frequent causes of death in women over age 35, it makes sense to develop a number of preventive strategies so that at least one would be applicable and acceptable to an individual woman regardless of her current biological life phase, reproductive desires, hormonal needs, cultural and financial constraints, and risk level. Epidemiologic studies have identified several conditions or behaviors such as early full term pregnancy, exercise, calorie restriction, and adequate intake of several vitamins and nutrients as potentially important

in breast cancer prevention. These conditions or behaviors would potentially be applicable to most women regardless of predicted risk, and several of these behaviors might also help decrease morbidity and mortality from cardiovascular disease.

Alternatively, chemoprevention, which generally involves ingestion of drugs with associated expense and side effects, would be expected to be more acceptable and cost-effective when used in high risk cohorts. Large adjuvant and Phase III chemopreventive studies have established the efficacy of tamoxifen, a selective estrogen receptor modulator (SERM), in decreasing breast cancer incidence in high risk premenopausal and postmenopausal women. A new Phase III trial in postmenopausal women will be initiated shortly comparing five years of tamoxifen to five years of raloxifene. Fenretinide, a retinoid derivative, has been associated with a decreased incidence of contralateral breast cancer in premenopausal women. Development of other potential chemopreventive agents such as selenium, bioflavonoids, vitamins, DHEA and its derivatives, indole-3-carbinol, limonene, peryillyl alcohol, difluromethylornithine, polyphenols, curcumin, other retinoids, and SERMs often have depended on the initial demonstration that these compounds inhibit carcinogen- or virally-induced cancer in rodent systems. Movement of many of these drugs into clinical testing has been slow mainly because models for cohort identification, optimal drug dose selection, and measurement of efficacy in small Phase I and Phase II clinical trials where cancer

cannot be the endpoint are incompletely developed. Cohort identification and subsequent enrollment in a clinical trial is dependent on a potential subject's possession of the variable to be measured and her willingness to enter the study and adhere to study parameters.

It has been demonstrated that adopting lifestyle changes and/or adhering to a long-term medication regimen are likely to be motivated largely by an individual's perception of risk, particularly short-term risk. Despite tremendous advances in genetics, risk factor identification and epidemiologic modeling, we still lack highly predictive short-term indicators that accurately identify those individuals who will develop clinical invasive cancer within a five to ten year interval. If identified short interval risk biomarkers were also reversible with successful prevention strategies, these markers (termed surrogate endpoint biomarkers, or SEBs) could also be used in clinical studies to identify the cohort and determine intervention efficacy. We then would have an efficient method of performing Phase I and Phase II trials and might be able to decrease the size and duration of Phase III trials. Developing validated SEBs to evaluate efficacy is thus also critical for timely and cost-effective evaluation of prevention drugs and behavioral strategies.

To identify potential human SEBs and develop and test prevention strategies, it is necessary to gain a better understanding of controls of normal mammary gland development, differentiation and involution, and genetic and epigenetic changes/interactions that are associated with precancerous proliferative breast disease. To accomplish this goal, researchers are working to develop better *in vitro* and *in vivo* models of animal and human precancerous disease. Preventive activity

observed in animal models, however, often does not correlate well with prevention of breast cancer in humans. Animal models used in preclinical studies should possess genetic and other biomarker abnormalities similar to their human counterparts. The recent development of transgenic and knock-out mice, human precancerous cell lines, human xenograft models, mammary gland transplant, laser-assisted microdissection techniques, and gene expression array technology have proven to be powerful tools to study normal and abnormal mammary tissue, develop SEBs, and test the potential efficacy of drugs or behaviors, but expense and proprietary issues limit their use.

After potentially effective strategies and their biologic endpoints are identified from preclinical testing, new strategies are needed to translate these findings to the clinic. Researchers have been working over the past several years to identify more efficient clinical trial models that are safe and acceptable to patients. Since the latent period between the earliest precancerous changes and clinical cancer may be several decades, every promising intervention cannot be evaluated by traditional randomized Phase III trials involving tens of thousands of subjects over several years. Several prevention trial models have been developed. These include (1) Phase III adjuvant studies in which the endpoint is reduced contralateral breast cancer incidence, (2) short-term Phase I and Phase II studies of ductal carcinoma *in situ* (DCIS) or small invasive cancers in which change in biomarker expression (such as proliferation fraction) between the initial biopsy and reexcision is used as an indicator of response (SEB), and (3) intermediate and long-term Phase II studies in which high risk women undergo random tissue sampling via biopsy or fine needle aspiration before and after the intervention and



change in morphology is used as the prime indicator of response (SEB). It has yet to be demonstrated, however, that proliferation fraction modulation in DCIS trials or tissue morphology improvement in random needle biopsy or fine needle aspiration (FNA) chemoprevention trials correlates with a decreased incidence of breast cancer.

Other studies are underway to determine if less invasive procedures such as experimental imaging techniques (e.g., Sestamibi, MRI, PET, or SPECT scanning) or measuring SEBs from a blood sample (e.g., IGF-1) might substitute for tissue SEBs in early chemoprevention trials. Validating SEBs obtained from these less invasive procedures would facilitate development of early clinical trial models.

Finally, preventive research can only be done if women enter the trials, and identified effective strategies cannot be implemented if women do not hear about them, lack access, are frightened of them, or will not use them. Behavioral research (see Chapter 7: Cancer Control and Chapter 8: Outcomes) has provided us with important leads on the diversity of reactions to risk information and factors influencing acceptance of and compliance with cancer treatment interventions. There is a dearth of research regarding behavioral and cultural determinants of participation in prevention trials. Behavioral and cancer control research as well as outcomes studies are integral to the prevention mission.

## **II. Goals for Breast Cancer Prevention Research**

The goal of breast cancer prevention research is to develop readily acceptable, minimally

toxic, and affordable strategies that will reduce breast cancer incidence, morbidity, and mortality without inducing increased morbidity and mortality from other conditions. These prevention strategies aim to delay or prevent the initiation, promotion and progression phases of cancer in women in a variety of risk categories. As treatment research has increasingly targeted earlier stages of disease, the boundary between prevention and treatment has become blurred, particularly at the level of DCIS. Most treatment strategies, however, focus on eliminating established invasive cancer and preventing clinical recurrence whereas prevention strategies aim to avoid development of invasive cancer altogether. Specific goals that are readily achievable in the next five to ten years if the recommendations are implemented are the following:

- P Achieve better short-term risk assessment by developing and validating molecular and imaging risk biomarkers.
- P Develop and validate surrogate endpoint biomarkers (SEBs) for several drug classes and behavioral interventions.
- P Standardize sampling and assay methods for SEBs.
- P Identify animal models for several classes of chemoprevention drugs and behavioral interventions. These models should be relevant to the several human life phases in which the intervention is to be applied (adolescence, childbearing years, premenopausal post-childbearing, perimenopausal, and postmenopausal periods).

- P Complete pivotal Phase II prevention trials of single or multiple agents that have been identified as promising in preclinical studies, and multiple Phase III prevention trials with SEB validation.
- P As a result of the Phase II and III clinical trials, identify one or more promising prevention measures for the majority of the different life phases outlined above (adolescence, peak childbearing years, premenopausal post-childbearing, perimenopausal, and postmenopausal periods).
- P Conduct behavioral research to determine how best to attract women into prevention trials and how to ensure their compliance with prevention recommendations.

### III. Barriers to Progress in Breast Cancer Prevention Research

The BC-PRG identified the key problem areas that must be addressed and pursued vigorously over the next ten years to bring the promise of basic research to clinical reality. These central issues are:

- P **We need to develop a better understanding of precancerous breast biology.** Gaining this understanding will require development of additional *in vitro* and *in vivo* animal and human models of precancerous biology.
- P **We need to critically examine the ability of preclinical preventive trials to predict efficacy in humans.**
- P **We need to identify and validate in prospective studies risk and surrogate endpoint biomarkers to effectively develop and test both drug and**

#### **behavioral prevention strategies.**

Validated SEBs are urgently needed for clinical trials, mechanistic studies in animal models, and *in vitro* models. Currently, morphologic changes are the only validated markers for human trials. These changes are difficult to quantitate and are thus subject to marked interpretive variance. Other potential markers identified in Phase I and Phase II studies must be validated in Phase III trials by demonstrating that marker modulation correlates with reduced cancer incidence.

- P **We need to develop more efficient clinical trial models that will be attractive to women and their physicians and perform more prevention clinical trials.** Conducting behavioral research and working with lay advisory groups to determine which types of intervention strategies will be most attractive and effective and will be key in this effort. A prime focus of this effort should be increasing minority participation since these groups have not previously been adequately represented.

Two general strategies will help address these problems:

**First, more NCI resources must be allocated to prevention research specifically for the development of biomarkers, models for precancerous biology, and models for early clinical trials. More funding is also needed to increase both the quantity and quality of prevention clinical trials.**

Currently, the proportion of the NCI budget allocated to prevention is 6.2 percent. The portfolio review identified 33 RO1s, 8 RO3s, 3 R29s, 8 R21s, 1 R35, 1 R44, 4 projects from PO1s, 11 UO1s, 1 U10, 2 projects from P50s, 17 N01s (contracts) and 10 NCI intramural

projects now receiving NCI support that in some way relate to the four main issues listed above. Often, however, these projects fail to address the issues directly. Moreover, almost no targeted support exists for developing human models of precancerous biology, developing Phase II clinical trial models, and validating SEBs in long-term prospective studies. Neither is there sufficient targeted support for developing preclinical models, including integration of transgenic technologies and improved access to specialized cell lines and animals; comparative studies on biomarker development; or for determining the relevance of these preclinical models. In view of these problems, NCI should at least double the percentage of funding allocated for prevention activities.

**Second, there is a crucial need for integration between basic and clinical scientists, including behavioral scientists. A National (or International) Prevention Research Working Group could be an effective mechanism for quickening the pace of progress and fostering interdisciplinary collaborative research on**

**prevention.** The Working Group would advise NCI concerning new opportunities for interdisciplinary research and provide a scientific forum through regular workshops and meetings to facilitate collaborative research efforts of basic and translational scientists. Regular interaction with representatives from lay advisory groups and incorporation of key members into the Working Group is also envisioned. This mechanism would serve to (1) bring knowledge of basic biological processes and new agents from the laboratory to the clinic, (2) bring clinical problems to the attention of laboratory investigators, and (3) facilitate clinical testing of promising interventions. As a practical matter, the Working Group might need to be subdivided into those working primarily in chemoprevention and those interested principally in behavioral interventions; however, a substantial interaction between these two subgroups is envisioned, particularly in their use of cohorts, SEB measurements, and outcomes measurement.

#### **IV. Key Scientific Questions and Opportunities for Breast Cancer Prevention Research**

To achieve the stated prevention research goals within five to ten years, the following key scientific questions/issues have been identified; these are shown in priority order. While all of the questions are important to progress in prevention research, the BC-PRG recognizes that resources are not limitless; therefore, funds should first be allocated to the highest priority scientific questions, and to the remaining questions/issues as additional resources become available.

**A. Better models of precancerous biology are urgently needed. These include animal and xenograft models, human precancerous cell lines, and *in vivo* human precancerous models for long-term study.**

**Current Support:** The NCI currently supports the use of a large number of transgenic, null, and other specialized animal models to study carcinogenesis. Development of human precancerous cell lines and *in vivo* human models is insufficiently supported.

**Barriers to Progress:** Defined animal and human tissue derived models are needed that more accurately reflect genetic and epigenetic changes in human breast tissue during breast cancer initiation, promotion, and progression. There is a dearth of research whose primary aim is to study precancerous biology in these models and to define appropriate model use. Reasons for these gaps are:

- P An attitude that animal model, human precancerous cell line, and human model development in and of itself is not critical research; as a result, it is difficult to secure funding for these studies.
- P Access to developed animal models is often restricted and some are proprietary.
- P Human precancerous cell lines are difficult and expensive to establish and maintain in stable condition. Existing lines often are not fully characterized.
- P Long-term clinical studies are lacking in which tissue for biomarkers is repeatedly sampled over time in a demographically and epidemiologically defined cohort and in which biomarkers are prospectively correlated with significant physiologic events and cancer.
- P Prospective human model development is impeded by concerns that serial biopsies in asymptomatic women may induce undue morbidity, concerns that potentially less invasive procedures such as FNA or nipple fluid aspiration may be prognostically inferior to material obtained from biopsies, and lack of enthusiasm or mechanisms for funding long-term observational studies.

**Resources Needed:**

- P Animal models with multiple genetic and epigenetic alterations that will more closely approximate human precancerous changes.
- P Viable precancerous tissue from which to establish cell lines and complete biomarker characterization of established cell lines.
- P Funding for long-term prospective human studies.
- P A central distribution source for cell lines and specialized animal models with on-line information available on both cell lines and animal models.

***Recommended Actions:***

1. Provide targeted funding for xenograft model development and characterization and for precancerous development and biology in specialized transgenic models with application to chemoprevention studies.
2. Address the problem of proprietary rights for the use of transgenic mice that may limit their use by investigators.
3. Establish several national laboratories as clearinghouses for transgenic mice.
4. Expand cell and tissue banks to include storage of viable cells and cell lines.
5. Establish a clearinghouse or website to publicize availability and organize distribution of samples.
6. Provide targeted funding for prospective biomarker studies that include serial human tissue sampling over time with concomitant capture of risk and demographic variables.

**B. Delineate the key surrogate endpoint biomarkers (SEBs) for breast cancer development.**

***Current Support:*** The NCI currently supports SEB discovery, but long-term validation studies are inadequately supported.

***Barriers to Progress:*** We have little understanding of how alterations in methylation, cell signaling, DNA repair, apoptosis, oncogene expression, angiogenesis, or other processes lead to critical events and morphologic changes in premalignant promotion and progression. The lack of emphasis on long-term prospective biomarker studies is a key barrier to progress in this area.

***Resources Needed:***

A confidential, prospective, long-term subject/tissue resource is needed that would combine morphologic, immunocytochemical, and genetic characterization of benign tissue with demographic, risk, and outcomes information, including potential prevention measures employed and cancer development.

***Recommended Actions:***

1. Provide targeted funding for a long-term, prospective subject/tissue resource or broaden the scope of existing resources.
2. Establish a National Prevention Research Working Group that, as part of its activities, would help develop guidelines for such a resource.

**C. Determine the degree to which preclinical prevention trials are indicative of outcomes in humans.**

***Current Support:*** Although the NCI supports preclinical prevention trials, little support is available for efforts to determine if preclinical trials are predictive of clinical efficacy.

***Barriers to Progress:*** Organized data are lacking on the comparability of animal model and human SEBs at different stages of preneoplasia and their relevance to outcome. Information is also lacking on comparative reversibility of SEBs by drug or intervention class. Inappropriate drug doses are sometimes used in preclinical studies or inappropriate cohorts for a drug class are used in Phase I and II biomarker trials; this occurs due to lack of communication between basic and clinical scientists.

***Resources Needed:***

- P More preclinical studies in dose-ranges that could be expected to be non-toxic in humans with emphasis on determining SEB modulation at different stages of preneoplasia and at different phases in an animal's life span.
- P A National Prevention Research Working Group that would work with the NCI and other members of the scientific community to prioritize drug development and facilitate preclinical and early clinical trials design.

***Recommended Actions:***

1. Provide targeted funding to address the comparability of various animal model chemoprevention trials to human chemoprevention trial outcomes.
2. Provide other targeted funding to develop preclinical trial models for behavior, lifestyle, and dietary interventions.
3. Make the establishment of a Prevention Research Working Group an NCI priority.

**D. Increase the number of new agents and strategies evaluated by increasing the number of Phase II pivotal trials with biomarker modulation as the measure of efficacy.**

***Current Support:*** Only eight Phase II randomized placebo controlled trials are now being supported by the NCI. Of these, two are RO1s or R2s, three are UO1s, one is a P50, and two are contracts. Clearly, more support and more studies are needed in this area not only for synthesized chemoprevention compounds but also for natural products and behavioral interventions.

***Barriers to Progress:***

- P We lack validated SEBs to serve as substitutes or surrogates for cancer:
- We lack standardized methodologies.
  - Phase II funding is inadequate for SEB development in behavioral and drug interventions.
  - Phase III validation studies are under emphasized.
  - Well-studied cohorts are lost to follow-up as studies close and new trials are not always available.
  - Organ-specific studies of optimal tissue sampling are lacking.
- P We lack sufficient health care provider/investigator and patient-focused behavioral research to define unique and important variables in assuring rapid accrual and adequate adherence to prevention trials.
- P Too few studies have been conducted of culturally relevant prevention interventions in minority and/or socioeconomically disadvantaged women and the best strategies for cohort screening and study implementation.
- P Women are reluctant to be identified as members of a high risk cohort because they fear loss of confidentiality and thus possible insurance and employment discrimination.
- P High risk subjects are reluctant to participate in randomized drug trials because of the lack of guarantee that they will get the investigational agent.
- P Non-drug strategies may be most effective very early in the neoplastic process. Long-term study and compliance of adolescents and young adults is often difficult, especially when attempting randomized studies of a lifestyle change or a behavioral intervention.
- P We lack a multidisciplinary, multi-institutional scientific infrastructure focused on breast cancer prevention that truly engages both the basic scientist and clinician.

***Resources Needed:***

- P Money and infrastructure (i.e., high risk clinics) to develop and screen for biomarkers of short interval risk that could also be used as SEBs for Phase II trials.
- P SEBs for behavioral interventions linked to validated SEBs for cancer.
- P More drug and behavioral strategy development and testing applicable to premenopausal women.
- P Monies targeted for methodology transfer and technique standardization for tissue sampling and SEB assay.
- P Increased funding to support more and better Phase II trials that will increase precancerous biology knowledge while testing drugs or behavioral strategies.
- P Insurance coverage for prevention visits so that identified high risk cohorts could be more easily followed and the cohort maintained.
- P Strategies for communicating risk information.
- P Strategies for increasing accrual to and retention of minorities and socioeconomically disadvantaged women in clinical trials.
- P Incentives for patient participation in Phase II double-blind placebo controlled chemoprevention trials (e.g., free and confidential genetic testing, crossover design so all participants receive drug).
- P Funding for prevention translational workshops.

***Recommended Actions:***

1. Provide targeted funding for resources identified above.
2. Efforts should be undertaken to end insurance discrimination based on disease risk or participation in prevention trials.
3. Develop a variety of prevention drugs and strategies that will be attractive to women of diverse backgrounds and risk status.
4. Create a National Prevention Research Working Group with subgroups to include those whose primary focus is in chemoprevention and those whose primary interest is in behavioral interventions.



**E. Increase Phase III accrual efficiency and maximize scientific information gleaned (e.g., validation of SEB, conduct of behavioral and outcomes research)**

**Current Support:** NCI is supporting only one large Phase III pivotal chemoprevention trial in high risk women without prior cancer. Because of their cost and length (approximately \$60 million per trial over 10 years) only the most promising drugs that undergo Phase II testing will progress to Phase III trials.

**Barriers to Progress:**

- P Prevention trials require large numbers of participants. We need to refine and improve models (e.g., the Gail model) to predict short interval (five to ten years) risk in asymptomatic women. By accurately predicting short interval risk, we could preferentially select women at highest short term risk, thereby lowering accrual needs.
- P Since tamoxifen has now been identified as an active prevention agent and will be utilized as a control arm in most Phase III trials of high risk women, accrual needs will rise if the primary endpoint is improved efficacy unless the average subject risk is also increased.
- P Unreimbursed and hidden trial costs for physicians and potential participants discourage entry and adherence. Budgets are generally insufficient to cover all trial costs.
- P Potential trial participants are concerned about insurance discrimination if they become identified as high risk.
- P Interference with normal routine or hormone replacement therapy discourages accrual.
- P Frequent or vigorous toxicity monitoring and subjective perceptions of side effects reduce adherence.

**Resources Needed:**

- P Risk biomarkers predictive of short interval risk.
- P Inexpensive, easy to sample, minimally invasive, quantitative SEBs that could be validated as part of a Phase III trial (e.g., breast density, IGF-1/IGFBP-3 ratio). There was no enthusiasm within the BC-PRG to dramatically increase the number of active Phase III trials given their expense, however, there was enthusiasm for maximizing accrual efficiency and increasing the amount of information gleaned from Phase III studies by using these studies to validate potential SEBs identified

in Phase II studies. This should include gathering tissue samples and performing behavioral studies.

P More robust trial funding to allow for cohort screening, biomarker validation, and toxicity monitoring without subjecting participants to out-of-pocket expense.

P Insurance coverage for prevention visits.

P Increased minority participation.

***Recommended Actions:***

1. Provide targeted funding for short interval risk biomarker development.
2. Increase funding for individual Phase III trials to allow for biomarker validation and provide monies for cohort screening.
3. Efforts should be undertaken to ensure that HMOs and other insurers pay for breast health prevention visits and ban discrimination based on risk.
4. Increase collaboration and bartering with pharmaceutical companies and industry to share expenses for Phase III trials.
5. Make large long-term pivotal prevention trials using non-invasive validated SEBs or cancer as endpoints a major target initiative of cooperative groups.
6. Give the highest priority to evaluating agents in Phase III trials with the potential for multi-organ benefit; share costs with other NIH institutes.
7. Increase emphasis on testing prevention drugs and/or strategies that are applicable to all women. This would include premenopausal women and postmenopausal women who wish to continue hormone replacement therapy.
8. Minimize whenever appropriate required visits, questionnaires, blood sampling, and embarrassing or invasive procedures to maximize adherence with protocols. Eliminate subject out-of-pocket costs.
9. Provide targeted funding to develop and test strategies to increase minority enrollment into prevention studies.

**F. What are the essential changes in breast cancer initiation?**

***Current Support:*** This area is generally well-supported by the NCI.

**Barriers to Progress:** We continue to lack a clear understanding of the array of genetic and epigenetic changes that are most frequently involved in breast cancer initiation.

**Resources Needed:**

New technologies are needed to examine multiple gene expression and interaction.

**Recommended Actions:**

1. Encourage and support studies that apply new technologies or strategies to examine events in initiation.
2. Support new xenograft and *in vitro* model development.

**G. Are we using appropriate human models in Phase I-II testing for optimal chemoprevention dose-range finding?**

**Current Support:** The NCI currently supports seven Phase I-II studies in breast cancer chemoprevention. The majority of these trials utilize a short-term model in which women with incompletely resected DCIS or a small invasive cancer receive the drug under investigation in the two to four week interval between the excisional biopsy and definitive excision. Although this is an excellent model for drugs already known to have chemotherapeutic efficacy or new agents whose molecular targets are commonly overexpressed in DCIS, this may not be the best model for other types of potential chemopreventive agents.

**Barriers to Progress:** It is unknown if short-term modulation of proliferation and morphologic markers in DCIS and small invasive cancer is predictive of appropriate drug dose, particularly for agents that may have minimal activity against invasive cancer. In addition, it is difficult to use conventional drug development paradigms to develop biologically active non-toxic dose ranges for Phase I and Phase II testing because of the lack of validated SEBs obtained by minimally invasive procedures. Asymptomatic women may not accept non-medically indicated invasive procedures in Phase I drug development.

**Resources Needed:**

Cohort identification and alternative Phase I model development.

**Recommended Action:**

1. Provide targeted funding for alternative Phase I model development.

## Chapter 5:

# Detection, Diagnosis, and Prognosis

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### I. The Status of Breast Cancer Detection, Diagnosis, and Prognosis Research

#### *Detection*

Breast cancer detection is currently based primarily on physical examination and conventional mammography. A key contemporary success in detection has been the increased awareness and use of screening mammography that has resulted in a recent significant decrease in overall mortality due to earlier detection of small, more easily treatable cancers. Other notable achievements include the development and increasing use of relatively noninvasive image-guided methods for obtaining tissue samples for pathologic diagnosis, such as stereotactic core needle biopsies and fine needle aspirates (FNAs). Several new imaging technologies have been developed with the potential to be even better than conventional mammography at detecting clinically significant breast disease; these include magnetic resonance imaging (MRI), positron emission tomography (PET), and digital mammography.

Major shortfalls remain, however, in our ability to detect breast cancer. Large segments of the population are not accessing currently available methods of detection such as screening mammography. Neither conventional mammography nor any other available technology can distinguish breast cancer from benign breast disease--or sometimes even normal breast tissue-- with certainty, resulting in relatively high rates of false-positive and false-negative reports. Current imaging technologies are also unable

to distinguish trivial benign disease from premalignant lesions which portend a higher risk for breast cancer development. Available imaging methods are also very poor at detecting micrometastases or early recurrent disease. There are virtually no effective serum-based methods for reliably detecting the presence of micrometastatic breast disease.

#### *Diagnosis and Prognosis*

Today, as it has been for more than a hundred years, the definitive diagnosis of all types of breast disease is based on histologic evaluation of tissue samples using the light microscope. The histologic criteria used to define most breast lesions are historic but nonetheless quite reproducible for identifying fully invasive breast cancers. Criteria are suboptimal, however, at identifying benign lesions at high risk for progressing to breast cancer.

The development and increasing utilization of FNAs and core needle biopsies for obtaining tissue samples have been major advances in both detection and diagnosis. Stereotactic image guidance of needle biopsies has tremendously improved our ability to sample suspicious lesions, particularly non-palpable masses, as small as a few millimeters in diameter nearly anywhere in the breast. This has dramatically increased the detection of small, more treatable breast cancers and decreased unnecessary surgery in an enormous number of patients with insignificant benign disease. Other notable achievements include the identification of certain benign lesions that are both risk factors and precursors for invasive breast cancer (e.g., florid hyperplasias, atypical hyperplasias, *in situ*

carcinomas), presenting new opportunities for identifying patients at risk. Recent accomplishments include the identification of a small number of tissue-based biomarkers that are helpful in predicting clinical outcome and response to therapy (e.g., S-phase fraction, estrogen and progesterone receptors, c-erbB-2) and the discovery of genes (BRCA-1 and BRCA-2) associated with familial risk for breast cancers.

However, diagnosing breast cancer still requires some type of biopsy procedure. In addition, current diagnostic and prognostic methods cannot absolutely distinguish breast cancers that are treatable by surgery alone from those that are likely to recur or have already spread through micrometastases. As a result, we over treat up to 50 percent of breast cancer patients with adjuvant therapy. Moreover, available methods are inadequate for predicting the response of breast cancers to specific types of adjuvant therapies.

## **II. Goals for Breast Cancer Detection, Diagnosis, and Prognosis Research**

In the coming decade, we should strive to develop noninvasive methods for detecting and characterizing with certainty precancerous and cancerous breast lesions when they are small and more easily treated. Ideally, this will be done using serum assays or imaging methods to detect tumor-specific physical, chemical, or biologic characteristics. Markers should be sought that will signal the presence and identity of specific types of lesions, indicate their prognosis if left untreated, and

predict the likelihood that they will respond to particular types of therapy. Clinically useful markers will most likely be identified and characterized first in tissue samples obtained during biopsy or surgical procedures.

Particular emphasis should be placed on identifying markers that predict the risk of precancerous lesions progressing to invasive cancers, thereby providing new opportunities for breast cancer prevention. This might be accomplished through the use of markers as contrast agents for “risk imaging” using conventional mammography or through refinements of newer technologies such as MRI or PET scanning. It may also be accomplished by evaluating biomarkers in small tissue samples obtained during relatively noninvasive procedures such as core needle biopsies. It would also be highly useful to identify treatment-induced biomarkers or changes in biomarkers that could be used as surrogate endpoints for predicting success in breast cancer prevention trials, thereby shortening the time required to test promising new prevention strategies.

Special emphasis should also be placed on identifying biomarkers that predict the response of fully developed invasive and metastatic breast cancers to specific types of treatments, so we may optimize the use of currently available therapies in patients who already have breast cancer.

### **III. Barriers to Progress in Breast Cancer Detection, Diagnosis, and Prognosis Research**

#### **Barriers to Serum- and Imaging-Based Detection Research**

##### *Science-Related Barriers:*

- P No known serum or imaging techniques are sufficiently sensitive and specific in all patients to: (1) identify the presence of or distinguish between clinically significant benign and malignant breast lesions, (2) monitor the response of breast cancer to therapy, (3) determine the extent (stage) of breast cancer, or (4) detect early recurrences. Even the serum tests that are FDA-approved for monitoring have not yet been shown to result in a survival benefit.
- P There are few, if any, sufficiently sensitive and specific biomarkers known today that could be used as diagnostic or prognostic imaging contrast agents, targeting agents, or as serum markers to detect clinically significant breast disease.
- P No molecular techniques are as yet directly applicable to breast disease imaging.

##### *Resource-Related Barriers:*

- P New imaging technologies often diffuse via commercial marketing into clinical practice before they have been proven (in randomized clinical trials) to be truly useful. This occurs largely because (1) trials in large unselected populations are not being funded, and (2) commercial development typically does not include extensive clinical testing.

- P Academic research in diagnostic and prognostic breast imaging is limited by insufficient funding of focused research projects, by limited access to the newest and potentially most useful imaging technologies due to insufficient funding, and by a scarcity of scientists interested in this translational, cross-disciplinary research.

#### **Barriers to Tissue-Based Diagnosis and Prognosis Research**

##### *Science-Related Barriers:*

- P Biomarkers have yet to be identified that can: (1) predict the “natural history” clinical outcome of fully developed invasive breast cancers, especially small early lesions, with a high degree of certainty, (2) accurately predict the response of breast cancers to specific types of anticancer therapies, (3) identify benign lesions that will eventually progress to invasive breast cancers, or (4) be used as surrogate endpoints that indicate response in chemoprevention trials.
- P The few prognostic and predictive biomarkers identified to date are individually weak and often present in heterogeneous combinations within the same tumor. We do not fully understand how to evaluate and interpret this complex information. Statistical models are still in development.
- P Inadequate/inappropriate cell lines or animal models of benign and malignant human breast diseases are currently available, especially models of premalignant breast diseases to support mechanistic studies of possible diagnostic and prognostic biomarkers.

- P Current technology, including “high throughput” technology, has not been adapted to study the very small, usually archival, human tissue samples characteristic of precancerous or early cancerous lesions at the DNA, RNA, and especially protein levels.
- P It is unclear how to analyze and interpret the enormous amount of data being generated from new high throughput technology such as genetic arrays, especially as it relates to specific clinical problems such as diagnostic and prognostic biomarkers in breast cancer.

***Resource-Related Barriers:***

- P Human breast tissue samples for research are scarce, particularly samples of premalignant disease. Samples from diverse populations are needed for correlative studies necessary to identify, characterize, and validate diagnostic, prognostic, and predictive biomarkers. Although fixation of breast tissues is usual, this often precludes RNA and some DNA analyses.
- P Legal and ethical barriers to obtaining human tissue for biologic or clinical studies in general are complex, escalating, and geographically diverse based on local and state regulations.
- P Correlative clinical studies and tissue banking efforts that are necessary to identify and validate useful diagnostic and prognostic biomarkers have historically been given such low priority by NCI study sections that they have been unfundable.

- P The academic research community has inadequate funds to purchase and staff with trained personnel the most advanced and potentially useful new technologies (e.g., tandem mass spectrometry, laser capture microdissection, genetic/expression arrays).

**IV. Key Scientific Questions and Opportunities in Breast Cancer Detection, Diagnosis, and Prognosis Research**

***Detection-Related Questions and Opportunities:***

- A. Determine the potential of newer imaging technologies (e.g., MRI, PET, digital mammography, mammoscintigraphy, sentinel lymph node localization/sampling, magnetic resonance elastography, electrical impedance imaging, microwave spectroscopy, near infrared spectroscopy) to detect and diagnose clinically significant breast disease better than is currently done by physical examination and conventional mammography.**
- B. Can computer-aided technologies further improve the interpretation of conventional mammography?**
- C. What are the imaging characteristics of specific types of benign and malignant breast lesions detected by newer imaging technologies? Can standardized interpretation rules be developed to identify these lesions for any of these modalities? Can they replace or augment conventional**

**mammography in screening general or high risk populations?**

studies evaluating the abilities of MRI, PET, and digital mammography to diagnose breast cancer.

**D. Can tumor-specific biomarkers be identified and used as contrast agents to improve the performance of any imaging modality?**

***Barriers to Progress:***

P There is very little support for studies pursuing tumor-related biomarkers as diagnostic or prognostic contrast/targeting reagents.

**E. Does early detection by any imaging modality truly change the mortality from breast cancer?**

P There is almost no support for “risk imaging” studies specifically directed at characterizing precancerous lesions using any modality.

***Current Support:*** NCI and several other organizations are funding a large number of

***Resources Needed and Recommended Actions:***

1. Continue supporting studies into the basic biology of cancer in general, and breast cancer specifically, because useful imaging contrast/targeting agents will most likely come from these studies.
2. Fund more translational research into using available biomarkers, and new ones as they become available, as contrast/targeting agents to detect and diagnose breast disease using conventional and newer imaging methodologies.
3. Foster more basic research into the most novel imaging technologies (e.g., MR elastography, electrical impedance imaging, microwave spectroscopy, near infrared spectroscopy).
4. Continue funding research evaluating the ability of newer imaging technologies, especially MRI, PET, and digital mammography, to detect and diagnose breast disease, especially in large Phase III clinical trials.
5. Provide more funds to the academic research community, perhaps through partnerships with industry, to purchase/obtain the newest and potentially most useful imaging technologies.



*Serum and Tissue-Related Questions and Opportunities*

**F. Develop new methods to diagnose clinically significant breast disease and predict clinical outcome better than conventional histologic examination and the few available biomarker assays (e.g., SPFF, ER, PgR, c-erbB-2).**

**G. Are there biomarkers that predict the clinical outcome of precancerous and cancerous breast lesions if left untreated (i.e., prognostic factors) with a high degree of certainty?**

**H. Are there biomarkers that predict the response of precancerous and cancerous breast lesions to specific types of therapy (i.e., predictive factors) with a high degree of certainty?**

**I. Premalignant and malignant breast lesions often have complex phenotypes involving abnormalities in many biomarkers simultaneously. How do we interpret and use this information?**

**Current Support:** Support of research in these areas is quite high in the sense that useful biomarkers will most likely come from basic biologic studies of the development and progression of cancer in general, which are already heavily supported. NCI alone funds more than 400 biologic studies in breast cancer, and hundreds more in other types of cancers. Support is inadequate, however, in the sense that the problem is enormously complex and there is still much to learn.

**Barriers to Progress:** There are major gaps in support, many having to do with inadequate translation of basic research discoveries to specific problems and clinical applications. Very few studies funded by NCI or other major organizations are specifically addressing the discovery and characterization of biomarkers as diagnostic, prognostic, or predictive tools in premalignant breast disease or early breast cancer. Even fewer studies are aimed at using biomarkers in noninvasive serum assays or as imaging contrast/targeting agents.

*Resources Needed and Recommended Actions:*

1. Enable academic institutions and investigators to purchase the most advanced and potentially useful new technology (e.g., tandem mass spectrometry, laser capture microdissection, genetic/expression arrays). The academic research infrastructure has become obsolete and institutions lack funds to modernize and rebuild it. This action is independent of any scientific breakthrough, yet could result in significant scientific progress.
2. Create additional normal and premalignant human breast cell lines. These are essential for mechanistic biologic studies of premalignant breast disease and early breast cancer evolution. Only a few normal cell lines exist; there is perhaps one premalignant cell line.

3. Create additional animal models of premalignant breast disease and breast cancer. These are essential for mechanistic biologic studies of premalignant breast disease and early breast cancer evolution. Only a few animal models of premalignant disease exist; none of these are satisfactorily representative of the human condition.
4. Fund more translational studies specifically addressing tissue biomarkers in human premalignant breast disease and early breast cancer. Place special emphasis on studying biomarkers that: (1) predict natural history clinical outcome, (2) predict response to specific types of adjuvant therapy, and (3) can be used as surrogate endpoints in prevention trials. These studies may be best accomplished in relatively small and efficient interdisciplinary settings such as SPOREs or program projects.
5. Create/maintain banks of normal, premalignant, and malignant human breast tissue, especially linked to clinical follow-up. Support for access to fresh tissues may be particularly critical, due to the rapid degradation of RNA and DNA with fixation and processing. Focus support on organizations with a sufficient critical mass of investigators to justify these banks (e.g., cooperative trials groups, SPOREs, and NCI-designated Cancer Centers). Also consider establishing a national registry of patients with premalignant disease modeled after the Surveillance, Epidemiology, and End Results (SEER) program. Many premalignant lesions are now being diagnosed by stereotactic core biopsy and the patients are being followed without surgery. Thus, a large and potentially valuable virtual bank of premalignant lesions could be created to support definitive studies of prognostic and predictive biomarkers.
6. Improve mathematical and statistical modeling of the complex data being generated by high-throughput array technology. We currently do not understand how to interpret this avalanche of new information.
7. Develop technology to manufacture miniaturized customizable genetic/expression arrays at the individual investigator level. Investigators need access to inexpensive arrays designed to study specific questions in very small tissue samples. Extend these technologies to be more applicable to fixed, banked samples.
8. Develop miniaturized high-throughput technology to study protein expression in very small tissue samples such as archival human premalignant breast lesions. There is currently no technology for protein that is equivalent to genetic expression arrays.

9. Support translational studies specifically addressing diagnostic and prognostic biomarkers in serum samples of patients with premalignant breast disease and early breast cancer. This is potentially a noninvasive, economical approach to screening large numbers of patients.
10. Continue the high level of funding of studies into the basic biology of cancer in general because useful diagnostic, prognostic, and predictive biomarkers will most likely come from these studies. Meaningful progress in translational breast cancer research is absolutely dependent on breakthroughs in basic cancer biology.
11. Establish reasonable national guidelines for human tissue banking that promote scientific progress while protecting patients' rights. Translational research will become impossible if access to clinical samples is further restricted. In this regard, coordination among organizations such as the Office of Protection from Research Risks (OPRR) and Public Responsibility in Medicine and Research (PRIM&R) is essential.

## Chapter 6: Treatment

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### I. The Status of Breast Cancer Treatment Research

The National Cancer Institute, through its intramural and extramural research programs, continues to be a major contributor to improved breast cancer treatment that has resulted in longer disease-free and overall survival for patients with all stages of disease. Important progress has been made in developing new agents and conducting large and influential Phase III studies in surgery, radiation therapy, and systemic therapy for early breast cancer. The accepted standard of care for primary breast cancer, which now includes breast conserving surgery along with breast irradiation, is a direct result of controlled clinical trials. Much of this research has been done by NCI's Cancer Trials Cooperative Groups, organizations that provide academic continuity, intellectual community, originality, and a well-constructed mechanism for addressing therapeutic questions efficiently. While focused initially on major institutions in large population centers, these groups have become geographically diverse because of efforts to include community oncologic centers and some private practices. The Intergroup mechanism, a collaborative endeavor of multiple groups, has been highly successful to date in acting as the steering process for the design of truly large scale studies. Also constructive have been efforts to use the tissue resources generated by the cooperative groups to correlate treatment effects with biological observations. In this way, several new prognostic and predictive factors--such as overexpression of the HER-2/neu oncogene,

p53, and S-phase fraction--have been identified. These efforts propose to meld the worlds of laboratory and therapeutic research in a manner that promises to be mutually profitable. Other efforts by the NCI to accumulate and distribute tissue resources are equally commendable, and should permit researchers to test hypotheses more rapidly. Minority representation in NCI-supported clinical trials has generally reflected the demographics of the American population. Efforts are increasing to involve representatives of the public, advocates, and consumers in all components of the clinical investigation process.

However, as a result of inadequate support, accrual to all clinical trials is too slow, with a particularly poor record of accrual of several key target populations, especially rural patients, the elderly, and the economically disadvantaged. The translation of laboratory observations to the clinic, especially in the burgeoning area of genomics, is happening at a disappointing pace. Support is insufficient for drug development in single academic centers and for small, innovative trials that could act as "pilots" for the design of larger studies. As a consequence, new ideas develop slowly, and many major questions remain inadequately addressed. Chief among these are: optimal allocation of early stage patients to adjuvant systemic therapy; proper drug therapy for given biochemical profiles of disease; the best use of combined modalities (surgery, radiation, and drug therapy) in early stage disease including when to eliminate axillary dissection, breast irradiation, and chemotherapy; the management of preinvasive

disease; optimal means of controlling metastatic cancer; treatment of the frail elderly; and truly effective and practical means of chemoprevention for all women and for those at especially high risk. There remains insufficient information on special problems of minority groups, rural patients, and those not geographically close to major treatment centers. Patient-oriented outcomes, especially those concerned with quality of life during and after treatment, have been inadequately addressed.

## **II. Goals for Breast Cancer Treatment Research**

The goal of breast cancer treatment research is to dramatically improve management and outcome of all stages of the disease. This research may be subdivided into four main endpoints: longer disease-free and overall survival, including “cure” (i.e., offering cancer-free survival comparable to age-matched peers without breast cancer); improved patient-oriented outcomes, including reduced treatment and improved quality of life; lower incidence of new breast cancers (i.e., prevention) and cancers caused by therapy (e.g., chemotherapy-induced leukemia, hormone-induced endometrial carcinoma); and improved access of the entire American population to the highest quality medical services, both established and investigational.

Achieving these endpoints will require improvement in several areas. We must set as primary goals the development of innovative biological approaches to treating breast cancer, better means of drug screening and evaluation based on more accurate preclinical models, improved methods and procedures for drug development, and more comprehensive clinicobiologic databases. Initiatives should

be in place to ensure that new ideas in breast cancer and tumor biology are developed for therapy in a rapid and functional process. Basic scientists, including chemists, should be encouraged to participate in drug discovery.

Administrative goals must include establishing a clinical trials study section, expanding and improving the existing system for NCI-sponsored multi-institutional trials, creating more multidisciplinary program project-type grants (e.g., the SPORE model), and re-establishing the Breast Cancer Task Force. Other organizational goals in the next decade should include support for high risk “idea” grants to encourage innovation and creating a grants review process that is more rapid and more responsive to the priorities of the research community, rather than to a predetermined set of rigid categories. That research community must include, in addition to laboratory scientists and health delivery specialists, investigators in the social and psychological sciences and experts in communications, law, and government. Another goal should be to expand conventional clinical trials to be larger and better distributed geographically. These trials should reflect innovative designs with surrogate biomarker endpoints and incorporate correlative (tissue-based) integrated science. For progress to proceed, however, reimbursement for the routine care of patients on clinical trials must be assured. Further, the training of clinical investigators in a new era that emphasizes both biology and clinical skill must be improved, both for conventional M.D.-Ph.D. candidates and to develop specialized “translational scientist-physicians.”

### **III. Barriers to Progress in Breast Cancer Treatment Research**

Section IV below lists several research questions that should be addressed to accelerate progress in breast cancer treatment. In addition to barriers specific to these questions, a number of other barriers cross-cut some or all steps in the therapeutic ladder-- laboratory science, lead drug development, the conduct of small pilot trials, investigator training, the conduct of large multi-institutional trials, and communication to professionals and the public about clinical trials and trial results.

Barriers in the laboratory include the lack of adequate means of drug screening (including genomics), and the lack of large clinicobiologic databases. These are needed to apply the increasingly powerful tools of modern molecular biology to problems in predicting disease course, predicting treatment response, and designing therapies with specific biological targets.

Barriers to developing lead and clinically-relevant compounds include our lack of knowledge of the vulnerable sites among the myriad signaling pathways, cellular functions, and recently identified mutated genes as well as inadequate support for the institutional development of drugs through Phase I testing. Also lacking are study designs and statistical methods for clinical studies using biological agents that may inhibit malignant behaviors while not causing cancer cell kill, or which may augment the activity of conventional cytotoxic agents while being inactive by themselves. Current clinical trial durations are too long to permit rapid testing of ideas in this field.

Clinical trials of all types are hampered by several impediments. One is that the requirements imposed by the Office of Protection from Research Risks (OPRR) requirements have become too complex, cumbersome, labor-intensive, and inconsistent. The current system of local implementation hampers the development and initiation of national trials. Another impediment is the paucity of clinical investigators who are trained in both modern biology and clinical investigation. Funding for research focused on defining and overcoming barriers to participation in clinical trials is insufficient. In particular, research has not been conducted to determine the reasons for inadequate accrual of elderly patients to clinical trials.

A major barrier to progress is insufficient funding of existing clinical research organizations, which limits the accessibility of clinical trials. Inadequate support by health care provider organizations is also a barrier, since few patients can choose participation in a research study if that decision will lead to the loss of reimbursement while on trial for routine medical care that would have been provided pursuant to standard care.

### **IV. Key Scientific Questions and Opportunities for Breast Cancer Treatment Research**

The BC-PRG has identified several areas on which research attention should be concentrated over the next decade. These are largely concerned with clinical trials: generating new ideas for clinical trials, conducting pilot studies, designing and implementing large (Phase III) trials, investigator training, and communications about clinical trials.

**A. How can we develop innovative biological approaches to the treatment of breast cancer, in the laboratory and via small (pilot) trials?**

In this era of expanding opportunities in biomedical science we now have the opportunity to develop innovative approaches to breast cancer treatment; these include antimatrix agents, antiangiogenesis agents, vaccines, gene therapy, and agents directed at many levels in mitotic regulation, apoptosis, and signal transduction. These approaches could complement and eventually replace current cytotoxic approaches. The recent discovery of clinically meaningful synergy between monoclonal antibodies to HER-2/neu and chemotherapy (taxanes in particular) indicates the potential for advances in this direction. Following laboratory investigations and preclinical testing, we will have to conduct small trials to establish the safety and feasibility--and suggest the efficacy--of innovative treatment strategies. The second step, performing large-scale, geographically well-distributed, often simple trials, with appropriate correlative laboratory components, is discussed in the following section.

**Current Support:** NCI provides some funding in translational biomedical science, but the level of funding could be enhanced. Current support for pilot studies is minimal; this research is now dependent almost entirely on volunteerism by individuals and institutions.

***Resource Needs and Recommended Actions:***

1. Consider encouraging legislation to protect corporate interests while fostering cooperative research. Develop mechanisms to protect corporate investment in new drugs while permitting research that uses agents, sometimes in combination, from different companies.

***Barriers to Progress:***

- P Coordination of effort is poor among industry, academia, and government, and between the molecular biology community and clinical investigators. Clinically-oriented programs lack access to high level (molecular) technical expertise. Proprietary concerns too often inhibit communication.
- P Non-mammalian organisms and mammalian genomics have significant, but underutilized potential to identify sites of sensitivity as new targets for drug discovery, develop new screening models, and better elucidate the actions of existing active agents.
- P Animal systems, including transgenic animals, are being used suboptimally. Current screening methods to identify better anticancer drugs are very expensive and suboptimally predictive.
- P Academic institutions face considerable difficulties in developing new drugs in-house and in conducting small, innovative clinical trials in preparation for large scale Phase III studies. NCI has only recently begun to address this problem with new initiatives.

2. Increase funding for improved integration of the molecular biological and clinical sciences, possibly through support of PO1-type, SPORE-type, multidisciplinary, multi-investigator activities focused on clinical translation of basic research findings.
3. Provide funds (in the form of grants or contracts), expertise, and central facilities (as funded core facilities in institutions or in the NCI's intramural program) for the preparation of clinically testable compounds within academic institutions. The NCI is currently implementing a new program, Rapid Access to Intervention Development (RAID), designed to facilitate translation of laboratory discoveries of new molecular entities to clinical trials. NCI resources for preclinical drug and biologics development will be made available on a competitive basis to the academic research community. If the program is successful, it may be expanded to include diagnostics and preventives.
4. Establish a study section for clinical investigation, comprised largely of clinical trialists and translational scientists, with a funding line adequate to encourage applications, and with rapid review and funding of successful applications.
5. Liberalize Food and Drug Administration rules concerning combinations of agents in pivotal trials (including those from different companies), the use of innovative schedules, and the inclusion of patients with diverse pretreatment characteristics.
6. Develop and emphasize new trial designs to evaluate biological agents that may inhibit tumor growth or prevent metastases but not meet conventional criteria for activity because they do not cause tumor volume regression. New agents that work through cytostatic or differentiation mechanisms may require less but more pertinent information per trial, early stopping rules for differences of small clinical importance, and the capability to perform multifactorial analysis of combinations of biological agents.
7. Conduct research on surrogate endpoints that correlate with clinically meaningful outcomes; trials of biological agents may take too long to be clinically useful.
8. Reinstatement of the Breast Cancer Task Force, or a similar governmental activity, involving clinical scientists, laboratory scientists, social and behavioral scientists, physicians, nurses, representatives of the NCI and the Food and



Drug Administration, industry, and consumers. The Task Force would advise the NCI and recommend research focus and funding, especially concerning small "idea" grants. Such a body would likely be constituted of subcommittees that represent individual disciplines and interests, with a mechanism to ensure interdisciplinary coordination.

**B. How can we facilitate the design and conduct of large clinical trials in breast cancer, focusing on the endpoints of:**

- P Longer disease-free and overall survival**
- P Reduced treatment toxicity**
- P Reduced breast cancer incidence**
- P Ease of delivery to the entire population (including rural patients, the elderly, the economically-disadvantaged, members of minority groups)?**

The final step in developing more effective, less toxic means of killing cancer cells and preventing their growth (following laboratory investigations, preclinical testing, and the performance of small trials) is to perform large scale, geographically well-distributed, often simple trials, with appropriate correlative laboratory components.

**Current Support:** NCI supports research on breast cancer management, but funding is insufficient, particularly concerning strategies

for delivering care to all segments of the population. This is especially apparent in the flat funding or minimally increased budgets for NCI's Cancer Trials Cooperative Groups.

**Barriers to Progress:**

- P** Accrual to nearly all clinical trials is slow; we have more ideas worthy of testing than we have patients.
- P** Accrual of many target subpopulations (e.g., rural patients, the economically disadvantaged, the elderly) to clinical trials is poor.
- P** Very large scale, geographically well-distributed, simple trials are rare
- P** Few studies emphasize treatment toxicity reduction.
- P** Our understanding of social versus biological determinants of clinical outcomes is inadequate.

**Resource Needs and Recommended Actions:**

1. Increase support to NCI-sponsored trials, as judged appropriate on a per case basis, to approach the level of support of industry-sponsored trials. Expand current organizations--including Cooperative Groups, Cancer Centers, and SPORES--to accomplish greater geographic diversity, include more community-based oncologists, and provide improved access for underserved populations.
2. Facilitate better coordination of the efforts of cooperative groups, cancer centers, and SPORES.

3. Encourage more liberal eligibility criteria for participation in clinical trials.
4. Encourage, through funding and cooperative agreement mechanisms, research in reducing treatment toxicity, preventing second cancers, and improving patient-oriented outcomes (especially those concerning quality of life).
5. Encourage, through funding and cooperative agreement mechanisms, integration of the social, psychological, and biological sciences.
6. Simplify and streamline Office of Protection from Research Risks (OPRR) rules to make them easier to implement and monitor. Standardize informed consent documentation to guarantee consistency and facilitate the design and initiation of national studies. Empower local and regional Institutional Review Boards (IRBs) to avoid duplicative institutional documentation requirements. In some cases the use of national IRBs, which has facilitated industry-sponsored clinical research, would decrease the demands on individual institutions without jeopardizing patients' safety.
7. Enlist cooperation from, or design other mechanisms to ensure, that insurers pay the cost of routine medical care for patients on approved clinical trials. Similarly, amend Health Care Financing Administration policies to provide Medicare coverage for trial participation.
8. Foster collaboration between advocacy groups and clinical investigators in the design of trials so as to make them more acceptable to patients; for example, by improving informed consent documents, and by tailoring communications for the public.

**C. How can we develop the expertise required for modern clinical investigation?**

The nature of clinical research in breast cancer is changing rapidly in that sophisticated laboratory science is becoming increasingly relevant to therapeutic investigation. To assure progress we will need investigators who can take ideas from the laboratory and develop them into clinical strategies, and take

observations from the clinic and influence laboratory experiments. These same investigators will need to train new investigators to maintain continuity.

**Current Support:** The current level of support for these efforts is inadequate.

**Barriers to Progress:**

- P Modern clinical investigation suffers from a relative lack of new, well-trained clinical

investigators, especially those capable of bridging the clinical and laboratory-based research environments. Data concerning the career decisions of graduates of approved oncology training programs are insufficient.

P Clinical investigators are accorded less prestige and fewer opportunities for academic advancement in many academic centers. This disadvantage diverts new talent away from clinical investigation and deprives laboratory investigators of potential collaborators.

P Potential mentors in clinical investigation are under increasing pressure to provide patient care and generate institutional income, diverting their efforts away from teaching.

P Translational scientists lack a good training system or solid locus in the current two-culture environment (i.e., basic and clinical science). Mentors for translational scientists are particularly hard to find.

***Resource Needs and Recommended Actions:***

1. Provide grants for potential clinical researchers early in their training to encourage them to pursue clinical research careers.
2. Develop innovative training opportunities at the post-graduate level in both the laboratory and the clinic, such as those involving mentor pairs (clinical and laboratory). Funds will need to be provided for both mentors (e.g., salary support) and trainees (stipends). A career track for a new oncologic specialty--the translational investigator--needs to be promoted. Techniques for monitoring the success of these programs and for enforcing the proper use of funds provided will also have to be implemented.
3. Training grants for clinical investigators should be for a minimum five year period to provide for the longer training period required for these investigators. In addition, training must be coupled with career opportunities, i.e., improved funding of clinical research.
4. Conduct research--involving academia, industry, and government, and including experts in health care economics, delivery, and administration as well as biology and medicine--to identify ways for academic centers to maintain their economic viability, research vitality, and academic independence in an era of cost-containment for clinical care.

**D. How can we learn more about the biology of breast cancer for the purpose of predicting clinical course and predicting response to therapy?**

As our therapies increase in sophistication, we will need improved methods of allocating patients to appropriate treatment. For example, adjuvant drug therapy improves disease-free and overall survival of patients with early stage breast cancer, but patients with an especially good prognosis may benefit so little from such treatment that it would be best that they not be so treated, especially if the treatments are toxic. Similarly, expensive or toxic chemoprevention should be applied only to women at high risk of developing the disease. Some drugs might work especially well in patients with tumors that have specific biochemical characteristics, and others--with a lesser chance of response--should be spared such therapy. Properly designed clinical trials should not only be able to demonstrate desirable therapeutic effects, but should facilitate an improved understanding of social versus biological determinants of clinical outcomes.

**Current Support:** The current modest level of support is inadequate.

***Resource Needs and Recommended Actions:***

1. Establish, by funding or cooperative agreement within existing clinical research organization, large databases of biological plus appropriate clinical information. These databases should extend excellent current efforts in maintaining tissue registries and repositories, should include normal as well as neoplastic or preneoplastic (ductal carcinoma *in situ*, lobular carcinoma *in situ*, atypical hyperplasia) tissue, and should be amenable to the application of microarray (chip) technology.

***Barriers to Progress:***

- P We lack large biological databases derived from human material with appropriate clinical correlative information. There is a need for more central organization for tissue resources.
- P Laboratory investigators are often discouraged by the existing grant system and by peer pressure from studying clinical specimens or from conducting research with applied (versus basic) value. Artificial model systems that are already well characterized are the mainstay of basic research. Studying complex human material is often viewed as "fishing" by review bodies and is typically assigned low or no priority for funding.
- P Clinical investigators have limited access to sophisticated (bio)technology. Similarly, laboratory investigators with the greatest potential productivity in this area are not routinely in contact with clinical investigators, and are therefore often unaware of clinical issues of relevance to their work.

2. Develop and implement communications to redirect the scientific cultural environment toward greater acceptance of laboratory investigation utilizing clinical material or clinically-relevant biologic systems.
3. Implement the recommendations of the National Action Plan on Breast Cancer concerning the development of an improved, uniform consent form for human tissues.

**E. Access to accurate information on treatment options, including available clinical trials, is critical for patients, their families, and providers. The NCI currently supports activities in this area. Chapter 7: Cancer Control, discusses in detail the research questions and opportunities for improving communications. Specific to clinical trials, however, the BC-PRG recommends:**

***Resource Needs and Recommended Actions:***

1. Implement a coordinated communications program to educate patients of diverse cultural and educational backgrounds as well as primary care physicians concerning the necessity of clinical research, the value of clinical research to the individual, and the availability of clinical trials in specific disease areas.
2. Continue NCI support for current initiatives concerning access to information about clinical trials, but augment the Physician Data Query (PDQ) database with recent communication technology advances to make it even more accessible and interactive.
3. Establish an automatic, interactive electronic mail link between the NCI and funded investigators, cancer center directors, and SPORE directors to convey information about new or special funding opportunities.

## Chapter 7: Cancer Control

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### I. The Status of Breast Cancer Control Research

The national cancer burden is typically understood in terms of incidence, morbidity, and mortality. One in eight women will develop breast cancer in her lifetime. This year, of the roughly 1.3 million new cancer cases in the United States; nearly 15 percent (approximately 180,000) will have breast cancer, and nearly 44,000 women will die of this disease. After decades of climbing breast cancer incidence and unchanged mortality rates, an unprecedented 6.3 percent drop in overall breast cancer mortality was documented for the period 1991-1995. Most of this improvement has accrued to white women below age 65 and mortality reductions were not observed in all populations. A similar decline in incidence and mortality has not been observed in African American women, and the reasons for this remain unexplained.

No single reason accounts for the landmark drop in breast cancer mortality; rather, it can be attributed to decades of research on early detection, and treatment; the dissemination of research findings, and their application in the population. Recent findings concerning the benefit of tamoxifen therapy for breast cancer prevention in high-risk women provide additional hope for further reductions in incidence and mortality from this disease.

#### *Definition of Cancer Control*

The definition of cancer control has evolved in recent years. From 1982-1997, it was defined as “the reduction of cancer incidence,

morbidity, and mortality through an orderly sequence from research on interventions and their impact in defined populations to the broad, systematic application of the research results.” The NCI Budget Proposal for FY 1998 defined cancer control research as that which “bridges the gap between laboratory, clinical, and population-based research and health care by focusing on how to bring our discoveries to the practice of cancer prevention, detection, treatment, and rehabilitation.” More recently, the FY 1999 Budget Proposal defined it simply as “the application of cancer research results and interventions to decrease the burden of cancer.” Because cancer control is optimally effective when it cuts across biomedical/behavioral/informational/public health paradigms, the 1997 NCI Cancer Control Program Review Group further elaborated on these precursor definitions to arrive at the following definition of cancer control research, which is embraced by this review group:

**“Cancer control research is the conduct of basic and applied research in the behavioral, social, and population sciences that, independently or in combination with biomedical approaches, reduces cancer risk, incidence, morbidity, and mortality.”**

#### *Key Successes and Continuing Shortfalls*

A July 1997 reorganization of NCI’s Division of Cancer Prevention and Control (DCPC) eliminated DCPC and replaced it with the Division of Cancer Prevention (DCP) and the Division of Cancer Control and Population

Sciences (DCCPS). The DCCPS is the new focus for NCI-sponsored research in defined populations (including special populations), behavior, surveillance, outcomes, and other aspects of cancer control. DCCPS now also houses the Office of Cancer Survivorship. The Breast Cancer Progress Review Group views this reorganization as a strong statement of support for a more robust cancer control research agenda. There is still cause for concern, however, because this reorganization leaves cancer control activities split between the new DCCPS and the DCP, where the Cancer Control Research Base program and the Community Oncology and Rehabilitation program still reside. The challenge will be to successfully integrate these two programs into a coherent strategy for cancer control that is able to garner greater fiscal resources.

NCI has supported and promoted significant gains in breast cancer control among healthy women by advancing breast cancer epidemiology, including important contributions to understanding environmental, individual, and genetic disease risks. Recently, gene mutations associated with increased breast cancer risk have been identified and now may be cross-referenced with other known risk factors such as reproductive history, weight control, exercise, alcohol consumption, and possibly, smoking behavior. Similarly, advances in screening technology and efficacy have increased the importance of understanding screening behavior, such as why some women who are presumed to benefit from annual screening fail to comply with recommendations.

A strength of the DCPC program in survivor-focused cancer control over the past seven years has been its successful development and management of several Requests For

Applications (RFAs). These RFAs have focused research attention on breast cancer management in older women; psychosocial interventions; quality of life assessment in special populations; outpatient cancer pain management; adult survivor issues; cancer education programs in pain management, rehabilitation, and psychosocial issues; and psychosocial research specific to younger women with breast cancer.

As much as half of FY 1997 DCPC-funded research in cancer control has been drawn from set-aside funds. With new grant funding under RFAs discouraged, a significant drop in funding for such research is likely. Efforts to correct acknowledged historical problems of inadequate study section review for cancer survivorship grants have corrected the population science/community interventions aspect of the problem, but there remains inadequate review for grants focusing on individual care issues. Advances in measurement and decision-analytic methods now afford us a unique opportunity to change that history with a major programmatic commitment to health care and policy research aimed at people with cancer. Progress in cancer control research will depend to a great degree on the existence of a critical mass of experts in this area willing and able to integrate (and centralize where possible) symptom management, outcomes research, and psychosocial/physiologic late-effect issues into larger program goals and directions.

The recently established Office of Cancer Survivorship and the Outcomes Section in the Applied Research Branch within DCCPS creates an opportunity to more formally and substantially foster high impact research in rehabilitation and survivorship. Clinical trials

quality of life evaluation is an example of an important research area supported by more than one division within NCI that would benefit from enhanced coordination, rather than the current more diffuse arrangement.

While improving incidence and mortality statistics are encouraging, we have not quantified morbidity sufficiently well to provide an interpretable metric to add to well-known incidence and survival statistics. The simple, dichotomous ratings of incidence and mortality carry the advantage of being easily tracked and used to measure success. This lack of a “morbidity metric” hampers our ability to integrate the morbidity component of burden and track it to measure success. This is a significant problem, given that nearly 1.3 million Americans are diagnosed with cancer each year, and approximately eight million are currently living with the disease. Most of these survivors have completed their primary therapy and are either in remission or may even be considered cured of their disease. Yet survivors face a vast spectrum of physical and psychosocial sequelae, many of which are iatrogenic. Second cancers are now the sixth-leading cause of cancer deaths. Adverse treatment effects on major organ systems, cognitive function, and quality of life have been documented and are likely to increase as treatments become more aggressive. Debilitating fatigue, for example, is a persisting complaint of the majority of cancer patients long after treatment has been completed. The emerging set of life-limiting and life-threatening problems of cancer survivors is in need of research aimed toward prevention where possible, and intervention/rehabilitation for problems that as yet cannot be prevented. The large and increasing number of cancer survivors, their increased organization and advocacy over the past 10 years, and unprecedented public

interest in the cancer burden, including cancer control, gives us a unique opportunity to partner with survivors to identify and prioritize areas for research. The combination of known and unknown burdens experienced by survivors is considerable, and not matched by current NCI resource allocation relative to other aspects of the Nation's cancer burden.

Health communications research holds significant potential for advancing cancer control. The spectrum of issues relevant to breast cancer is broad, including, for example, the mechanisms underlying behavior change and the requirements for effective message diffusion to diverse audiences. Recent years have brought an explosion of new media--on-line services, CD-ROMs, and Web sites accessible through computers, TVs, kiosks, and other venues. These communication tools can allow patients, families, friends, caregivers, and health professionals to send and receive information on almost any issue, such as screening guidelines, therapies, treatment options (including clinical trials), and alternative medicines. Research is needed to assess the effectiveness of these new media, and to determine how best to use them to motivate behavior change, facilitate informed decision making, and help consumers evaluate the quality of cancer information available through these sources. The optimal use of these or more traditional communication tools in cancer control is complicated by audience diversity, including differences in gender, ethnicity, educational level, age, cultural beliefs, and language ability. We need to know more about which strategies, messages, formats, and channels are most powerful for which groups so that effective interventions can be designed. Message pre-testing for clarity, comprehension, believability, acceptability, personal relevance, cultural



sensitivity, and reading level is an essential component of this work.

New public/public and public/private collaborations between existing networks, like the NCI's Cancer Information Service (CIS), and other Federal and non-Federal service and information agencies (e.g., the Centers for Disease Control and Prevention) will provide excellent opportunities for investigating new methods of information dissemination and behavior change. Research should also explore how agencies with overlapping goals and audiences, but often competing agendas, can partner successfully, and identify the qualities and means needed to successfully undertake and implement both public and private partnerships.

## **II. Goals for Breast Cancer Control Research**

The ultimate goal of cancer control research is to eliminate the cancer burden. While achieving this goal is not feasible in the next five to ten years, it is realistic to strive to minimize the toll taken by these diseases. To reduce the burden of breast cancer, we must sustain a vigorous and substantial commitment to basic and applied cancer control research conducted by scientists from diverse disciplines. Such an integrated research effort should address monitoring, prevention, surveillance, detection, treatment, and follow-up, including the provision of compassionate palliative care to those who die of the disease.

Cancer control is frequently, though not always, devoted to finding the best way(s) to apply current knowledge about cancer to diverse populations as a means of reducing the national cancer burden. School-based comprehensive health education provides one such opportunity that as yet remains largely

unexploited. Despite impressive epidemiological data suggesting that a low fat, high fiber diet and regular exercise are protective against breast and other cancers, many school-based health education programs neglect these topics in favor of substance abuse prevention, reproductive health education and, at times, anti-tobacco curricula. Policy research into the health impact of school-specific disincentives and incentives for comprehensive health education, including the serving of healthy lunches, would be one potent focus of further study. As the positive health consequences of a comprehensive school-based health education program have potential to extend beyond breast cancer and even cancer in general, partnerships between NCI and other institutes such as the National Heart, Lung, and Blood Institute (NHLBI) would provide a means of sharing resources and further ensuring comprehensive health outcome assessment.

A tremendous amount of information has been learned about optimal screening activity as a function of age and level of personal risk. Far less is known about the value of screening a given population relative to cost, or about what personal factors influence variability in actual screening behavior among patients for whom regular screening is clearly cost-effective from a societal perspective (e.g., mammograms in moderate to high risk women aged 50 and older). The behavioral aspects of screening hard-to-reach ethnicities, the issues of low re-screening rates, and the use of brief behavioral messages to foster screening behavior need further exploration. Current opportunities to conduct large-scale Phase IV studies to demonstrate successful diffusion and cost-effectiveness of proven screening practices in defined populations are unprecedented, particularly given recent

advances in genetic testing and screening technology.

Many well-controlled clinical trials (and one meta-analysis of 45 controlled studies) have documented that relatively brief, inexpensive psychological and educational interventions improve the quality of life of cancer patients. Yet little diffusion research or formal adoption of these interventions in NCI-funded cancer centers can be found. Less is known about the efficacy of interventions for long-term survivors; an important focus for future research. Our health care arena is changing-- psychosocial care is often seen as a luxury, "value added" rather than essential, and the need for continued psychosocial research is questioned. In this era of cost containment and minimal standards of care, the discoveries made by researchers to date may be disregarded, and the opportunity for advancing cancer control with cancer patients themselves may be greatly diminished.

### **III. Barriers to Progress in Breast Cancer Control Research**

The current level of funding in this area is low relative to prevention, screening, and cancer treatment research. Most of this funding is from recent RFAs through which continued funding is now less assured. Without sufficient resources and funding, the potential of cancer control research to make a meaningful contribution to cancer care in future years will be lost.

Over the past 10 years, the CCOP research base and clinical trials mechanism have produced a successful chemoprevention effort; however, the CCOP research base approach toward behavioral prevention and control has been a failure in the eyes of many researchers in this field. Many explanations for this

failure have been offered, including inadequate incentives (i.e., low credit assignment) for participation by treatment centers, insufficient enthusiasm of investigators, competition with chemoprevention studies that provide better incentives, unfamiliarity with behavioral science methods in the treating centers, and lowered enthusiasm for behavioral research at NCI. All of these factors have contributed to the current situation, which could be improved dramatically by providing separate funding pools so that cancer control and behavioral prevention research no longer have to compete with chemoprevention and treatment research at CCOP-funded cancer treatment centers.

Another key barrier to progress in cancer control research is the failure to date to exploit the potential of information systems to facilitate care decision and outcomes monitoring and to provide both general and tailored information about cancer risk, prevention, detection, and treatment. To a great extent, this potential is untapped because the pace of advancement in information technology far exceeds that of practical, integrated application. For example, advances such as the Internet, the Intranet, computer networking, the increasing power and decreasing size of personal computers, and computerized clinical recordkeeping have not yet evolved into integrated information systems that readily interrelate, enabling users to easily traverse environments for data connectivity and/or enhanced cancer communication.

Several other barriers impede cancer control research. These include a lack of understanding of basic behavior to apply to cancer control research; failure of the clinical/science community to understand the importance of behavioral/psychosocial

research as it applies to cancer control; a lack of appropriate reviewers for grants in this area; the lack of reproducible, validated measures of morbidity; and the lack of a clearly articulated, coordinated and promoted approach to research in this area.

#### **IV. Key Scientific Questions and Opportunities for Breast Cancer Control Research**

The BC-PRG identified eight priority areas for cancer control research that, if pursued, will solidify previous accomplishments and maximize future opportunities in cancer control. These priority scientific questions and opportunities were selected based on: (1) strength of the existing scientific evidence; (2) potential for reducing the cancer burden; (3) responsiveness to opportunities arising from advances in basic science and technology; (4) availability of current technology; (5) likelihood of successful implementation; and (6) achievable and measurable goals and outcomes. These eight areas are listed below in priority order; it is recommended that resources first be allocated to address the highest priority issues, but it is essential that allocations be made to all the priority areas as soon as possible.

##### **A. What are the mechanisms responsible for basic behavioral change?**

Cancer control research priorities set by NCI have historically emphasized practical intervention and applications research to the exclusion of basic behavioral research. Basic research in the behavioral and social sciences can further our understanding of fundamental mechanisms underlying behavior that are highly relevant to cancer control. For example, such investigations may address fundamental mechanisms important in

smoking, screening, or decision-making behavior. As in basic biomedical research, basic behavioral research does not always address outcomes directly, but instead provides essential knowledge of mechanisms and universal principles necessary for improved cancer control. Growing recognition of the relevance of basic behavioral research for cancer control should encourage researchers in this area who have not historically received funding from NCI to apply.

**Current Support:** Review of the breast cancer funding portfolio did not produce evidence of active research into basic behavioral mechanisms that relate to cancer control; however, the concept for a new RFA on “basic biobehavioral research on cancer-related behaviors,” has been approved. This RFA will support 10 to 12 R-21 (exploratory) awards, with a \$2,000,000 first year set aside, to address the link between biology, behavior, and environment as they affect cancer-related behaviors. With limits of \$100,000 per year direct costs over two years, this initiative is likely to ignite but not sustain the required long term commitment to this area.

**Barriers to Progress:** Although NCI supports a variety of intervention strategies to modify behavior, there is little understanding of the processes underlying behavior as these relate to diverse breast cancer issues ranging from screening utilization to treatment compliance. Traditionally, behavioral researchers have not been funded by the NCI; as a result, these investigators typically have not focused on the cancer problem. Animal models and bench research, the traditional paths to funding for basic research within the NCI funding umbrella, are not usually appropriate for behavioral research, which typically studies humans in a controlled

laboratory environment. Further, these basic behavioral mechanisms and processes are likely to vary among women of different cultural, age, and economic groups, requiring additional study. Finally, because initial

studies in this area are theoretical and not likely to have direct or clear clinical relevance, they are viewed unfavorably by reviewers (NCI and peer) who require immediate results from behavioral research.

***Resources Needed:***

The primary resource required is a sufficient pool of qualified investigators trained in basic behavioral research, with an interest in applying this knowledge to the cancer control needs of the person at risk for cancer or receiving treatment for cancer. Developing this cadre of investigators will require strong training in mechanisms of human behavior at the graduate and post-doctoral levels.

Assuming this pool of investigators is created, the second major resource required will be sufficient funding to attract these investigators to apply their skills to the cancer control challenge. Such funding from NCI should come from targeted extensions of the recently-announced RFA.

***Recommended Actions:***

1. Provide targeted research funding directed at basic behavioral mechanisms, expanding on the recent RFA in exploratory research (R21 awards).
2. Create a unit focused on basic behavioral and social research within the new Division of Cancer Control and Population Sciences. Ideally, this unit would focus on biopsychosocial research in cancer control, examining the interactions of biological, psychological, and social processes in cancer etiology and progression, and on basic methods development, including innovative measurement and analysis techniques for use in behavioral research.
3. Stimulate graduate and postgraduate training in basic behavioral research as it may apply to cancer, including an annual opportunity for trainees and faculty to convene and share methodologies and preliminary findings.

**B. Do psychosocial factors, including but not limited to interventions, influence traditional disease outcomes (e.g., overall survival, disease-free survival, disease response)?**

Due to advances in early detection and treatment, people are living longer with cancer, increasing dramatically the number of cancer-affected life-years being lived by the

approximately eight million cancer survivors in the U.S. The quality of these added years of survival, however, has been called into question, particularly concerning cancer survivors' productivity and family functioning. Interventions are needed to reduce short- and long-term morbidity, restore functional status, improve palliative care delivery, and reduce future health risks.

**Current Support:** Several currently active grants, primarily RFA-supported R-01 awards, are now studying theoretically-based and practical psychosocial interventions. Outcomes covered by these projects include disease endpoints (e.g., treatment response, disease progression, disease-free survival, and overall survival), and quality of life, including disease symptoms, treatment symptoms, mood, functional status, overall health, and general well-being.

**Barriers to Progress:** We have insufficient knowledge of the specific mechanisms underlying the known association between social, economic, and cultural influences on

traditional outcomes. Historically, NCI has emphasized prevention and screening over treatment when prioritizing psychosocial and behavioral research. Most funded research focuses on psychosocial interventions or late effects research, with incomplete regard for socioeconomic and cultural factors, including their relationship to access and outcomes of care. This area of research suffers from relatively low priority and credibility among most scientists, clinicians, and funding sources directed by peer review. Also, because psychosocial interventions are labor-intensive to perform and to validate, conducting well-controlled studies is difficult and may appear inordinately costly.

**Resources Needed:**

The ideal infrastructure for progress in this area is a comprehensive health services research agenda that concurrently evaluates disease factors, treatment factors, psychosocial factors, and economic factors in the context of caring for women with breast cancer. Partnerships between NCI and vertically-integrated health care delivery organizations with information systems that effectively capture information on structure, process, and outcomes of care offer a unique opportunity to contribute to our knowledge base in this area. These organizations, however, may require persuasion and/or supplemental funding to participate in this activity.

**Recommended Actions:**

1. NCI should sponsor a consensus conference on the current state of knowledge in the area of impact of psychosocial factors on disease initiation and progression. Much of this research is funded by the National Institute on Mental Health (NIMH), the American Cancer Society, and the California Breast Cancer Research Program; a partnership with those agencies may help ensure that the conference is attended by investigators representing the breadth of research in this area.
2. NCI should forge partnerships with health care organizations having information systems that successfully integrate and concurrently analyze clinical, biological, and psychosocial data. Through these partnerships, mount efficient, controlled studies of psychosocial interventions to evaluate their impact in the context of a contained system of health care delivery.

3. Encourage focused research on populations/subgroups known to be at high risk of poor outcomes.
4. Utilize current cooperative group structure to evaluate these endpoints, encouraging the activity with supplemental funding.

**C. How can we facilitate better patient decision-making, especially that based on risks and benefits?**

Very few of the decisions that must be made about cancer treatment are simple. Most contain uncertainty, probability weightings, and the need to reconcile likely treatment outcomes with patient values and preferences. The science behind these decisions is progressing but requires improvements in patient measurement, decision analytic methods, physician-patient communication, and program implementation. This priority is consistent with the National Research Council's 1989 recommendation identifying risk communication research as an important priority area. Issues such as the use of tamoxifen for breast cancer prevention have again brought the issue of risk communications to the forefront.

**Current Support:** NCI has provided some support for decision-making research in the context of cancer risk notification, prevention, screening, and treatment decisions. Most of the current activity and interest seems to be in the area of cancer genetics; yet patient decision making concerning cancer screening and treatment could be enhanced by knowledge that could be gained from bringing decision science into the clinical and policy setting.

**Resources Needed:**

A workforce of decision scientists able and willing to turn their expertise to the cancer problem is vital to progress in this area. Macro- and micro-level communications research also must be stimulated; this research can help us understand why people

**Barriers to Progress:** Progress has been hampered by a lack of basic research aimed at understanding the underlying processes involved in complex decision-making under conditions of uncertainty. Substantial gaps exist in our knowledge of the individual and social processes that influence cancer risk perception and informed decision-making. Little information is available about how to communicate breast cancer risk (e.g., genetics, testing, breast self examination, screening/rescreening, early diagnosis, treatment, follow-up) in a manner understandable to various subgroups of the public, including but not limited to the patient population. It is recognized that population differences may influence these processes, dictating the need for tailored strategies and messages. To date, concepts and messages have seldom been pre-tested in the groups for whom the messages are meant. We lack a sufficient understanding of how women make decisions (e.g., whether to enter a clinical trial or seek mammography screening) based on risk/benefit assessment. In general, the risk/benefit balance is difficult to communicate in this content area, and that difficulty may be exacerbated in special populations such as those with low literacy, those with cultural variation from the mainstream, or the economically disadvantaged.

respond to some messages and not others, and how different subgroups respond to standardized versus tailored messages. Finally, additional funding is needed for decision-making research, for training communications researchers, and for concept and message pretesting.

***Recommended Actions:***

1. Initiate a program of basic research to elucidate factors in decision-making under conditions of uncertainty, such as cancer.
2. Fund a program of health communications research, emphasizing risk/benefit communication to varied audiences. Include funding to research the roles of public/public and public/private partnerships.
3. Integrate the pre-testing of concepts, messages, and visual techniques fully into the research process.
4. Support graduate and/or postgraduate communications and decision analysis research training.

**D. Can the delivery of breast cancer care from diagnosis and screening through treatment, follow-up, and end of life be improved in ways that maximize desirable outcomes and minimize cost?**

The delivery of breast cancer care across the continuum from risk identification to screening, early diagnosis and treatment, including caring for advanced disease, is guided by a large and expanding database of information gained from clinical research. However, although we have learned much about ideal care at each point along the continuum of care, we know very little about best care in the context of existing healthcare delivery systems, including considerations of providers and payers regarding ideal breast cancer management which takes relative costs and benefits into account. Often, the positive effects of a diagnostic or screening procedure or treatment intervention can be demonstrated, but these have not been weighed against competing negative effects, including side

effects and cost. Health services research, specifically cost-effectiveness research in the context of care delivery, offers an opportunity to address complex questions about the relative value of new and effective approaches which may or may not be advisable on a large scale.

***Current Support:*** NCI support for this area of activity is limited, even with recent initiatives to work collaboratively with large, integrated healthcare delivery organizations concerning cancer control and the delivery of care. As the health care system evolves toward the merging of delivery organizations into large, comprehensive systems, more research in this area will be important.

***Barriers to Progress:*** We lack important information on cost-effective practices in breast care, including prevention, screening, treatment, and treatment of advanced disease, particularly costly high-dose chemotherapy with stem cell or bone marrow transplantation.

Phase III trials with cost-effectiveness and cost-utility components are needed, particularly related to multidisciplinary care (e.g., follow-up by surgical, medical, and radiation oncology), and aggressive therapies with marginal benefit.

Health system evolution is ongoing, and continues to be a “moving target.” Cost-

effectiveness and cost-utility methodology is expensive, and can be controversial because of differing perspectives on cost and cost-effectiveness, and on the utility and cost-utility of various medical actions. In addition, health care organizations and health care payers are not generally aligned with cancer researchers in a common quest for advancement of knowledge.

***Resources Needed:***

A network of health care delivery systems with the infrastructure necessary to conduct diagnostic screening and interventional research is needed. Information systems are an important component of this capability. Specifically, health care delivery organizations require improved information systems and shared network databases in order to conduct meaningful breast cancer control research in defined populations.

***Recommended Actions:***

1. NCI can play a major role in inducing health care organizations and payers to participate in partnerships addressing cancer control objectives. One component of such partnerships could be NCI support for creating and developing enhanced information systems to manage and organize cancer control information in breast cancer databases. NCI might also take a proactive role in establishing stronger contractual and research linkages with both large and small healthcare delivery systems.
2. Conduct focused research in health services, decision science, and policy within a broad range of groups and organizations (i.e., not limited to large integrated health delivery organizations).

**E. What psychosocial benefits do patients obtain from unproven treatments that cause them to seek out such treatments?**

It has been estimated that Americans spend more money out of pocket for alternative medicine than on conventional treatment. Clearly, these diverse therapies, that collectively are not known to be of benefit, have perceived value to the patient. It would

be desirable to determine either the evidence for benefit of these therapies (particularly the high volume and high cost therapies), or to determine what it is about these treatments that attracts patients.

***Current Support:*** Other than work supported by the Office of Alternative Medicine (OAM), no currently funded research in this area was identified.



**Barriers to Progress:** Our understanding of the psychological processes that cause patients to adopt any unproven treatment is very limited. Belief in the efficacy of the unproven therapy, when viewed against a perception of minimal risk, may be sufficient to justify the cost incurred by the patient. Little is known about how physician factors may influence these choices, although it is generally assumed that they are contributory. As physicians have become less directive and authoritarian in recent decades, implicit (and even explicit) endorsement of relatively non-toxic adjuncts to conventional treatment appears to have become the norm. This conclusion, however, is based on limited empirical data. One

barrier to studying this area is a general apathy (or antipathy) on the part of the scientific community toward the study of unproven treatments, particularly those that have toxicity or compete with conventional therapy as “alternative therapy.” Understanding their appeal may shed important new light onto the study of needs and preferences of people with cancer, including the possibility that seeking unproven remedies may indicate dissatisfaction with existing conventional health care. It may provide important leads toward understanding satisfaction with conventional care and the kinds of ancillary services that would have value.

**Resources Needed:**

An organized program of psychosocial research into satisfaction with care and unmet patient need in the current health care delivery system could be supported with infrastructure development. We require a better understanding and clarification of the overall psychosocial needs of breast cancer patients, and women at high risk for breast cancer, a group that may be predicted to show emerging interest in unproven prevention strategies.

**Recommended Actions:**

1. Increase collaboration with the NIH Office of Alternative Medicine in developing a research agenda on the appeal of unproven therapies.
2. Support investigators capable of studying the interface between conventional care and complementary/alternative care, with the goal of better quantifying and characterizing women seeking remedies that have not been accepted by traditional medicine.

**F. How can advances in communications technologies best be used for research in health communications and behavior change and for delivering breast cancer information?**

Recent years have provided sweeping advances in communication technologies that are changing how patients, their families, and

the general public access and receive health information. New technologies and new media (e.g., Web TV) will continue to emerge and will expand the opportunities for innovative approaches to health communication. These technologic advances have untapped potential for research into behavior change.

**Current Support:** NCI has historically been more supportive of cancer communications activity than of formal cancer communications research. This is now changing, as NCI has increased its commitment to communications research, particularly that pertaining to tailored communication and its impact on subgroups of patients outside of the mainstream in terms of factors that influence the way information is delivered and processed.

**Barriers to Progress:** Little research has been conducted on how to make the most effective use of new information technologies (e.g., World Wide Web) to reach a large segment of the population with breast cancer messages, and to effect behavior change relevant to breast cancer control. Initiatives in this area must be very sensitive to sociodemographic, cultural, and ethnic background factors. The plethora of information can bewilder even the

most knowledgeable consumer. We do not yet understand some of the most basic issues related to each of the various new technologies, such as how to provide breast cancer-relevant health-promoting messages through them, which are best suited to which populations, or how to use them to deliver customized messages for different populations. Therefore, more research is needed on using tailored communications technology to reach target audiences with breast cancer messages, and on using the multitude of community media (e.g., information kiosks; computer terminals placed in public locations) and upcoming Web TV technology to reach segments of society with limited access to computers or the Internet. There is an urgent need for health information quality standards and for methods of judging the validity of information, especially on the Internet.

**Resources Needed:**

The existing Internet infrastructure, and possibly the newer Internet II infrastructure, along with Web TV, offer a solid base for launching health communication efforts related to breast cancer control. An opportunity is emerging to bring increased health awareness into the living rooms and daily lives of the U.S. population. Breast cancer, as a high volume, significant women's health issue in which new developments across the continuum of management occur frequently, is well suited to innovative applications of information technologies.

**Recommended Actions:**

1. Fund a research program on the application of new informatics technologies to cancer information and communications and their effects on behavior change.
2. Initiate cooperative arrangements between NCI and other organizations with extensive information sharing commitments relative to breast cancer (e.g., American Cancer Society, Cancer Care) to limit duplication of efforts and maximize both research and service-related gains in this area.

**G. What is the impact of breast cancer on the family? Specifically, what is its impact on other family members and the family unit, and what is the impact of the family unit on breast cancer outcomes?**

Cancer is regarded by most experts as a family illness, inasmuch as its effects reverberate throughout the family unit. Families play a very large role in the decision-making and recovery process, and family members themselves are affected, adversely *and* favorably, by the cancer experience.

**Current Support:** NCI currently funds a modest amount of descriptive research in this area. No funding could be identified, however, for intervention studies in which the family is the unit of intervention and analysis. A few intervention studies are directed at couple adjustment (communication/sexuality)

**Resources Needed:**

The organizational locus at NCI most appropriate to promote increased focus on family-based research must be identified, and then enhanced to support programmatic requirements in this area.

**Recommended Actions:**

1. Sponsor a workshop on family issues in breast cancer, including NCI-funded investigators and other experts, to establish consensus, common ground, and recommendations for future research.
2. Provide set-aside funding for family research related to breast cancer.

**H. What kind of communication strategies are needed to reach the diversity of health care providers in the area of breast cancer?**

The changing face of the health field, both in health care delivery and in information technologies, affects mechanisms for

during and after breast cancer diagnosis; other descriptive studies are moving toward a better understanding of the impact of breast cancer on the family. No research support was identified for studies exploring the impact of the family on breast cancer outcomes.

**Barriers to Progress:** Information gaps in this area are pervasive, requiring further descriptive studies. At a practical level, it is difficult to study entire families, and family research is a low priority across all of health care research. Further, because perceptions of family adjustment often vary markedly depending on the family member providing the perspective, assessment of the family unit is at best complex and may require observer rating. These problems are exacerbated by a paucity of assessment instrumentation for measuring family adjustment and family functioning.

communications to health care providers. These changes offer important opportunities to explore new ways of more effectively reaching this key group.

**Current Support:** NCI has a moderate portfolio in this area.

**Barriers to Progress:** We lack knowledge as to how to use the new technologies to reach the medical and health communities, especially in rural areas. Because we have little understanding of the personal, situational, and environmental factors that drive health delivery behaviors of health care providers and organizations, we remain ill-

equipped to motivate health care providers (especially those in managed care) to change their own behaviors (e.g., referring patients more readily to prevention and treatment clinical trials more readily, offering screening), especially in caring for disadvantaged populations.

***Resources Needed:***

A common, comprehensive communication network linking the NCI and health providers, particularly those who are not breast cancer specialists but who treat women with breast cancer and those at risk, would provide a very useful infrastructure upon which multiple research questions about breast cancer knowledge, attitudes, and behavior could be investigated.

***Recommended Actions:***

1. Provide funding for studies to examine the behavioral mechanisms and motivation-related characteristics of health care providers, including studies in managed care settings.
2. Explore opportunities for establishing a communications/information network with health care providers, especially providers who are not breast cancer specialists, but who treat women at risk for breast cancer and women diagnosed with breast cancer. This approach might be particularly beneficial in reaching populations with little access to specialists.

## Chapter 8: Outcomes

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### I. The Status of Breast Cancer Outcomes Research

“Outcomes” is a word popularly used to describe a variety of endpoints or products of health care. Classical models of health care delivery focus on the *structure* of care (e.g., numbers of health care facilities, physicians, nurses, laboratory services), the *process* of care (e.g., How are services delivered? Are the best standard treatments applied?) and the *outcomes* of care (e.g., Is mortality improved? Are more women receiving screening mammography? Is quality of life improved as a result of treatment?). This chapter focuses on outcomes relevant to breast cancer, emphasizing in particular *patient-focused* outcomes as distinct from *disease-focused* outcomes. Disease-focused outcomes such as tumor response, disease-free survival, and overall survival are well-described endpoints of clinical cancer treatment and are applied widely in clinical trials research with breast cancer patients. In contrast, patient-focused outcomes have had limited inclusion in breast cancer research yet are equally salient targets for scientific inquiry.

Patient-focused outcomes include:

**Quality of life (QOL)**, which has physical functioning (e.g., pain, limited arm motion), social functioning (e.g., stigmatization, isolation, vocational/role functioning), and psychological well-being (e.g., anxiety, fear of recurrence, depression, positive well-being) components.

**Economic outcomes**, including patient-related outcomes such as financial impact on the patient/family, loss of job, and loss of insurance; medical institution/health system outcomes as demonstrated through cost-benefit analyses; and societal outcomes (e.g., lost productivity).

**Quality of death**, including pain and symptom control, psychological distress, existential and spiritual concerns, as well as the setting of death and caregiver/family needs.

**Patient preferences and factors affecting treatment decision making** that may vary with differences in age/life stage, time since diagnosis, race/ethnicity/culture, level of social support, resources, and other factors.

**Treatment toxicities** (acute, early, and late) and their effects on function.

**Recovery and rehabilitation**, including short- and long-term issues related to breast cancer survivorship.

**Quality of care**, including access to care, and use of state-of-the-art prevention, detection, surgical, radiation, adjuvant, and other treatments that are appropriate for a woman’s age and comorbid conditions.

Although favorable patient-focused outcomes have always been a goal of medical therapy, only during the last quarter of the twentieth century has the technology become available to quantify and evaluate these outcomes scientifically. Further, application of this

technology to the health sciences is quite recent. Nevertheless, these patient-focused outcomes are of great interest to scientists, physicians, and society, as well as to breast cancer patients/survivors and their families.

## **II. Goals for Breast Cancer Outcomes Research**

At the September 1997 Breast Cancer Roundtable, the Outcomes discussion group proposed a framework for studying outcomes in breast cancer during the next five to ten years. The paragraphs below synthesize that discussion and provide a blueprint for how work should proceed in this area.

### ***A Framework for Examining Outcomes in Breast Cancer***

The framework takes a three-pronged approach to exploring patient-focused outcomes in breast cancer: improving our understanding of outcomes (by defining/identifying key issues and understanding underlying mechanisms), improving outcomes for women (through new interventions and dissemination of research findings on intervention efficacy), and enhancing methods and process for studying outcomes (by strengthening existing mechanisms, conducting observational studies, and using meta-analytic techniques to evaluate intervention efficacy).

#### **1. Improve Understanding of Outcomes**

**P Conduct studies to accumulate the body of descriptive research needed to define and improve our understanding of key patient-focused outcomes.** Currently, little is known about key outcomes for women following a diagnosis of breast cancer in the following areas: (a) treatment (acute, intermediate, late), (b) living with

cancer after diagnosis, and (c) family effects. We know little about the impact of breast cancer on a woman's social system (including but not limited to her partner and/or children, and the balance between caregiving/medical and family roles in managing problems associated with early discharge, outpatient treatment, or other aspects of care). In particular, how does social support affect mortality and patient-focused outcomes? Information is also lacking to demonstrate whether a history of breast cancer affects risks for other chronic diseases (e.g., cardiovascular disease, osteoporosis) or whether breast cancer and/or its treatment affects the risk of non-breast cancer related morbidity and mortality.

Breast cancer is largely a disease of older women (and will be increasingly so as the population ages). Little is known about the efficacy of various treatments in older women, since they have been excluded from clinical trials because of comorbid conditions or have not been encouraged to participate in clinical trials. Research should strive to determine which comorbid conditions are important when considering treatment and outcomes in older women with breast cancer or older women at risk for breast cancer (being considered for prevention and screening).

**P Capitalize on the many opportunities that exist to expand our knowledge about the mechanisms underlying patient-focused outcomes after breast cancer.** Many biological and psychosocial factors affect patient outcomes associated with breast cancer and tremendous research opportunities exist to identify and understand the mechanisms underlying these factors. We need to know the key

factors affecting quality of life outcomes (e.g., ethnicity, geography, age) and how risk groups and subgroups should be defined for poor or favorable outcomes. Similarly, we need to understand what factors influence outcome variations among women undergoing the same treatment. There is a need to focus on the range of outcomes rather than the central tendency, and to develop interventions that mimic or promote characteristics common to well-functioning women. These findings may facilitate understanding of patient and disease heterogeneity to promote more appropriate treatment choice, preferences, and outcomes.

A fuller understanding is needed as to which groups of women are at risk for poor quality of life and psychosocial outcomes, and at what points along the disease or care continuum risks are elevated. Methodologic studies are needed to determine the best times to measure patient-focused outcomes. In this regard, longitudinal studies of diverse patient populations are critical. When linked to mortality or disease outcomes, these will provide the potential to study the interaction between disease and patient-focused outcomes (e.g., the relationship and interaction between the quality of life and the quantity of life). Such interactions may be manifest in the role of psychosocial and behavioral factors on compliance/adherence to therapy, with a subsequent impact on survival.

## 2. Improve Patient-Focused Outcomes

- P **Develop and test interventions needed to improve patient-focused outcomes.** Intervention research provides an opportunity for hypothesis-driven

investigations to improve patient-focused outcomes after breast cancer. One of the many important questions is whether interventions aimed at enhancing quality of life after breast cancer reduce mortality in addition to their likely impact on patient-focused outcomes. The need to develop and test such interventions in randomized controlled trials at all phases of the disease is urgent. While a small number of studies are ongoing in this area, the heterogeneity of the disease and the limited participation of older women with breast cancer limit the generalizability of current research. Efforts must be increased to include all elements of the breast cancer population in intervention research. Interventions must be practical, feasible, and easily disseminated to have an impact on the general population of breast cancer patients. Finally, it will be critical to integrate descriptive information on prognosis and risk (both biomedical and psychosocial) to allow treatment to be tailored to the individual. The goals should be to minimize comorbidity, enhance quality of life, and answer scientific questions about relevant subgroups.

- P **Disseminate research findings related to patient-focused outcomes to have an impact on the care of patients in the community.** As intervention efficacy is demonstrated in research settings, avenues must be developed so those findings can be disseminated widely and incorporated into the care of patients. Ample evidence shows that the efficacy of medical treatments (e.g., breast conserving surgery) is slow to disseminate to the general community. In addition, practitioners must be available to provide an intervention once it is determined to be

efficacious. Some research resources must be devoted to determining the best way to disseminate information on effective intervention strategies to patients and providers. Sufficient resources must be available to train community practitioners to provide the interventions that are effective and research must be conducted to evaluate the interventions' impact on the quality of care in the general community (effectiveness research).

### **3. Enhance Methods/Process for Studying Outcomes**

- P Enhance NCI's existing research infrastructure/mechanisms to provide a platform for advancing outcomes research.** Two established research mechanisms could be expanded to facilitate the study of breast cancer outcomes. The first is the network of clinical trials groups that conduct prevention and treatment trials for breast cancer. These groups work in a coordinated fashion and have close working relationships with NCI program staff. The breast cancer clinical trials network provides an excellent infrastructure for appending studies of patient-focused outcomes to randomized controlled trials. The second mechanism, the Surveillance, Epidemiology, and End Results (SEER) program, is a population-based cancer registry system that tracks incidence and mortality rates for cancer in the U.S. population. The SEER program has only begun to address endpoints beyond the disease-focused outcomes, yet this mechanism could be expanded to include research on patient-focused outcomes. These two mechanisms offer outstanding platforms upon which to build a breast

cancer outcomes research program. Nevertheless, certain obstacles currently block this undertaking. Patients' and physicians' acceptance of and participation in outcomes research studies must be improved. Clinic-based compliance with quality of life research in NCI-sponsored clinical trials is below standard for acceptable, interpretable data and NCI funding incentives to compensate groups for compliance is too low to assure success. With the addition of the appropriate resources and priority by the NCI, this should be possible. Patient-focused outcomes and patient preferences may become critical components of evaluations of clinical trials in early stage breast cancer in which the therapeutic benefits are small. Currently, patient-focused data are missing from these analyses.

Barriers within the SEER program are more complicated and relate to the passive collection of data obtained through regional tumor registries. Upgrading this program to collect a core set of patient-focused data (e.g., information on education, income, type of health insurance, marital status, ethnic self-identification), might allow greater precision in understanding the disease- and patient-focused outcomes of breast cancer. However, systems will be required to protect patient confidentiality if such data are collected. The population-based registry system also can be used to evaluate quality of care by examining medical treatments received and their impact on breast cancer outcomes. Linkage of the Medicare and SEER databases has enabled such analyses relevant to older women with breast cancer, but this capacity should be



available more broadly across the population. Currently, only limited treatment information on the first course of therapy is collected regularly by SEER, and the reliability and quality of the data are uncertain at this time. Finally, quality of life outcome data on breast cancer survivors could be collected through SEER, providing a better picture of long-term outcomes of interest to patients and their families. The major strengths of the SEER mechanism are that it is population-based and lacks the selection bias inherent in data collected from clinical trials or research study participants.

- P Include observational research designs in studies of breast cancer outcomes.** In addition to studies utilizing the existing clinical trials and cancer registry mechanisms, other types of observational studies of breast cancer patients are important for exploring patient-focused outcomes. Epidemiological research demonstrating the value of such studies (e.g., the Nurses Health Study, the National Health Interview Study, the Women’s Health Initiative Observational Study) has a long tradition, but this type of research is applied less commonly in oncology. Observational studies can have greater relevance to the general population of breast cancer patients than results from selected participants in clinical trials or other research studies. This may be particularly true for studies of patient-focused outcomes in elderly and underserved populations. In constructing observational study designs, specific study questions and clear endpoints must be developed carefully.
- P As data become available, conduct meta-analyses to summarize breast**

**cancer outcomes data.** Meta-analytic techniques are now quite familiar to clinical breast cancer researchers. This approach permits the summarization of multiple observations from randomized treatment trials to study an outcome of interest (e.g., the efficacy of oophorectomy or ovarian ablation as an adjuvant treatment for breast cancer). As data are generated, researchers examining patient-focused outcomes would like to apply meta-analysis techniques to evaluate the effectiveness of interventions designed to improve patient outcomes or to summarize other observational data on patient outcomes after various breast cancer treatments. Greater use of these analytic methods is an important goal for outcomes research; there has been limited work in this area thus far.

### **III. Barriers to Progress in Breast Cancer Outcomes Research**

Outcomes research technology has been rapidly advancing but has been largely separated from clinical health care research. Barriers to the application of outcomes research to clinical health care research are numerous. They include the need to apply scientific disciplines that are different from the biomedical sciences (e.g., survey research, psychology, health services research, statistics, economics), the need for resources to collect additional data/information beyond that which is part of clinical care, a lack of scientific infrastructure within the NCI to develop and nurture scientific inquiry of this kind, and limited coordination and collaboration among researchers working in this field. Other barriers are intrinsic to breast cancer as a disease, and include its heterogeneity--across the age span, across the phases of disease, and across ethnicity and different socioeconomic

groups. Though difficult, these disease-related challenges are not insurmountable.

Furthermore, the underemphasis and trivialization of outcomes research as “soft and non-scientific” has been a major obstacle to its incorporation into traditional clinical cancer research. Efforts to educate the biomedical community about the scientific aspects of health care and outcomes research could contribute substantially to the acceptance and prioritization of this research agenda. Clearly, consumers and purchasers of health care find these endpoints compelling. To date, however, communication to patients about the impact of treatments on patient-focused outcomes has been limited (based on relatively limited research thus far); what information there is needs to be disseminated to the clinical practice community and to patients. Broader discussion of these endpoints and their value should enhance both participation in outcomes research and its broader support in the medical community.

Another major challenge in outcomes research is its multidisciplinary and cross-disciplinary nature. Mechanisms, such as special scientific conferences, research opportunities (e.g., RFAs), and public/private partnerships are needed to attract social scientists and health services researchers to the study of breast cancer outcomes research. Current research funding mechanisms strongly discourage cross-disciplinary collaboration. Most importantly, the existing peer review process is not structured to provide appropriate evaluation of interdisciplinary research. In addition, as for treatment studies with survival endpoints, long-term funding mechanisms must be developed for both observational and clinical trial studies of patient-focused outcomes. The traditional investigator-initiated research project grant is four years in

duration, an inadequate length of time to examine the impact of these outcomes on mortality or morbidity in breast cancer patients. Other critical needs include scientific training of outcomes researchers and the development of improved informatics systems that encompass patient-focused outcomes in addition to the traditional disease-focused outcomes. Resources must be committed to provide an adequate infrastructure for this research area.

Meeting some of the challenges that currently stifle outcomes research will require additional resources and creative efforts, but substantial opportunities and mechanisms exist that can be used to facilitate this important research. For example, simply acquiring a core set of demographic data from all patients participating in NCI funded research studies (e.g., ethnicity, income, education, marital status, insurance status) would greatly facilitate outcomes research. As noted earlier, using existing computerized databases (e.g., modification of SEER, the National Health Interview Survey) to collect observational data on patient-focused outcomes has significant potential for fostering outcomes research. Confidentiality issues, however, must be addressed. Observational studies of subsets of patients participating in clinical trials can also be conducted through the existing cooperative groups.

To help remove methodologic and information-related barriers, methodological resources (e.g., study instruments, web sites, CD-ROMs) should be made more available and should be better coordinated. Data sharing and increased collaboration in data collection and analysis should be promoted; NCI and the extramural communities could facilitate this through a formal review of the

state-of-the-field before initiating new research. An NCI task force or state-of-the-art working group could facilitate such efforts, which would identify research gaps and help ensure consistency in future data collection.

Consensus recommendations for easily applied, standardized measures of QOL endpoints (e.g., performance status and pain indices) might enhance their clinical use and the general clinical awareness of patient-focused outcomes. Creative approaches to educating providers about patient-focused

outcomes are needed. These could include interactive computerized teaching modules, print materials, and use of other media. Consumer involvement at all levels of research is essential. Involvement of the existing advocacy network should be encouraged to identify priority outcomes and help facilitate data gathering on non-mortality outcomes among women with a history of breast cancer. A task force might be useful in determining how to ensure that patients and health professionals have ready access to the results of outcomes research.

#### **IV. Key Scientific Questions and Opportunities in Breast Cancer Outcomes Research**

The BC-PRG identified 16 scientific questions that should be pursued over the next five to ten years to advance the field of outcomes research and improve patient-focused outcomes for women with breast cancer. These questions, discussed below, are listed in the priority order assessed by voting of the BC-PRG rather than thematically.

##### **A. What are the short- and long-term effects of multi-modal treatment for breast cancer?**

**Current Support:** No ongoing studies are examining patient-focused outcomes from multi-modal therapies (surgery, chemotherapy, hormones, and radiation). In both the NCI portfolio and research funded through other agencies, few resources are devoted to examining either the short- or long-term effects of treatments for primary breast cancer. The few studies that have been funded have mostly examined single treatment modalities and therefore underestimate the potential interaction or potentiation of effects of multiple treatments on patient-focused outcomes.

**Barriers to Progress:** The failure to attach patient-focused outcomes endpoints to breast cancer treatment trials is a critical factor in our continuing gap in knowledge about key non-disease outcomes. The main barrier is a lack of financial resources within the clinical trials cooperative groups. While the scientific expertise is available in many of the groups, there have been no additional resources available to append this research to the treatment trials. Responsibility for funding patient-based outcomes research has for 10 years been shared by the Division of Cancer Treatment and Diagnosis (DCT) and Division of Cancer Prevention and Control (DCPC); this arrangement has proven to be suboptimal. It is unclear how outcomes research will fare with the recent

reorganization of DCPC. It will be important to ensure that sufficient resources are available in this division if outcomes research is to receive a high priority.

***Resources Needed:***

Resources required for patient-focused research are greater than for typical treatment trials since treatment trials can take advantage of data collection from standard clinical care (e.g., blood work, radiographic studies).

***Recommended Actions:***

1. Use the NCI clinical trials groups to foster outcomes research beyond the minimal attention it has received to date. The Division of Cancer Treatment and Diagnosis should be given additional resources to support these activities and assume leadership responsibility in this area.
2. Expand and support scientific committees within each clinical trial group to focus on patient-focused outcomes.
3. Invest resources to augment the existing clinical trials infrastructure and thereby minimize overall costs for outcomes research.

**B. How can patient-focused outcomes be studied across the continuum of age? The impact of breast cancer treatments may be different among different age groups.**

***Current Support:*** No current NCI research support.

***Barriers to Progress:*** Women of all ages who enter clinical trials are a select group; older women in particular are underrepresented in clinical treatment trials because of comorbid conditions and because of treatment toxicities. Investigator-related barriers may also exist. Moreover, older women are less frequently treated at cancer centers and have lower participation rates on all types of research. Therefore, age appropriate protocols and outcomes research mechanisms other than clinical trials are critically needed to obtain outcomes data on representative samples of women of all ages who develop breast cancer.

***Resources Needed:***

Funding mechanisms are needed to support research on patient-focused outcomes that can be generalized to the population of women with breast cancer. Collaborative opportunities should be explored with SEER and other population-based cancer registries.

***Recommended Actions:***

1. Upgrade SEER and forge collaborations with other cancer registries (e.g., CDC) to capture routinely additional data on patient-focused outcomes.
2. Provide funding sources and supplements for registry-based research to encourage the use of population-based registries in outcomes research.

**C. What are the patient-focused outcomes for women with in situ breast cancer?**

***Current Support:*** Review of the NCI portfolio identified only two trials involving DCIS patients; these are treatment trials and do not address patient-focused outcomes.

***Barriers to Progress:*** Ductal carcinoma in situ (DCIS) represents approximately 15 to 20 percent of new breast cancer cases. These women will have near normal survival but may experience short and long-term morbidity from treatment. DCIS is seriously understudied from a disease- and patient-focused outcomes perspective. The reason(s) DCIS has received so little attention are unclear, but may relate to the more frequent treatment of these patients in community or non-research environments. The sample size requirements of prospectively randomized trials to address mortality outcomes for different treatment strategies would not be feasible; however, much smaller sample sizes could be used to address patient-focused outcomes.

***Resources Needed:***

It may be necessary to forge alliances with community physicians that go beyond the current CCOP mechanisms to recruit patients for these trials.

***Recommended Action:***

1. Explore new mechanisms for studying patient-focused outcomes in women with in situ breast cancer.

**D. How can patient-focused data be integrated with biological prognostic information to make the best treatment decisions?**

***Current Support:*** No research in this area was identified in the NCI portfolio.

***Barriers to Progress:*** Because of the paucity of patient-focused research sponsored by NCI, limited patient-focused data (e.g., age, comorbidity, ethnicity/culture, living situation, income, social support) are available to integrate with biological prognostic information. These data are not collected as part of clinical trials, but other research has shown, for example, that

socioeconomic status as a variable can have an effect on mortality that is comparable to the effect size of some treatments.

***Resources Needed:***

Resources should be provided to collect these data along with information on disease-focused outcomes.

***Recommended Actions:***

1. Convene a working group to identify the key patient-focused variables and make recommendations for their systematic inclusion in clinical trials databases.
2. Make better use of SEER and forge collaborations with other registries (e.g., CDC) to conduct for research to identify prognostic variables.

**E. How can we improve patient outcomes, including the physical, emotional, and social dimensions of health-related quality of life?**

***Current Support:*** Only two studies on this topic were identified in the NCI portfolio.

***Barriers to Progress:*** This is an underfunded area of research given that breast cancer is the most common cancer in women. Some of the barriers to this research include the expense of intervention research and the challenges inherent in pilot testing interventions. Study sections are often not attuned to the “applied” type of research required, therefore grant applications may not be viewed favorably. Mechanisms for funding pilot studies for intervention development are not readily available (R03 budgets are too limited for these personnel-intensive studies).

***Resources Needed:***

Appropriate review mechanisms and funding opportunities are needed.

***Recommended Actions:***

1. Expand opportunities and funding mechanisms for developing interventions and measuring outcomes that are important to patients (i.e., pain control and quality of life issues).
2. Develop appropriate review mechanisms for intervention-oriented and applied studies.

3. Recognize that these studies may be expensive and require long-term funding.

**F. How are the health care needs of breast cancer survivors being met within the current health care system?**

***Current Support:*** This research area is not addressed in the NCI portfolio.

***Barriers to Progress:*** More descriptive and observational studies are needed on how the health care needs of breast cancer survivors are being addressed by primary care providers. The interactions between primary care physicians and breast cancer specialists in the new health care environment require study. At this time, no research component within NCI is specifically interested in health services research.

***Resources Needed:***

Greater involvement of health services researchers is needed to address these strategic issues.

***Recommended Actions:***

1. Foster interactions between funders of health care, provider organizations, and patient advocacy groups to determine optimum strategies for long-term management of breast cancer survivors within the health care system.
2. Encourage collaboration among health services researchers, health economists, primary care providers, breast cancer specialists, and patient advocates to advance research in this area. Targeted funding mechanisms are necessary to attract investigators to participate in a multidisciplinary effort.
3. Expand collaboration between the Agency for Health Care Policy and Research (AHCPR) and NCI to facilitate research in this area.

**G. What treatment research resources exist to foster research on patient-focused outcomes?**

***Current Support:*** NCI has multiple cooperative clinical trials groups that are funded to examine disease-focused outcomes. Several of the groups have committees or working groups that address quality of life and other patient-focused outcomes. This is the extent of NCI support of such research.

***Barriers to Progress:*** Research in this area is impeded primarily by financial limitations. Minimal resources are available within the cooperative groups to

support investigator-initiated protocols on these outcomes (across many disease sites), and the pace at which trials are often activated precludes the opportunity to obtain extramural funding to support outcomes research to be conducted in parallel with the treatment trials. In addition, since the clinical trials groups are seriously underfunded, they are hesitant to undertake outcomes research, particularly if they have had an experience in this research that they perceived as unsuccessful or expensive.

***Resources Needed:***

More funding to facilitate this work through the existing infrastructure.

***Recommended Actions:***

1. Develop an inter-group mechanism on patient-focused outcomes that will parallel the treatment-oriented breast inter-group committee, and coordinate and share existing and new technologies for assessing patient outcomes.
2. Train more researchers to conduct outcomes research.
3. Develop mechanisms to disseminate patient outcomes information to providers and patients.

**H. How can the management of disease symptoms and treatment side effects be improved?**

***Current Support:*** Eight studies in this area are listed in the NCI portfolio; of these, three are related to pain and palliative care. Not listed are some prior studies conducted by the North Central Cancer Treatment Group.

***Barriers to Progress:*** This research is limited by few data on treatment side effects (see question A above). Some of the other barriers to this research include the expense of intervention research and the challenges inherent in pilot testing interventions. Study sections are often not attuned to the “applied” type of research required, therefore grant applications may not be viewed favorably. Mechanisms for funding pilot studies for intervention development are not readily available (R03 budgets are too limited for these personnel-intensive studies).

***Resources Needed:***

More financial support to the clinical trials groups is needed to incorporate this research.



***Recommended Actions:***

1. Foster research on disease symptom and treatment side effect management within the cooperative group setting, either as part of treatment trials or as separate cancer control/symptom management studies.
2. Train more individuals to do research in this area.
3. Foster a public/private partnership to move this field ahead; currently, most work in this area is conducted by the pharmaceutical industry. In addition, since there is no incentive for pharmaceutical companies to continue research on drugs that no longer have patent protection, NCI should take the lead in testing such drugs to identify potential new uses for cancer patients.

**I. How can the long-term medical and psychosocial outcomes for breast cancer survivors be improved?**

***Current Support:*** A number of studies in this area are listed in the NCI portfolio. This research has been successfully initiated through the RFA mechanism.

***Barriers to Progress:*** Longer-term grants are needed to conduct research for some endpoints. Greater collaboration with the SEER registries and cooperative groups could facilitate this research. The NCI-funded research has focused primarily on psychosocial outcomes. More attention should be paid to the late medical effects of treatment such as premature menopause, osteoporosis, cardiac morbidity, breast edema, and arm problems. More research is needed in different age groups, particularly the elderly, for whom comorbidity and treatment morbidity may be more important. In general this research does not fare well through the traditional study sections.

***Resources Needed:***

These studies should be fostered within the cooperative group setting, where they would be a natural add-on to clinical trials, or as separate trials. In addition, we need to train more investigators, especially physicians, and encourage them to consider this research area.

***Recommended Actions:***

1. Facilitate the integration of these long-term follow-up studies within the cooperative groups and SEER registries.
2. Provide funding for longer-term studies in this area.

3. Train more investigators, especially physicians, to participate in this research.

**J. What secondary prevention and health promotion efforts are effective and appropriate for breast cancer patients/survivors?**

**Current Support:** This research area is not currently funded or supported through the NCI. With the population of cancer patients and survivors growing, this is an important area for inquiry and intervention research.

**Barriers to Progress:** The principal barriers are that no funding is currently available and appropriate study sections do not exist to review applications for this research. The participation of health promotion researchers in breast cancer research is needed.

**Resources Needed:**

Funding mechanisms are needed, especially support for pilot studies.

**Recommended Actions:**

1. Create new funding mechanisms to stimulate research in this area and attract health promotion researchers who do not typically work with cancer patients.
2. Promote public/private partnerships to advance this field.

**K. What are the economic and health care outcomes for patients/survivors with breast cancer?**

**Current Support:** This research area is not addressed in the NCI portfolio.

**Barriers to Progress:** More systematic research is needed to describe economic and health outcomes after breast cancer from three key perspectives: (1) *patient level*--financial impact on patient and family, loss of job or insurance; (2) *health care system level*--cost-effectiveness analyses, patient care guidelines; and (3) *societal level*--lost productivity, families that have lost a parent. Currently, no funding mechanisms exist for this type of research. Further, this research requires multidisciplinary expertise, especially from economists and health services researchers.

**Resources Needed:**

More training and interdisciplinary interactions are necessary to begin to study these patient-focused outcomes.

***Recommended Actions:***

1. Develop interdisciplinary research training and teams to study this group of patient outcomes.
2. Promote collaboration with health services researchers and health economists through targeted workshops and conferences.

**I. How can patient preferences be incorporated into treatment decisions?**

***Current Support:*** This area is not addressed in the NCI portfolio.

***Barriers to Progress:*** Few tools are available to explain complex statistics and risk/benefit. There is an urgent need to develop ways to explain prognostic variables to patients simply and to develop methods to incorporate patient preferences into treatment decisions.

***Resources Needed:***

Tools are needed to help elicit patient preferences and communicate complex prognostic information. More data on patient-focused outcomes, collected in parallel with treatment trials, are needed so that this information can inform the development of preference models/schemes.

***Recommended Actions:***

1. Use available expertise in outcomes and decision analysis to develop resources from the clinical trials groups and the research community to address this problem.
2. A national consensus or working group should be established to guide efforts in this area.

**M. What patient outcome data are being collected in prevention trials?**

***Current Support:*** The Breast Cancer Prevention Trial (BCPT) is collecting quality of life outcome data.

***Barriers to Progress:*** This issue has not been on the research agenda for prevention as it is quite new. Understanding patient outcomes is critical to the acceptance of and adherence to prevention strategies. It is essential to collect outcome data in conjunction with prevention trials so that women will feel confident that the preventive therapy, though proven effective against breast cancer, will not also result in toxicities or other potential harms. Different outcomes need to be measured for different treatments. Patient self-report is more desirable than observer rating of

toxicities and adherence. The BCPT data will be very important for decision making regarding the widespread use of tamoxifen. These same considerations will be relevant for any new chemoprevention strategy that is tested in the future.

***Resources Needed:***

Groups of outcomes investigators are needed to work with prevention researchers in assessing patient-focused outcomes. Training of more investigators in prevention and outcomes research is needed to support collaboration in this new and expanding research area.

***Recommended Action:***

1. NCI should encourage the development of common mechanisms for reporting patient outcomes in breast cancer prevention studies.

**N. What kinds of prevention research resources exist to facilitate patient-focused outcomes research?**

***Current Support:*** No prevention research resources are currently listed in the NCI portfolio.

***Barriers to Progress:*** Barriers include the lack of resources and coordinated effort across prevention activities.

***Resources Needed:***

More investigator training and cross-disciplinary interaction are needed.

***Recommended Action:***

1. Encourage public/private partnerships and consumer involvement to foster research in this area.

**O. How can patient-focused outcomes for women with advanced metastatic breast cancer be improved?**

***Current Support:*** No support is listed except for three studies on pain and symptoms; only one of these deals with breast cancer patients specifically. One such study is currently funded by the Department of Defense.

***Barriers to Progress:*** More research is needed on quality of life outcomes and psychosocial support services for this neglected group of breast cancer patients. Women with advanced metastatic cancer experience many symptoms other than pain, e.g., fatigue, nausea, and anxiety. This research is hampered by the expense of intervention research and the challenges inherent in pilot testing interventions.

Grant applications are often not viewed favorably in study sections because reviewers are not attuned to applied research. In addition, funding mechanisms for personnel-intensive pilot studies for intervention development are needed.

***Resources Needed:***

These studies should be fostered within the cooperative group setting, where they would be a natural add-on to clinical trials, or as separate trials. We need to train more investigators with an interest in this area of research; there is a serious shortage. Most work in this area is done through pharmaceutical industry; public/private partnerships should be fostered.

***Recommended Actions:***

1. Use the cooperative groups and the CCOPs as a platform for conducting this research.
2. Train more investigators to undertake research on patient focused outcomes in women with advanced metastatic breast cancer.
3. Foster public/private partnerships; most work in this area is done by the pharmaceutical industry. Include patient advocates in these partnerships.

**P. What cancer control and survivorship research resources are available to advance the field of outcomes research?**

***Current Support:*** No resources are currently listed in the NCI portfolio.

***Barriers to Progress:*** These include a lack of infrastructure at NCI or through the cooperative groups and the lack of funding available to support this research infrastructure. Mechanisms are needed to encourage data sharing and collaboration among investigators. The state of the field needs systematic review (meta-analysis) on a regular basis to understand what we know and develop hypotheses for future research. Formal availability and coordination of methodologic resources (e.g., study instruments, web sites, CD-ROMs) is needed. Improved informatics would enhance health care research on patient-focused outcomes. In addition, we need mechanisms for disseminating outcomes research results so that findings have an impact on patient/survivor care.

***Resources Needed:***

Improved informatics and data capture procedures are needed. Cross-disciplinary working groups focused on outcomes research, both intramurally and extramurally, are also required to advance this research.

***Recommended Actions:***

1. Improve informatics systems to facilitate data capture.
2. Increase training opportunities, especially for multidisciplinary training.
3. Establish an intramural and extramural working group to foster research.
4. Conduct regular and systematic assessment to determine the state of the field and develop hypotheses for future research.

## **III. Conclusions**

## Conclusions

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A new era in breast cancer research is at hand. Our arrival at this threshold is the result of remarkable progress achieved over the past two decades. Far better than ever before, we understand several basic biological processes important in breast cancer, including hormonal and growth factor regulation of breast epithelial cell proliferation, mechanisms of cell cycle regulation, and the processes that control development and differentiation. Breast cancer, like most malignancies, is now known to be caused by both inherited and somatic mutations in a specific subset of genes. Inherited mutations in two genes, BRCA1 and BRCA2, have been shown to account for a significant proportion of inherited breast cancer. Animal models have been developed that provide insight into the basic biology and genetics of normal breast development and the carcinogenic process and provide models for testing prevention and treatment strategies. Potential predisposing factors for breast cancer have been identified, including hormonal status, dietary factors, and exercise. Advances in early detection have led to earlier diagnosis and treatment with improved survival rates. Treatment for established breast cancer has improved significantly with multimodality therapy involving surgery, radiation, and chemotherapy. Anti-estrogen therapy has been shown to be beneficial not only for treatment but also for prevention. Substantial improvements have been made in disease-oriented outcomes and quality of life research has entered the mainstream. These successes justify optimism that even greater strides can be made across the continuum of breast cancer research and care, leading to the eventual prevention of many cases and cure for women who do develop this disease.

Through intensive discussions, the Breast Cancer Progress Review Group has mapped paths to progress in each of eight major areas of breast cancer research. Also emerging from these discussions were several broad research directions and infrastructure needs that span the major areas of breast cancer research. All of these must be addressed if we are to continue and accelerate progress in preventing, detecting, diagnosing, and treating breast cancer. Therefore, in addition to the recommendations specified in Chapters 1 through 8, the Breast Cancer Progress Review Group recommends strongly that the National Cancer Institute:

**1. *Increase basic research on the biology and developmental genetics of the normal mammary gland.*** A more complete understanding of the normal mammary gland at each stage of development is essential for future advances in detecting, preventing, and treating breast cancer, necessitating increased support for studies on mammary gland development. It is recommended that a genetic definition of each type of normal mammary epithelial and stromal cell be created. This should be accompanied by a biological and biochemical elucidation of the functions of mammary gland gene products that appear to have regulatory functions. A special effort should be made to identify and locate breast stem cells and to elucidate the relationship between stem cells and preneoplasia. Additional research should focus on developing molecular markers for different lineages of cells, including stem cells, with a determination of which lineages are more likely to give rise to tumors. It is important to characterize the components of signaling pathways between epithelial cells,



between epithelial and stromal cells, and between cells and extracellular matrix that are involved in regulating cell growth and morphogenesis.

**2. *Develop better model systems for breast cancer.*** Appropriate animal models and models of human mammary cell and organ culture are urgently needed to accelerate progress in breast cancer research. Targeted funding for developing these models, and for maintaining and distributing them, is required. Experimental human genetics should be carried out in mice, by generating mouse strains with both wild-type and mutant human genes. The effects of these genes on mammary gland development and susceptibility to tumor formation, progression, and metastasis must then be determined. The effects of mutations against different genetic backgrounds should be determined with the goal of identifying genetic modifiers of mutant alleles. Additional cell strains and cell lines from human mammary glands should be developed. These should represent both stromal and epithelial cells with normal, premalignant, preinvasive malignant, invasive malignant, and metastatic phenotypes. Additional efforts should be devoted to developing three-dimensional multicellular model systems in culture and in xenografts. Ideally, these models will also be suitable for initial preclinical testing of new prevention and therapy strategies.

**3. *Increase research on the genetics and biology of precancerous lesions and their progression to invasive, metastatic cancers.*** A major effort should be undertaken with appropriate funding to determine the genetic (mutation and gene expression) profile of mammary epithelial cells through all stages of cancer development and progression, including metastasis with the principal goal of

identifying target molecules to be used as agents of prevention, detection, and therapy. Genetic changes and expression differences must be correlated with cellular, histologic, and clinical phenotypes. This will require access to carefully collected and catalogued human tissues across the spectrum of breast neoplasia.

**4. *Identify key biomarkers and surrogate endpoints for epidemiologic studies and prevention and therapy trials.*** Current and future advances in basic biology and genetics should be used to identify and validate markers that could improve early detection of breast cancer. It is hoped that such markers also could serve as risk and surrogate endpoint biomarkers to develop and test prevention and therapeutic strategies, thereby expediting the lengthy clinical trials process. To date, efforts to fully exploit the utility of biomarkers have been hampered by a lack of consensus on criteria for accepting biomarker endpoints and by issues relating to technology transfer. Interdisciplinary working groups sponsored by NCI could facilitate consensus building in this field by addressing problems related to methodology, technology transfer, and trial design. Such groups could advise the NCI on how best to prioritize resources as obtaining definitive answers about the utility of individual biomarkers often requires large clinical trials and/or access to extensive biorepositories.

**5. *Enhance availability of new technologies and funding for equipment.*** Funding is seriously deficient for developing and disseminating new technologies and for purchasing expensive equipment for breast prevention, diagnosis, and treatment research. Though costly, these tools are indispensable to progress in breast cancer research and strategies must be implemented to increase

access to them. For example, laser microdissection and microarray/chip technology should be made available as a shared resource at centralized facilities throughout the academic community. NIH should facilitate technology development by making maximal use of all available technology transfer mechanisms to promote the optimal development and dissemination of microarray/chip technologies. Generic arrays should be developed for standardized general use, allowing for reliability and reproducibility. All human breast expressed sequence tags (ESTs) should be cataloged for open and widespread distribution. Bioinformatics should be developed to ensure that the wealth of existing information can be assimilated and exploited for maximal benefit. Current databases (e.g., Cancer Genome Anatomy Project) should be expanded, and additional databases should be developed. Better image analysis software tools should be developed to quantitate and discriminate tissue gene expression patterns.

**6. Facilitate novel therapeutic approaches in academic health centers and via public/private partnership.** Advances in the cellular and molecular biology of breast cancer have identified more promising targets for drug development and other innovative treatment approaches than can be exploited by current mechanisms. Support should be provided for drug screening, genomics, and chemistry infrastructure at academic institutions. Further, support mechanisms should be established for developing drugs for specific targets at institutions with the appropriate infrastructure. Finally, it is critical that the NCI lead the effort to forge academic/industry/NCI partnerships for drug development. Effective collaboration between these parties with their unique and complementary strengths could greatly

facilitate development of novel therapeutic strategies.

**7. Modify and enhance support for prevention and therapy clinical trials.** It is imperative that we develop faster mechanisms for designing and conducting innovative clinical and translational trials at single academic health centers or consortia of academic health centers. In addition, since the majority of patients are treated in the community, research mechanisms such as the cooperative groups must be more strongly supported with appropriate funding and they should strive for enhanced minority participation. Translational research must also receive heightened emphasis in the cooperative groups.

**8. Assure that all breast cancer basic and clinical research and communications efforts reflect and address patient and survivor needs and concerns.** Where appropriate, research efforts in biology, etiology, genetics, and clinical activities should integrate patient-focused priorities--the values of those most directly affected by the current breast cancer burden (high risk or recently diagnosed patients, long-term survivors, and their families) should be embraced by the NCI breast cancer research agenda and action plan. Effective and understandable education and communication about risk, detection, and treatment must take into account the differing motivations, concerns, and characteristics of diverse groups of women, including those typically underserved. Interventions should be designed to improve quality of life across the full continuum from risk assessment to treatment at the end of life, including prevention of morbidity and long-term effects over the increasing duration of survivorship. The expertise and collaboration of patient advocates representing our ethnic diversity

must be sought in developing research priorities and in designing and implementing programs recommended in this report.

**9. Increase focus on and support for basic and applied research into biobehavioral mechanisms and decision-making relevant to cancer prevention, detection, and treatment.**

There is inadequate understanding of the processes and mechanisms underlying behavior related to diverse cancer issues from genetic testing to prevention, screening utilization, treatment, and palliative care preferences in advanced disease. Basic behavioral research is needed to further understand these fundamental mechanisms and processes. In addition, decision-making about cancer-relevant behavior from prevention through treatment, and the disease- and patient-focused outcomes associated with these decisions, are highly complex and individual--both are influenced by demographic, cognitive, personality, and cultural differences among people, and by the support provided to help people make informed and healthy decisions. We need to better understand how different people use both traditional and new media to process information and make healthy decisions across the continuum of breast cancer care. The progress required in this area can be achieved by a focused program of support in basic behavioral change, decision-making, and tailored communication of research findings and their health implications to the individual.

**10. Expand training opportunities and support, especially for multidisciplinary training of translational investigators, and to attract new talent to breast cancer research.**

The need to train additional investigators to apply their talents across the spectrum of breast cancer research is urgent. Increasingly, new investigators whose talents are needed to

achieve the next generation of progress against breast cancer are choosing careers in industry or private practice because they do not perceive the likelihood of a viable career in academic breast cancer research. This situation grows more dire with each passing year. We believe that incentives for academic researchers are needed if both academia and private industry are to make optimal contributions to progress against breast cancer. In addition to enhanced support for existing training mechanisms, new funding mechanisms are needed to train individuals in a multidisciplinary manner so that they can participate effectively in multi-investigator collaborations that translate basic research discoveries into breast cancer prevention, detection, and treatment interventions, and improved quality of life.

**11. Promote multidisciplinary research focus and communication.** A common theme permeating many of the Progress Review Group discussions was the need for more effective communications, both among investigators in different disciplines and for the public. Mechanisms to enhance multidisciplinary focus and communication in specific areas of breast cancer research are recommended in preceding chapters. To promote communication across the breast cancer research continuum, a breast cancer task force should be established with representation from all of the major disciplines and with oversight and fiscal resources to address critical areas of breast cancer research not covered by other mechanisms. It is also recommended that a special effort be made to develop better communication tools for sharing resources, databases, and other information. Further informatics development for all types of research will be essential. Regarding communications to the public, the NCI should concentrate on a balanced

program of breast cancer information and education that includes patient education materials, media campaigns, and the cancer information service telephone and outreach programs, with an emphasis on at-risk and medically underserved audiences.

**12. Develop mechanisms to support innovation and enhance support for specific areas of research.** The current mechanism of peer-reviewed, investigator-initiated research project grants has served us very well over the years. This approach should be continued and enhanced such that funding is awarded for grants approved by peer review up to the 40<sup>th</sup> percentile. Additional pathways are needed, however, to support important research not currently well served by existing mechanisms. Seed money should be provided for innovative, higher risk ideas, and peer review of these idea grants should be through mechanisms other than current NIH Center for Scientific Review (formerly Division of Research Grants) and NCI Division of Extramural Activities study sections. Establishing special study sections comprised of a high percentage of more experienced investigators offers one approach to this issue. Another approach that should be considered is the development of idea-driven review and funding groups operated outside the government. Contract mechanisms will likely be needed to accomplish the genetic dissection of the developing normal mammary gland and the progression from normal to precancerous to invasive and metastatic cancer. Targeted funding and special peer review will also be needed for developing and disseminating cell lines, organ cultures, and animal models. There is a critical need for more reasonable review and improved funding of multidisciplinary grant applications. Longer term funding mechanisms are needed for tissue resource development and for

longitudinal epidemiologic studies and prevention and therapeutic trials.

**13. Address informed consent and confidentiality issues.** Current informed consent processes are excessively complex, posing a major impediment both to basic research on human tissues and to patient-oriented research. The need to protect the rights and confidentiality of the patient is recognized fully; however, current consent procedures are so cumbersome that they impede the flow of research and may actually discourage both clinicians and patients from participating. Methods to encourage women of all races and ethnicities to donate tissues for research purposes while simultaneously protecting them from harm must be developed. In addition, ways to streamline the consent process for clinical trials, such as empowering regional or national Institutional Review Boards (IRBs), must be addressed. Although not specific to breast cancer, this issue has the potential to become a bottleneck to our ability to capitalize on our growing understanding of this disease.

\* \* \* \* \*

The past two decades of painstaking research and substantial national investment have yielded major advances in our ability to care for women with breast cancer and those at risk. This report offers a plan for the next decade of progress. It is the firm belief of the Breast Cancer Progress Review Group that by charting the course and implementing the recommendations described in this report, the National Cancer Institute and the Nation will take the next crucial steps toward the ultimate goal of removing the threat of breast cancer from the lives of women and their families.

# Appendices

# Appendix A

## NCI Breast Cancer Progress Review Group

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# Appendix B

## NCI Task Force on Breast Cancer

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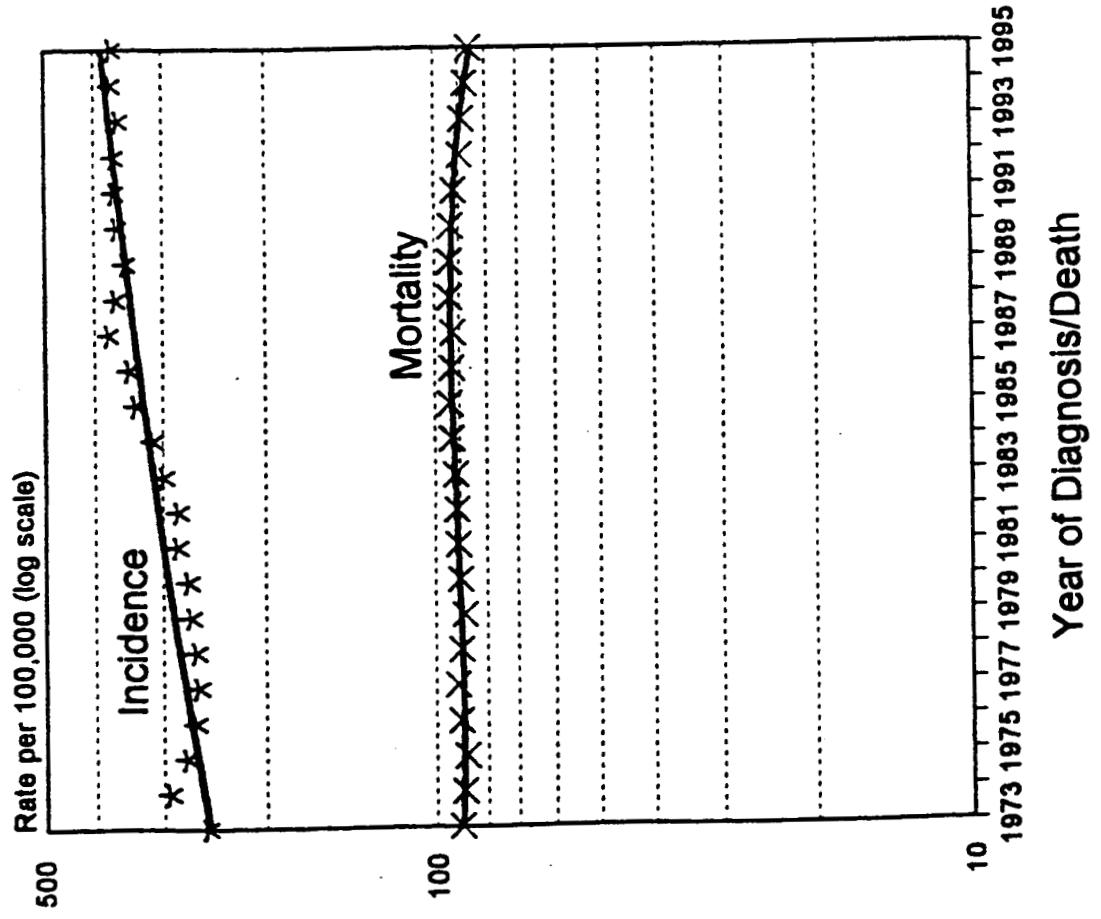
## Appendix C:

Breast Cancer Incidence and Mortality Rates and Trends:  
Selected Data, Surveillance, Epidemiology, and End Results  
Program

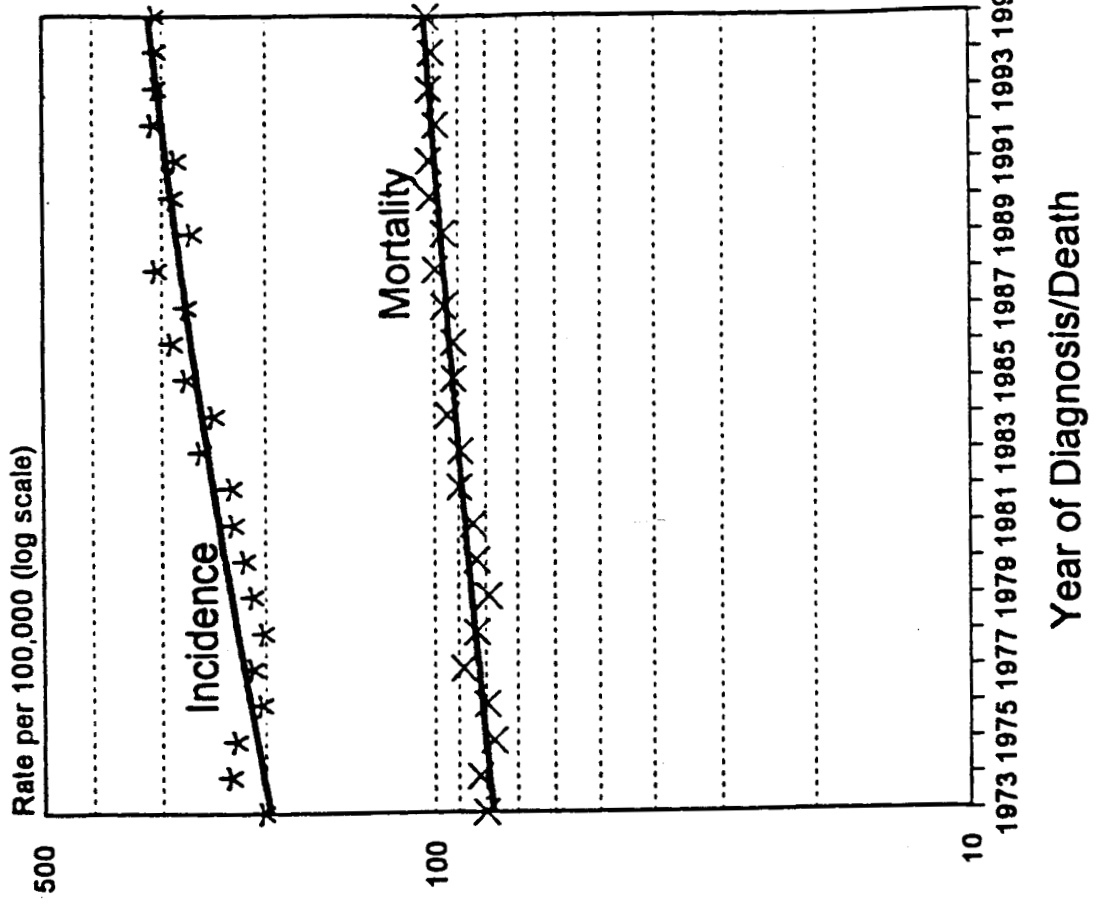


# SEER Incidence and U.S. Mortality Female Breast Cancer, Ages 50 and Over By Race

## White

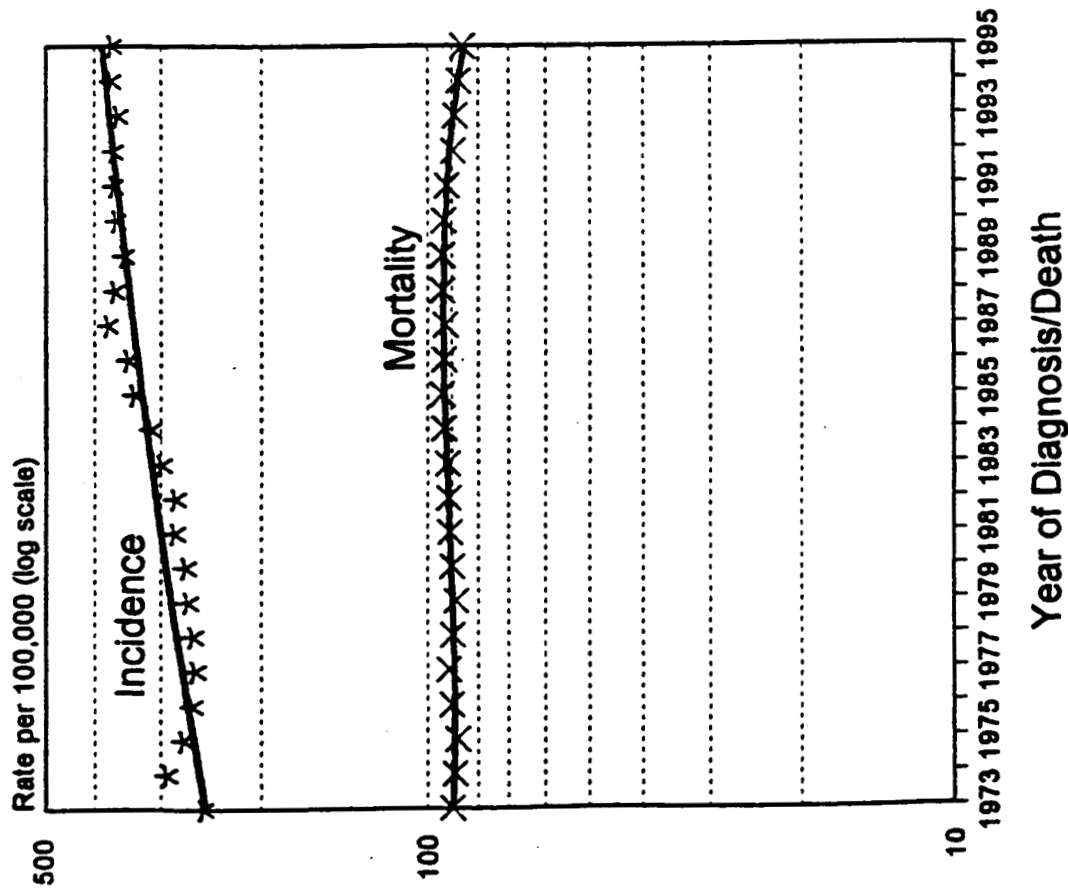


## Black

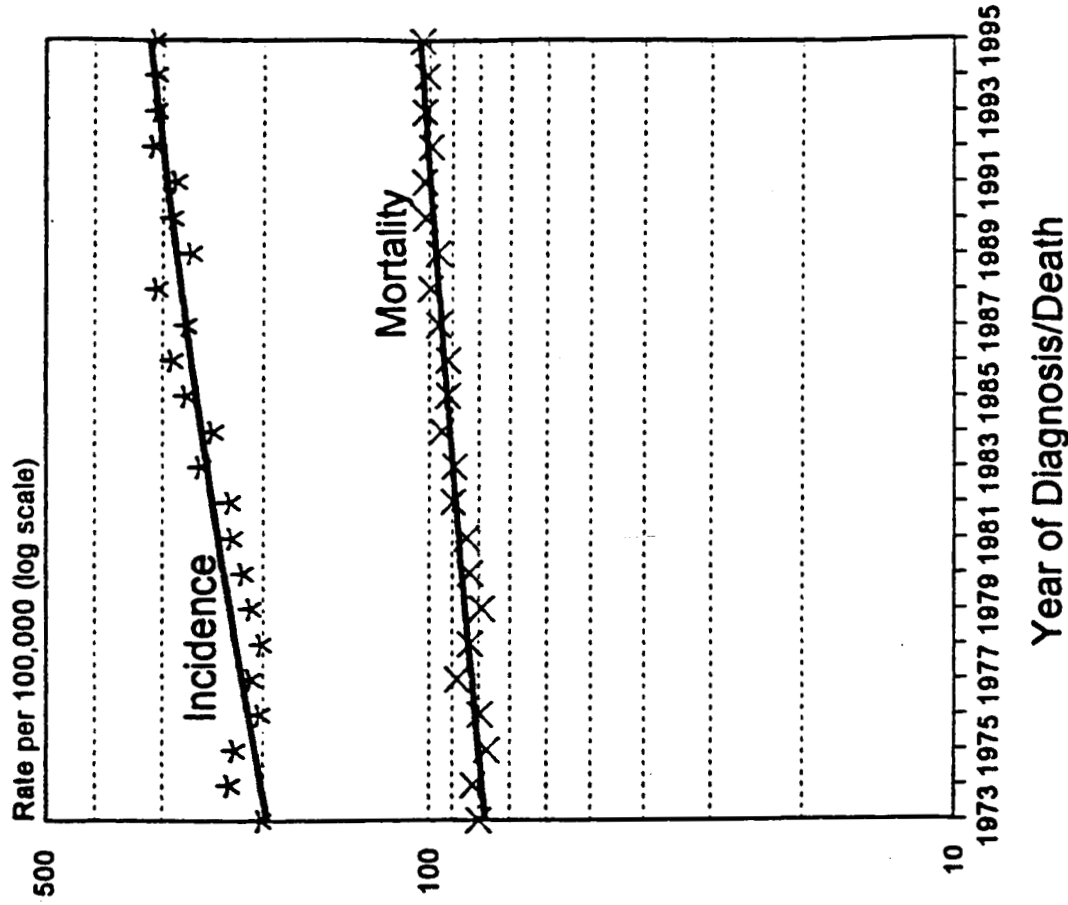


# SEER Incidence and U.S. Mortality Female Breast Cancer, Ages 50 and Over By Race

## White



## Black



# Breast Cancer Incidence & Mortality White Females vs. Black Females

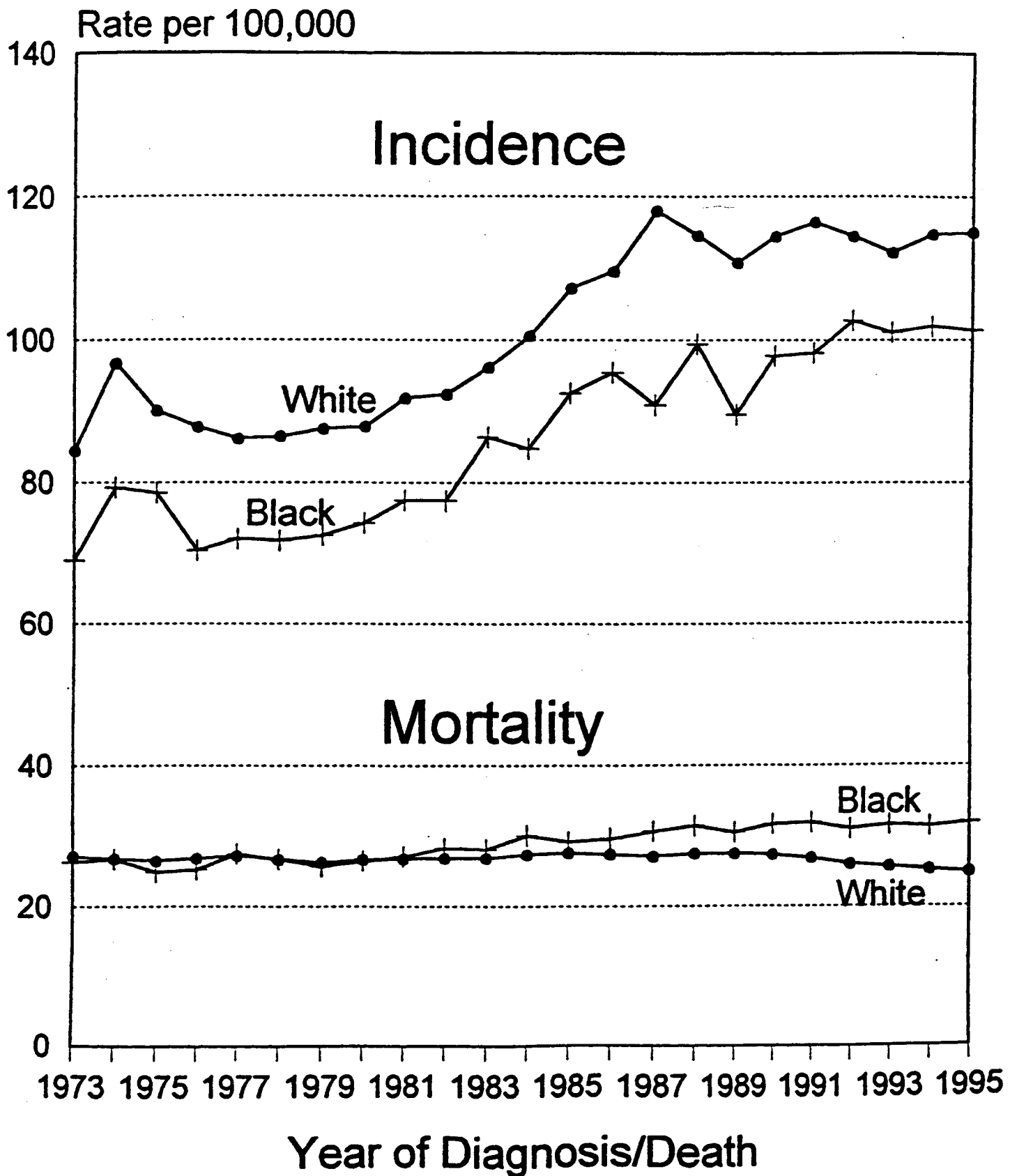




Table IV-1  
**FEMALE BREAST CANCER (Invasive)**  
**TRENDS IN SEER INCIDENCE AND U.S. MORTALITY, BY RACE AND AGE**

	All Races, Females		White Females		Black Females	
	All	50+	All	<50	All	<50
<b>INCIDENCE TRENDS (expressed in percentages)</b> <sup>1</sup>						
<b>1973-95</b>						
<b>All Ages</b>						
Percent Change (PC)	25.2	1.5	26.9	1.2	37.0	20.7
Est. Annual PC (EAPC)	1.6*	0.6*	1.6*	0.5*	1.9*	1.2*
<b>Under 65</b>						
Percent Change (PC)	17.9	-	19.1	-	32.0	-
Est. Annual PC (EAPC)	1.2*	-	1.2*	-	1.7*	-
<b>65 and over</b>						
Percent Change (PC)	38.7	-	40.9	-	46.6	-
Est. Annual PC (EAPC)	2.2*	-	2.3*	-	2.4*	-
<b>1975-79 - ALL AGES</b>						
Percent Change (PC)	-2.3	-5.2	-2.2	-5.5	-3.1	-1.8
Est. Annual PC (EAPC)	-0.8	-1.8*	-0.7	-1.7*	-1.4	-1.4
<b>1991-95 - ALL AGES</b>						
Percent Change (PC)	-0.6	-5.7	-0.5	-5.6	1.2	-5.3
Est. Annual PC (EAPC)	-0.2	-2.1	-0.2	-2.0	0.6	-2.2

**MORTALITY TRENDS (expressed in percentages)**<sup>2</sup>

<b>1973-95</b>						
<b>All Ages</b>						
Percent Change (PC)	-5.3	-21.4	-7.1	-24.9	19.4	-1.3
Est. Annual PC (EAPC)	-0.1	-0.9*	-0.2	-1.1*	1.2*	0.5*
<b>Under 65</b>						
Percent Change (PC)	-16.1	-	-18.8	-	8.2	-
Est. Annual PC (EAPC)	-0.7*	-	-0.8*	-	0.8*	-
<b>65 and over</b>						
Percent Change (PC)	10.3	-	9.2	-	39.5	-
Est. Annual PC (EAPC)	0.7*	-	0.6*	-	1.8*	-
<b>1975-79 - ALL AGES</b>						
Percent Change (PC)	-0.4	-3.4	-0.8	-5.1	4.6	8.9
Est. Annual PC (EAPC)	-0.2	-1.3*	-0.2	-1.8*	1.2	2.4
<b>1991-95 - ALL AGES</b>						
Percent Change (PC)	-4.6	-7.6	-5.3	-9.0	0.6	-3.1
Est. Annual PC (EAPC)	-1.6*	-2.6*	-1.9*	-3.1*	0.1	-1.0*

The Est. Annual PC is the Estimated Annual Percent Change (EAPC) over the time interval.

<sup>1</sup> SEER Program.  
<sup>2</sup> NCHS public use tape.  
 \* The EAPC is significantly different from zero (p<.05).  
 † The EAPC for 1991-95 is significantly different from the EAPC for 1975-79 (p<.05).  
 ‡ The EAPC for 1991-95 is significantly different from the EAPC for 1975-79 (p<.10).  
 § Statistic could not be calculated.

Table IV-10  
FEMALE BREAST CANCER (Invasive)

AGE-ADJUSTED SEER INCIDENCE AND U.S. MORTALITY RATES

By Race/Ethnicity and Sex

Incidence<sup>x</sup>

RACE/ETHNICITY	Rate 1990-1995	Trend 1990-1995
	Rate per 100,000 persons	EAPC (%)
	Females	Females
All Races	108.9	0.0
White	113.2	0.0
White Hispanic	73.2	-1.3
White Non-Hispanic	117.7	0.2
Black	99.0	0.6
Asian/Pacific Islander <sup>†</sup>	71.4	0.2
American Indian	31.9	10.9
Hispanic <sup>•</sup>	69.3	-1.6

Mortality<sup>†</sup>

RACE/ETHNICITY	Rate 1990-1995	Trend 1990-1995
	Rate per 100,000 persons	EAPC (%)
	Females	Females
All Races	26.2	-1.7*
White	26.0	-1.9*
White Hispanic	16.1	-1.7*
White Non-Hispanic	26.6	-1.9*
Black	31.5	0.0
Asian/Pacific Islander <sup>†</sup>	11.6	0.4
American Indian	11.7	2.0
Hispanic <sup>•</sup>	15.3	-1.9*

- The EAPC is the Estimated Annual Percent Change over the time interval. Statistic not shown. Rate based on less than 10 cases per year within the time interval.
- x Incidence data are from the 11 SEER areas (San Francisco, Connecticut, Detroit, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, and Los Angeles). Unless specified, other tables use data from 9 SEER areas (San Francisco, Connecticut, Detroit, Iowa, New Mexico, Seattle, Utah, and Atlanta).
- Hispanic is not mutually exclusive from whites, blacks, Asian Pacific Islanders, and American Indians. For incidence, all 11 SEER areas are included. For mortality, information is included for all states except Connecticut, Oklahoma, Louisiana, and New Hampshire.
- † Mortality data are analyzed from a public-use file provided by the National Center for Health Statistics (NCHS).
- † Population estimates for the Asian Pacific Islanders rates are adjusted Census Bureau estimates. The population estimates used in Wingo PA, Ries LAG, Rosenberg HM, Miller DS, Edwards BK. Cancer Incidence and mortality, 1973-1995. Cancer 82:1197-207, 1998 were unadjusted.
- \* The EAPC is significantly different from zero (p<.05).

Table IV-11  
**FEMALE BREAST CANCER (Invasive)**  
**AGE-ADJUSTED SEER INCIDENCE RATES AND SEER MORTALITY RATES**  
**By Registry, Race and Age**

	All Races, Females			White Females			Black Females		
	All	<50	50+	All	<50	50+	All	<50	50+
<b>SEER INCIDENCE RATES, 1991-95</b>									
<b>REGISTRY</b>									
11 registries	109.0	31.5	347.9	113.3	31.6	365.1	99.4	33.8	301.5
9 registries	110.9	32.2	353.8	114.5	32.3	368.3	101.0	34.6	305.8
San Francisco-Oakland	113.1	34.0	357.1	126.7	35.9	406.6	94.7	33.9	282.0
Connecticut	116.7	34.1	371.4	118.8	34.6	378.5	93.8	31.9	284.4
Metropolitan Detroit	114.2	33.3	363.6	115.0	32.1	370.7	104.3	35.2	317.7
Hawaii	99.4	31.8	307.8	128.1	33.7	419.2	-	-	-
Iowa	107.0	30.1	344.2	106.8	30.0	343.9	-	-	-
New Mexico	94.6	28.8	297.5	98.5	30.3	308.9	-	-	-
Seattle-Puget Sound	118.3	32.2	383.6	120.8	32.5	393.1	101.9	34.9	308.7
Utah	96.4	23.3	321.7	97.5	23.6	325.3	-	-	-
Metropolitan Atlanta	110.7	34.4	345.7	111.7	33.6	352.4	105.7	35.7	321.3
San Jose-Monterey	113.6	31.3	367.3	119.7	32.3	389.2	94.0	25.7	304.6
Los Angeles	101.8	29.6	324.6	107.4	29.5	347.7	96.0	32.6	291.7
<b>SEER MORTALITY RATES, 1991-95</b>									
<b>REGISTRY</b>									
11 registries	25.3	5.3	86.9	25.8	5.1	89.7	31.9	8.7	103.5
9 registries	25.3	5.2	87.4	25.6	4.9	89.5	32.1	8.8	103.7
San Francisco-Oakland	25.0	4.9	86.9	26.9	4.5	96.0	30.1	9.3	94.4
Connecticut	26.0	5.0	90.7	25.7	4.7	90.5	29.7	8.1	96.6
Metropolitan Detroit	28.8	6.2	98.3	27.6	5.1	97.0	32.7	9.4	104.6
Hawaii	17.5	3.7	60.1	24.5	3.4	89.7	-	-	-
Iowa	25.1	5.1	86.8	25.1	5.2	86.6	-	-	-
New Mexico	22.7	4.9	77.5	23.7	5.2	81.0	-	-	-
Seattle-Puget Sound	25.2	5.1	87.2	25.9	5.3	89.4	26.5	5.5	91.2
Utah	22.0	4.3	76.5	22.3	4.4	77.4	-	-	-
Metropolitan Atlanta	26.7	6.2	89.9	24.0	5.1	82.3	36.5	9.2	120.6
San Jose-Monterey	23.6	4.8	81.3	25.3	5.2	87.2	33.7	4.4	124.1
Los Angeles	25.4	5.6	86.6	26.5	5.5	91.2	31.6	8.5	102.7





## **Appendix D**

### **NCI and Other Federal On-Line Resources Related to Breast Cancer**

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National Cancer Institute	<a href="http://www.nci.nih.gov">http://www.nci.nih.gov</a>
Cancer Genome Anatomy Project (CGAP)	<a href="http://www.ncbi.nlm.nih.gov.ncicgap">http://www.ncbi.nlm.nih.gov.ncicgap</a>
CancerNet	<a href="http://cancernet.nci.nih.gov">http://cancernet.nci.nih.gov</a>
Cancer Trials	<a href="http://cancertrials.nci.nih.gov">http://cancertrials.nci.nih.gov</a>
Glossary of Cancer-Related Terminology	<a href="http://rex.nci.nih.gov/PATIENTS/INFO_PEOPL_DOC.html">http://rex.nci.nih.gov/PATIENTS/ INFO_PEOPL_DOC.html</a>
Information for Patients and the Public	<a href="http://rex.nci.nih.gov">http://rex.nci.nih.gov</a>
Physician Data Query (PDQ)	<a href="http://cancernet.nci.nih.gov/pdq.htm">http://cancernet.nci.nih.gov/pdq.htm</a>
Surveillance, Epidemiology, and End Results (SEER)	<a href="http://www-seer.ims.nci.nih.gov">http://www-seer.ims.nci.nih.gov</a>

<b>National Institutes of Health</b>	<a href="http://www.nih.gov">http://www.nih.gov</a>
Biology of the Mammary Gland	<a href="http://mammary.nih.gov">http://mammary.nih.gov</a>
Combined Health Information Database	<a href="http://chid.nih.gov">http://chid.nih.gov</a>
National Library of Medicine	<a href="http://www.nlm.nih.gov">http://www.nlm.nih.gov</a>
PubMed	<a href="http://www.ncbi.nlm.nih.gov/PubMed/">http://www.ncbi.nlm.nih.gov/PubMed/</a>
Office of Research on Women's Health	<a href="http://www.4.od.nih.gov/orwh">http://www.4.od.nih.gov/orwh</a>

<b>Department of Health and Human Services</b>	<a href="http://www.dhhs.gov">http://www.dhhs.gov</a>
Directory of Breast Cancer Organizations	<a href="http://www.napbc.org/napbc/orglist.htm">http://www.napbc.org/napbc/orglist.htm</a>
Federal Breast Imaging Technology Inventory	<a href="http://www.4woman.org/owh.bcimage/index.htm">http://www.4woman.org/owh.bcimage/index.htm</a>
National Action Plan on Breast Cancer	<a href="http://www.napbc.org">http://www.napbc.org</a>
National Women's Health Information Center	<a href="http://www.4woman.org/nwhic/index.htm">http://www.4woman.org/nwhic/index.htm</a>



## **Appendix E**

### **Agencies Providing Information On Breast Cancer Research Programs**

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The following Federal and non-governmental organizations provided information on their current breast cancer research activities to the Breast Cancer Progress Review Group:

- P American Cancer Society
- P Department of Defense
- P National Institute on Aging
- P National Institute of Environmental Health Sciences
- P State of California
- P State of New York
- P The Susan G. Komen Foundation