PROGRESS REPORT

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Ending Breast Cancer: **A Baseline Status Report**

National Breast Cancer Coalition

The **Breast Cancer** Deadline **2020**

Founded in 1991, the National Breast Cancer Coalition's (NBCC) mission is to eradicate breast cancer through the power of action and advocacy. On September 20, 2010, NBCC set a deadline to reach its mission: **Breast Cancer Deadline 2020®**—the end of breast cancer by January 1, 2020.

NBCC increases federal funding for breast cancer research; monitors how research funds are spent; expands access to quality health care for all; and ensures that trained advocates influence all decision making that affects breast cancer.

NBCC links hundreds of organizations and tens of thousands of individuals from across the country into a dynamic, diverse coalition that gives breast cancer a meaningful voice in Washington, DC and state capitals, in laboratories and health care institutions, and in local communities everywhere.

Ending Breast Cancer: **A Baseline Status Report**

National Breast Cancer Coalition

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There are many myths and misunderstandings that surround breast cancer. In order to make real progress toward saving lives and ending breast cancer, we need to better understand its reality at all levels. The reality is troubling. We have not made much progress in reducing mortality or in knowing how to prevent breast cancer. The National Breast Cancer Coalition (NBCC) is calling for a radically new approach and an end to breast cancer. We cannot afford to continue along the path we have followed for the past 40 years; it has not led us anywhere near the goal.

NBCC has set a deadline and launched a plan to achieve it. **Breast Cancer Deadline 2020®** is a call to action for all stakeholders to focus efforts on ending the disease by the end of the decade. This first **Breast Cancer Deadline 2020®** Progress Report is a baseline. It provides a snapshot of the current state of breast cancer and presents a framework of NBCC's plan of action. With a review of breast cancer trends, research, advocacy and public policy, it sheds light on the reality of breast cancer and gives an advocate perspective on the issues. Future annual reports will track progress and how NBCC is moving toward achieving **Breast Cancer Deadline 2020®**.

Breast cancer continues to take a toll in the US and globally despite significant attention and resources directed at the disease. Billions of dollars have been invested in breast cancer research over the past 20 years, and many organizations and public health officials continue to focus attention on early detection and awareness campaigns as the primary approach to addressing breast cancer.

Given the attention and resources directed to breast cancer, the public understandably believes that we have made significant progress. As this report shows, that is not the case. We know little about how to prevent breast cancer or how to prevent deaths from the disease. While we have discovered new ways to treat breast cancer, they have not had a great effect on the important outcomes: preventing breast cancer and making certain no one dies of it.

> ....the public understandably believes that we have made significant progress....that is not the reality.

The Numbers Tell A Compelling Story

Worldwide, breast cancer accounts for nearly a quarter of all cancers in women. In 2008, there were 1.4 million women diagnosed with the disease and 458,503 deaths.[1] In the United States, in 2010, it is estimated that 261,100 women and 1,970 men were diagnosed with breast cancer. 39,840 women and 390 men died of the disease.[2] That is one death every 14 minutes.

By any standard, we have not made adequate progress. Despite years of campaigns to raise awareness, ever expanding screening programs, increased fundraising efforts and research, there has been little impact on the important outcomes in breast cancer. Breast cancer incidence and mortality have not changed significantly. By 2030, with no major changes in prevention or treatment, it is estimated that 747,802 women will die each year from breast cancer worldwide.

In the United States, the chance of a woman developing breast cancer during her lifetime has increased from about 1 in 11 in 1975 to 1 in 8 today.[3] US breast cancer mortality has been declining but only slightly. In 1991, in the United States, 119 women died of breast cancer every day. Last year, that number was estimated to be 110. If we continue making progress at the current rate, it could take a few centuries to end breast cancer. These are not merely statistics, they represent millions of lives. These losses are unacceptable.

INCIDENCE

Overall incidence of breast cancer has fluctuated over the years. The median age at diagnosis is 61.[3] Because of increased screening beginning in 1980, there has been a dramatic increase in the incidence of ductal carcinoma in situ (DCIS), abnormal cells contained within the milk ducts that have not spread to other parts of the body. Most of DCIS will never become cancer. However, we are not able to distinguish between the harmful kind of DCIS (that will develop into cancer) and the harmless kind; as a result, many women are treated with interventions that will not help them and could hurt them.[3]

MORTALITY & SURVIVAL

Women do not die of primary breast cancer. Over 90% of breast cancer deaths are due to the spread of the disease to other parts of the body. While we want to believe we have made significant progress in saving lives, that is not the case. The incidence of women diagnosed with advanced breast cancer has not changed. Rates of diagnosis of truly lethal disease have remained stable since 1975.[3] Mortality rates have not changed significantly. Between 1975 and 1990, the mortality rate increased slightly then began decreasing slightly in the late 1990s for all women, with the highest rate of decrease in white women.[3] Yet this year, 39,840 women and 390 men will die of breast cancer. While a slight decrease in mortality is an accomplishment, it is far from success.

We tend to view five-year survival statistics as a sign of progress, yet that statistic leads to a false sense of security and is misleading. Survival statistics do not reflect the real experience of people with breast cancer. The National Cancer Institute (NCI) reports that five-year breast cancer survival is 98% for localized disease. Survival rates are skewed by screening: the more you screen, the more you find and thus more women will be alive at five years. But they were not going to die of breast cancer in that time frame even if they had not been screened.[4] And these numbers do not take recurrence into account. A significant percentage of women who are included in the five-year survival statistics will have a recurrence, and many of them will die of the disease.

THE UNCOMFORTABLE REALITY BEHIND EARLY DETECTION

A great deal of attention and resources have focused on the area of early detection. A mantra that has been drummed into our consciousness over the past forty years is that early detection saves lives. The reality is otherwise. About 70% of women in this country over age 40 have had a mammogram in the last two years.[5] Unfortunately, randomized controlled trials for mammography have shown, at best, a marginal benefit.[6,7] Breast self-exam (BSE) has also long been a key women's health mantra. But research has demonstrated that routine BSE does not lead to a decrease in mortality from breast cancer nor does it find breast cancer at an earlier stage.[8,9]

Yet many resources are devoted to giving the message of early detection and promoting breast self-exam and mammography screening for younger and younger populations. Attempts to apply evidence to the message of early detection are often met with anger and derision, as evidenced by the response to the revised screening guidelines issued by the United States Preventive Services Task Force in 2009. But these are matters of science. As our knowledge progresses, our beliefs must change to accommodate new information, no matter how much this challenges long-held beliefs and no matter how much we do not like the answer.

WE HAVE MADE PROGRESS IN THE TREATMENT OF BREAST CANCER

We have made some progress in breast cancer treatments. We have learned that not all breast cancers are the same. We now divide breast cancer into subtypes, based on the biology of the tumor. We have made some progress toward developing treatment targeted to different subtypes. But the majority of women with breast

cancer still receive the same treatment as though all breast cancer were the same. In reality, to date, our knowledge of the biology of breast cancer has not been translated into many new therapies to treat it.

For decades, breast cancer treatment has included surgery, radiation therapy, chemotherapy, and/or hormonal therapy, and within the past 15 years, targeted therapy. Ironically, much of the recent progress in treatment has been in doing less. In the 1970s, the primary treatment for breast cancer was a radical mastectomy, but once researchers found no difference with respect to outcomes in patients with lumpectomy versus total mastectomy patients, the standard of care shifted to a less invasive surgery. Recently, studies have shown that removing a few lymph nodes has the same survival advantage as removing most if not all.[10] These two developments have a major impact on quality of life. While important, they do not change the mortality statistics.

Meanwhile, the cost of treating breast cancer continues to rise without accompanying significant decreases in breast cancer mortality. The national cost of cancer care in 2010 was estimated to be $124.6 billion, with female breast cancer care leading all cancer sites at an estimated $16.5 billion.[11] Despite that investment, a person with a new diagnosis of cancer has approximately a one in five chance of failing to receive elements of cancer care that are evidence-based and consistent with practice standards.[12] And millions of Americans have no insurance, which not surprisingly has an impact on the quality of their health care.

Like all medical treatments, breast cancer treatments can be harmful as well as helpful. Common morbidities include cardiac complications and lymphedema, among others. And the treatments can themselves be life-threatening. We need treatments that prolong life or significantly increase quality of life, with minimal risk. Too often progress is defined by new treatments that do neither.

BREAST CANCER RESEARCH MAY BE WELL FUNDED. BUT ARE THE FUNDS WELL SPENT?

More than a billion dollars is invested in breast cancer research each year in the US alone. The US Government is the largest funder of breast cancer research in the US; although the NCI invests the most resources, a variety of other agencies are also involved. The Department of Defense Breast Cancer Research Program (DOD BCRP) has a unique program that includes consumer advocates at all levels of decision-making and is specifically designed to encourage innovative, collaborative federally funded research.

There are state-funded breast cancer research programs, the most notable in Texas and California.

Non-profit organizations also play a significant role in funding breast cancer research. The largest among them are the Susan G. Komen Breast Cancer Foundation (Komen), the American Cancer Society (ACS), the Avon Breast Cancer Crusade, and the Breast Cancer Research Foundation (BCRF).

Private philanthropy underwrites a significant amount of research in breast cancer. From gifts in the hundreds of millions of dollars to local walks that raise a few thousand, these funders exist across the country. With the diversity of supporters and vast number of donations and events, it is not possible to determine the amount of funding in this category.

Private industries, such as pharmaceutical companies, invest in breast cancer research but are not required to report expenditures on specific diseases. Proprietary concerns are often identified as the explanation for the lack of transparency.

Publication is key to oversight of research. However, it is well documented that authors typically submit positive results for publication and do not submit negative studies.[13]

PUBLIC POLICY PLAYS A SIGNIFICANT ROLE IN ALL ASPECTS OF BREAST CANCER

Breast cancer is a political issue. The level of government funding for research, the expansion and regulation of access to health care, the regulatory process for drug approval, and health insurance are just some of the issues that are determined through the political process.

Since 1991, over 830 resolutions and bills with the words "breast cancer" have been introduced in the United States Congress. Many more have been introduced in state legislatures. On the federal level, of the hundreds introduced since 1991, 11 resolutions were agreed to and 42 bills became law. All laws, however, are not created equal. These policies range from the substantive, such as the Centers for Disease Control and Prevention (CDC) Breast and Cervical Cancer Treatment Act, which expanded access to care for underserved, uninsured women, to a law authorizing the illumination of the St. Louis Gateway Arch in pink in October.

BREAST CANCER ADVOCACY HAS MADE A DIFFERENCE

There are probably thousands of breast cancer groups in this country alone and a growing global movement.

Breast cancer advocates can help shape the breast cancer research agenda, the federal drug approval process, and federal and state legislation. They can serve as liaisons between patients and physicians, as well as patients and the scientific community. Some groups provide direct services such as hotlines, support groups, counseling, educational materials, financial aid, and community presentations.

In 1991, NBCC formed with the mission to end breast cancer. It is a coalition of hundreds of organizations and tens of thousands of individuals focused on that goal, challenging the status quo. NBCC advocacy brought about more than 2.5 billion new dollars for research through the DOD program, designed and advocated for the CDC Breast and Cervical Cancer Treatment Act, launched innovative science training programs for advocates, and helped create new models of research. Frustrated with the lack of progress in breast cancer, in September 2010 NBCC launched its **Breast Cancer Deadline 2020®** Campaign.

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THE BREAST CANCER DEADLINE 2020® STRATEGY

The purpose of **Breast Cancer Deadline 2020®** is to create a paradigm shift in the breast cancer world—in government, the media, research, and advocacy—to refocus resources and efforts to the areas that lead us to the goal of ending breast cancer. Toward this end, NBCC has developed an innovative, advocate-led model to catalyze research in areas that have promise for contributing to the end of breast cancer. The focus is on primary prevention and on the causes and prevention of metastasis.

As part of these efforts, NBCC has launched the Artemis Project®, which is designed to create a strategic, systematic approach to the development of a breast cancer preventive vaccine. In late 2011, Summits will bring together advocates, scientists and other stakeholders, to focus on breast cancer prevention and the causes and prevention of metastasis.

Why Is This Necessary?

It is clear that "more of the same" will not be effective; additional funding and time can only be used fruitfully if efforts are part of a larger strategic plan focused exclusively on the one goal of eradicating breast cancer. This effort will require a critical look at research and health care priorities, financial incentives, funding mechanisms and advocacy efforts. It will require a concentrated strategy to expand quality, evidence-based care. It must embrace unprecedented coordination, information sharing and accountability.

It will require individuals and institutions to cooperate in new ways and to an extent never before considered. Vision, urgency, unwavering focus, and creative collaboration under true leadership will be the key ingredients for success. A collaborative deadline-driven mission approach to breast cancer has never been attempted. But examples of success in other fields suggest that often it is the lack of vision, willpower, accountability and leadership—not level of knowledge or the science itself—that stymies progress.

CONCLUSION

The current infrastructure and focus in breast cancer has not led to significant progress in ending the disease or in preventing deaths from the disease. This is true for research and health care and also advocacy: more of the same will not produce different results. NBCC has no desire to increase awareness of breast cancer, or funding for research, without a commitment from all stakeholders to ending breast cancer.

The current infrastructure and focus in breast cancer has not led to significant progress in ending the disease or in preventing deaths from the disease.

Much has changed since 1971 when the war on cancer was launched. Our understanding of the biology, etiology and genetics of breast cancer has increased. New disciplines have shed light on the process of innovation and how organizational systems evolve. And of course our capacity to gather, synthesize and analyze information is beyond anything even conceivable 40 years ago.

These developments create opportunities to conduct breast cancer research differently. The goal is not to create better tools to identify breast cancer or better mechanisms for managing it. The goal is to take what is already known and build upon that knowledge for the sole purpose of ending breast cancer.

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1 | INTRODUCTION

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The National Breast Cancer Coalition has set a deadline to end breast cancer: January 1, 2020.

This first annual **Breast Cancer Deadline 2020®** Progress Report serves as a baseline, giving an overview of the state of breast cancer today, and describing NBCC's initial efforts to refocus action towards eradicating the disease by the end of the decade. With a review of breast cancer trends, research, advocacy, and public policy, this report sheds light on the reality of breast cancer, and offers an advocate perspective on barriers that have hindered progress. Future annual reports will track updates on progress made towards achieving **Breast Cancer Deadline 2020®**.

The National Cancer Institute (NCI) estimates that 261,100 women and 1,970 men in the US developed invasive and in situ breast cancer in 2010, and 39,840 women and 390 men died from the disease.[1] This translates to one death from breast cancer every 14 minutes.

With a review of breast cancer trends, research, advocacy, and public policy, this report sheds light on the reality of breast cancer, and offers an advocate perspective on barriers that have hindered progress. Future annual reports will track updates on progress made towards achieving Breast Cancer Deadline 2020®.

Worldwide, breast cancer accounts for nearly a quarter of all cancers in women. In 2008, there were 1.4 million women diagnosed with the disease and 458,503 deaths.[2] In 2015, an estimated 1.6 million women will be diagnosed with breast cancer around the world, and this number will continue to rise to an estimated 2.2 million in 2030.[3] In 2030, breast cancer is predicted to take the lives of 747,802 women globally.[3]

Billions of dollars have been invested in breast cancer research in this country over the past 20 years, and many organizations and public health officials continue to focus attention on early detection and awareness campaigns as the primary approach to addressing the disease. The underlying belief is that all breast cancers are the same, and if found "early" enough through mammography or breast self-examinations, there will be no serious threat from these breast tumors.

The reality of the disease is much harder to accept. In 2011, despite a long history and great attention to the disease, those who are diagnosed will likely be surprised at how little we know about how to prevent death from the disease.

What do we actually know? Do we know how to prevent breast cancer? Is early detection reliable? Once detected, can breast cancer be cured? Will more research help? More awareness?

This report attempts to answer those questions and issues a call to action for all those who want to see the end of breast cancer.

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2 | BREAST CANCER STATISTICS & MORE

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In 2011, despite great attention directed to breast cancer, those who are diagnosed will likely be surprised at how little we know about how to prevent death from the disease. They may find that what they thought they knew about breast cancer is wrong. Myths and misunderstandings about breast cancer are widespread and promoted in the media and through industry marketing every day. "Early detection saves lives" has become a mantra, and the underlying belief is that all breast cancers are the same, and if found "early" enough through mammography there will be no serious threat from these breast tumors.

In 2011, despite great attention directed to breast cancer, those who are diagnosed will likely be surprised at how little we know about how to prevent death from the disease.

The reality of the disease is otherwise. All breast cancers are not the same, and we lack good evidence that early detection has had much impact on the most lethal forms of breast cancer. Many of the tumors that are found "early" would not have become life-threatening metastatic cancers, and, unfortunately, some of the treatments for these "early" cancers themselves have life-threatening side effects.

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In the US, the National Cancer Institute (NCI) estimates that 261,100 women and 1,970 men developed invasive and in situ breast cancer in 2010, and 39,840 women and 390 men died from the disease.[3] The chance of a woman developing breast cancer during her lifetime has increased from about 1 in 11 in 1975 to 1 in 8 today.[3] US breast cancer mortality has been declining but only slightly. In 1991, in this country, 119 women died of breast cancer every day. Last year, that number was estimated to be 110.[3] These are not merely statistics; they represent millions of lives.

2.1 INCIDENCE OF INVASIVE BREAST CANCER

The National Cancer Institute gathers information on the incidence of breast cancer by race and age, but not by subtype of disease. In the United States, the age-adjusted incidence rate for invasive breast cancer (where malignant cells have spread outside the milk ducts and into normal tissue) for all races was 122.9 per 100,000 women per year in 2003-2007. The median age at diagnosis was 61 years of age, with 24.1% of diagnoses occuring between ages 55 and 64.[3] Incidence rates have stabilized among white, black, and Hispanic women,[4] after fluctuating for several years. Incidence increased by 4.0% per year from 1980 to 1987, leveled out through 1994, and then increased again by 1.6% per year for the next five years.[4] Overall incidence declined after 1999 through 2003,[5] with the greatest decline among white women (Figure 1).

Globally, breast cancer is the second most common cancer overall and the most frequent cancer among women with an estimated 1.45 million new cases diagnosed last year.[2] The age-adjusted incidence rate varies greatly by region, from 19.3 per 100,000 women in Eastern Africa to 89.9 per 100,000 women in Western Europe, and 76.7 per 100,000 women in North America.[2] Eastern Europe, South America, Southern Africa, and Western Asia have moderate incidence rates (30-45 per 100,000 women), but these are increasing. The lowest incidence rates are found in most African countries, Central America, and Eastern and South-Central Asia, but it is projected that these rates will continue to rise.[2]

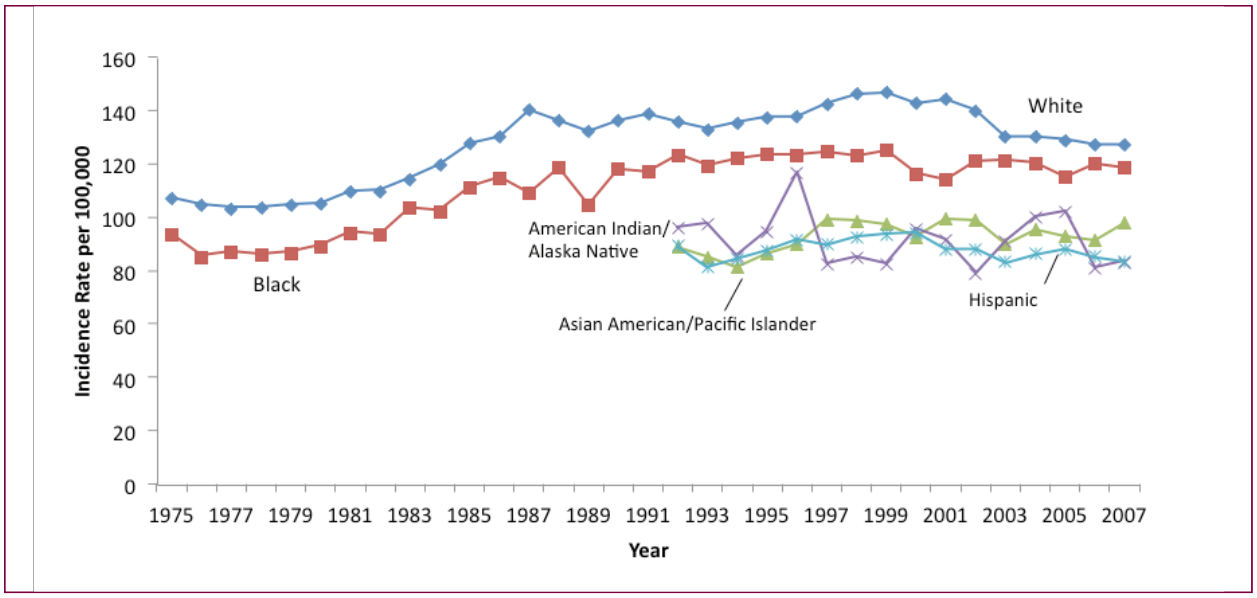

Figure 1. Female Breast Cancer Incidence Rates* by Race & Ethnicity, US, 1975-2007

*Rates are age-adjusted to the 2000 US standard population

Data source: Surveillance, Epidemiology, and End Results (SEER) Program, 1975-2007, Division of Cancer Control and Population Science, National Cancer Institute, 2011. Data for whites and blacks are from the SEER 9 registries. Data for other race/ethnicities are from the SEER13 registries.

In the United States, while overall incidence has fluctuated over the years, the incidence of women diagnosed with advanced breast cancer has not. As depicted in Figure 2, rates of diagnoses of breast cancer that has metastasized have remained stable since 1975.[3]

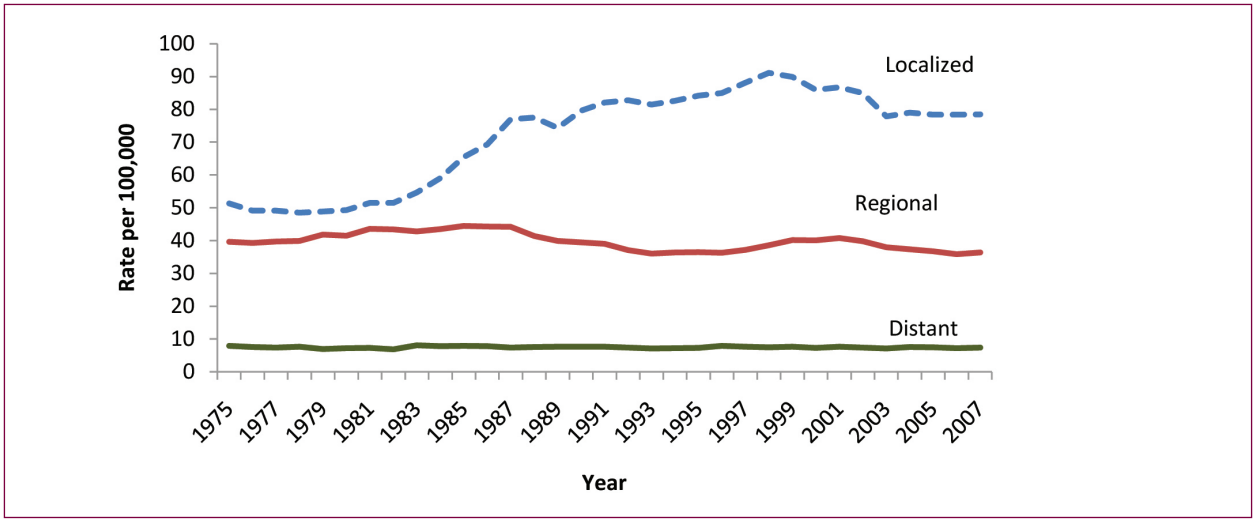

Figure 2. Female Breast Cancer Incidence Rates* by Stage**, US, 1975-2007

* Rates are age-adjusted to the 2000 US standard population.

**Localized—confined to primary site in breast; regional—spread to regional lymph nodes; distant—cancer has metastasized

Data source: Surveillance, Epidemiology, and End Results (SEER) Program. SEER 9 Registries, 1973-2007, National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2010, based on the November 2009 submission.

2.2 INCIDENCE OF DUCTAL CARCINOMA IN SITU (DCIS)

In 2010, while 207,090 women were diagnosed with invasive breast cancer, an estimated 54,010 women were diagnosed with non-invasive in situ carcinoma—a condition where abnormal cells are found within the milk ducts or lobules and have not spread to the surrounding tissues in the breast or other parts of the body.[5] Of these cases, about 85% will be ductal carcinoma in situ (DCIS), meaning the abnormal cells are contained within the milk ducts, and approximately 15% are lobular carcinoma in situ. The terms are misleading however, as these lesions are not cancer. Incidence rates of in situ carcinoma increased rapidly during the 1980s and 1990s with widespread use of mammography screening, and this increase was the largest in women aged 50 and older.[3] The incidence of DCIS increased over seven-fold from 1980 to 2007, from 4.8 per 100,000 to 34.6 per 100,000. Today, approximately one woman is diagnosed with DCIS for every four women diagnosed with invasive breast cancer.[6]

Although DCIS is a risk factor for invasive breast cancer, the natural history of DCIS and the likelihood that DCIS will progress to invasive disease is unknown. The most direct evidence regarding the progression of DCIS to invasive cancer comes from studies where DCIS was initially misdiagnosed as benign and treated by biopsy alone. These studies suggest that between 14–53% of DCIS may progress to invasive cancer over a period of 10 or more years.[7] A review of autopsy records showed that somewhere between 9% and 15% of women have undetected DCIS at death.[8] This supports the idea that a proportion of DCIS occurrences will not progress into invasive cancer or become life-threatening. The problem is that we do not yet know how to identify which DCIS will progress and which will not.

Neither is there at present a definitive way to distinguish those cases that will remain within the milk ducts —and may even disappear—and those that will become invasive.[7] DCIS is typically treated like early-stage invasive breast cancer—with breast-conserving surgery (BCS) and radiation therapy (RT), or mastectomy, and often hormonal therapy. But the survival rate is high—at ten years after diagnosis, 96% to 98% of women are alive.[6] So the issue becomes whether there are patients who could get by with less treatment, or no treatment at all.

This increase in the incidence of DCIS as a result of mammography has resulted in overtreatment for many women, without a concurrent decrease in the incidence of later stage diagnoses.[3] We now know it is not just the size of the tumor that determines outcome, but that the biology of the tumor and its surrounding environment are important.

A panel of experts agreed at a 2009 National Institutes of Health State of the Science Consensus Conference on DCIS that much is still unknown about the natural history of untreated disease, and no clear consensus was reached on management of the increasing number of cases of DCIS. However, because of the noninvasive nature of DCIS, coupled with its favorable prognosis, "strong consideration should be given to removing the anxiety-producing term 'carcinoma' from the description of DCIS," the panel concluded.[6]

2.3 EARLY DETECTION: MAMMOGRAPHY SCREENING & BREAST SELF-EXAMINATIONS

Between 1987 and 2000, mammography screening of healthy women who do not have any symptoms more than doubled in the United States but has remained relatively stable and decreased slightly in recent years. As depicted in Figure 3, the percentage of women aged 40 and older who reported having had a mammogram within the past 2 years increased from 29% in 1987 to 70% in 2000.[9] This dramatic increase in screening of healthy women was experienced by all racial/ethnic groups and women of all ages over

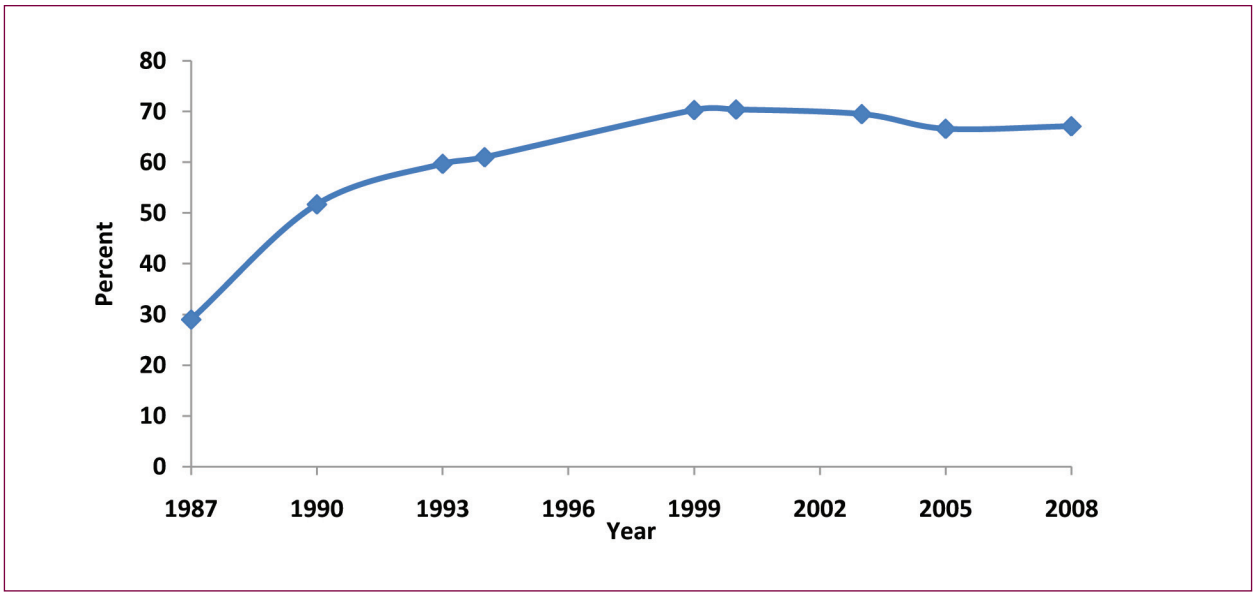

Figure 3. Percent of Women Aged 40 & Older* Who have had a Mammogram within the Past 2 Years

* Rates are age-adjusted to the 2000 US standard population. **Data source: National Health Interview Survey**

40.[10] However, the evidence of a mortality reduction from screening is conflicting and continues to be questioned by some scientists, policy makers, and members of the public. The analyses to date of all randomized controlled trials for mammography have concluded marginal benefit.[11,12]

Using mammography to screen women with no symptoms is different from having a diagnostic mammogram to evaluate a symptom, such as a lump in the breast or a discharge. The debate is not about whether to perform mammograms on women with symptoms; the mammography controversy is about its efficacy as a screening tool. How effective are mammograms in finding breast cancer and saving lives in women without symptoms, particularly younger women? A good screening tool rapidly and accurately sorts out who probably has the disease from those who probably do not. Women with abnormal screening mammograms must undergo further tests, such as biopsies, in order to make a definitive diagnosis.

The reality is that many of the tumors that are found "early" would not have become life-threatening metastatic cancers, and, unfortunately, some of the treatments for these "early" cancers themselves have life-threatening side effects. Some aggressive tumors aren't picked up by mammography, and still others that are may continue to be life-threatening even when found "early."[13]

The results of prospective randomized clinical trials have demonstrated that routine breast self-examinations (BSE) do not lead to a decrease in mortality from breast cancer nor do they find cancer at earlier stages.[14,15] The United States Preventive Services Task Force (USPSTF) no longer recommends health care providers teach the procedure to women. The National Cancer Institute states that "based on solid evidence, formal instruction and encouragement to perform breast self-examination leads to more breast biopsies and to the diagnosis of more benign breast lesions" and based on evidence "does not reduce breast cancer mortality."[16] About 80% of breast cancers not discovered by mammography are discovered by women themselves, but this is most often as part of daily living—for example, showering or getting dressed—and not as part of a systematic, regular breast self-examination.[17]

2.4 TUMOR BIOLOGY

We know that not all breast cancers are the same. Though we have known for some time that some breast cancers express excess estrogen receptors, we now know that there are several types of breast cancer based on the biology of the tumors. These subtypes respond to different treatments and have different prognoses. Though more will likely be identified in the future, breast tumors are currently classified using five immunohistochemical (IHC) tumor markers: estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER-2), HER-1, and cytokeratin 5/6 (CK 5/6).[18] Based on expression of these markers, breast tumors are classified into the following subtypes: luminal A (ER+ and/or PR+, HER-2-); luminal B (ER+ and/or PR+, HER-2+); HER-2+ (and ER-, PR-); basal-like (ER-, PR-, HER-2-, HER-1+, and/or CK 5/6+); and normal (negative for all five markers).[19] Approximately 70% of "triple negative" breast cancers (TNBC) are basal-like, therefore triple negative is often used as a surrogate for basal-like subtype.[20,21]

These different subtypes of breast cancer behave differently, are associated with different populations of women and different risk factors, and may have different causes. However, current annual incidence and mortality statistics are reported for breast cancer overall and not by subtype. Many cancer registries around the country still have incomplete recording of the expression of IHC markers, and therefore registries may know if a patient is ER/PR+ or -, but not her HER-2 status. As a result, we do not have information on incidence and mortality trends over time for the different subtypes.

2.5 MORTALITY & SURVIVAL

Despite fluctuations in breast cancer incidence, and dramatic increases in the use of mammography, there has not been a significant change in the rate of breast cancer deaths, or breast cancer mortality, over time. Between 1975 and 1990, the mortality rate increased by 0.4% annually, but began decreasing in 1990, at rates of 1.8%, 3.3%, and 1.9% between 1990-1995, 1995-1998, and 1998-2006, respectively.[3] The reason for the slight decrease in mortality during the late 1990s, which was greatest among white women (Figure 4), is subject to debate among investigators. Many believe that some of the decrease in breast cancer mortality may be due to improved treatments, rather than any shift to earlier detection. A 2010 study from Norway demonstrated that the majority of improvements in mortality after the introduction of a screening program were because of the increased focus on the disease which led to prompt attention to lumps, and improvements in multidisciplinary treatments and treatment teams, rather than increases in screening itself.[22]

Despite fluctuations in breast cancer incidence, and dramatic increases in the use of mammography, there has not been a significant change in the rate of breast cancer deaths, or breast cancer mortality, over time.

There is also belief that the decrease in breast cancer mortality, as well as both the recent decline in breast cancer incidence, and the sharp decline, particularly in women aged 50-69 between 2002 and 2003, are likely due in part to decreased use of hormone replacement therapy following the results of the Women's Health Initiative (WHI) randomized trial in 2002.[23,24] After 5.2 years of follow-up of healthy postmenopausal women in the WHI trial of estrogen plus progestin versus placebo, the researchers reported a 26% increased risk of breast cancer in women taking estrogen plus progestin.[23]

Breast cancer survival statistics, particularly five-year survival data, do not portray the impact of breast cancer, nor the progress or lack of progress over time, as accurately as mortality statistics. Survival statistics are often used by policymakers, advocates, and the media to make the case for broad-based

and routine mammography screening for women, despite the lack of evidence that screening has led to any significant decrease in breast cancer mortality. NCI data show that five-year breast cancer survival is 98% for localized disease, 84% for regional disease, and 23% for distant-stage disease,[3] and this is often used to encourage women to get regular screenings to catch their cancers before they are at later stages. However, this is misleading. There is no evidence that the screening tools we currently have prevent later stage diagnoses. The false assumptions are that all breast cancers are the same, that they all can be caught early with the tools we currently have, and that catching a breast cancer early prevents eventual spread or metastasis of the cancer. These were the same assumptions made about breast cancer several decades ago when mammography screening was first introduced, but we have since learned that breast cancers are not all the same, and that some breast cancers can be caught "early" and still be life-threatening after treatment. Some breast cancers grow slowly and are found by mammograms and treated, but never would have been life-threatening. Still other breast tumors are fast-growing "interval" cancers and are detected in between regular mammography screenings.[25]

An estimated 20% to 30% of women will have a recurrence of their disease,[26] and may go on to die of the disease, but are included as survivors in the five-year survival statistics. Between one-half and two-thirds of American women diagnosed with Stage II and Stage III breast cancer will develop metastatic disease within five years of diagnosis, though they may still be alive and considered "survivors" at five years after their initial diagnosis.[27] We still do not know how to prevent recurrence and metastasis or how many of the women reported to have survived five years will go on to recur.

2.6 DISPARITIES IN INCIDENCE & MORTALITY

Breast cancer mortality has varied over time by race, with women of non-Caucasian groups benefiting less than Caucasian women from improvements in breast cancer treatment (Figure 4). In fact, the black and white mortality curves actually diverge further over time, indicating persistent disparities in treatment or

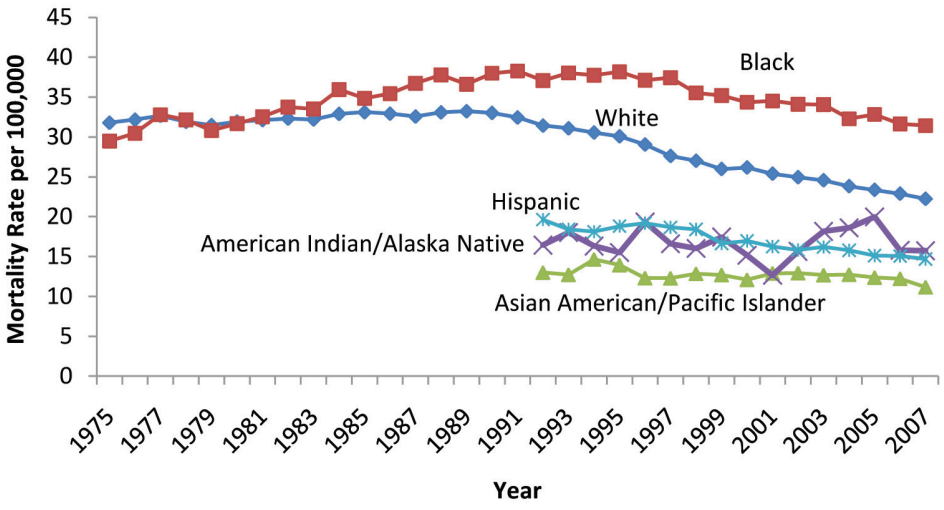

Figure 4. Female Breast Cancer Mortality Rates* by Race & Ethnicity, US, 1975-2007

*Rates are age-adjusted to the 2000 US standard population
Data source: US Mortality Files, National Center for Health Statistics, CDC. Rates for American Indian/Alaska Native are based on the CHSDA (Contract Health Service Delivery Area) counties.

a greater incidence of difficult-to-treat, more aggressive basal-like tumors in African Americans, or other biology not yet known.

Sociodemographic variables, such as income and education level, and behavioral and cultural differences have been implicated in survival and mortality disparities.[28,29] Research has also indicated that lower rates of adequate surgical, radiation, and systemic therapy among African American women, and higher rates of delays between diagnosis and treatment, as well as premature discontinuation of primary and adjuvant therapy, may contribute to poorer survival.[30-35] However, studies have also found that survival disparities persist even in settings with equal access to health care for all women.[36,37] While access is equal in these studies, it is not clear if all women are receiving equal treatment in these settings.

2.7 BREAST CANCER METASTATIC DISEASE

Women do not die of primary breast cancer. Over 90% of breast cancer deaths are due to the spread of the disease to other parts of the body, such as bone, lungs, liver and brain. Approximately 155,000 women are living with metastatic breast cancer in the United States, and this is projected to rise to 162,000 by the end of 2011, according to one expert.[38] However, the exact numbers are neither collected nor maintained, and we do not have information on historical trends. The NCI's Surveillance, Epidemiology, and End Results (SEER) Program, which is the primary source of population cancer statistics, only records information on the stage at diagnosis, initial course of treatment, and date of death. SEER does not have information on what happens in between initial diagnosis and death, such as recurrences and additional treatments.[27] Close to one-third of the women considered "cured" of breast cancer will suffer recurrences and metastatic spread of the disease, often many years after their initial diagnosis. While researchers have identified treatments that sometimes shrink or slow metastatic tumors, such as estrogen blockers, radiation and chemotherapy, they are most often temporary. Treatments to eradicate metastasis do not exist. There is no cure.

2.8 BREAST CANCER RISK

Why one person develops breast cancer and another does not, why some breast cancer is fatal and other breast cancer seems to regress and even disappear, is largely unknown. Over the years, epidemiologic studies have established a handful of risk factors for breast cancer (Table 1).[24,39] These studies give us information about risk factors in a population, but do not tell us much about any individual woman's risk of breast cancer. And on a population level, these factors only account for a small percentage of breast cancer cases.

Why one person develops breast cancer and another does not, why some breast cancer is fatal and other breast cancer seems to regress and even disappear, is largely unknown.

Most risk factors are not modifiable, including age, family history, and breast density. The amount of lifetime exposure of breast tissue to circulating ovarian hormones is only partially under one's control—modifiable with respect to exogenous hormone use. Similarly, the age at which menarche and menopause occur are generally out of one's control.

Other risk factors are sometimes modifiable, including obesity, use of combined estrogen and progestin menopausal hormones, alcohol consumption, smoking, and physical inactivity. For example, a recent study found that women who smoke or have extensive exposure to second-hand smoke are at an increased risk of developing breast cancer after menopause compared to those who have never smoked.[40]

Evidence attributes the majority of cancers to not one single factor but various physical, environmental, and genetic factors that impact women's bodies. Factors affecting obesity, immunity, and the tumor's environment within the body, as well as exogenous environmental exposures, are all examples of variables in the development of disease. To date, studies have not found clear associations between environmental pollutants and breast cancers; however, this remains an area of research.

Radiation exposure is a well established risk factor for breast cancer, and secondary breast cancer is strongly associated with high-dose radiation therapy to the chest for young women between the ages

Table 1. Established Risk Factors* for Breast Cancer

Relative Risk (RR)	Factor
> 4.0	Female Age Family history of breast cancer – two or more first-degree relatives Personal history of breast cancer Inherited genetic mutations (BRCA1/2, and others) High breast density Atypical hyperplasia
2.1 – 4.0	Family history (one first-degree relative) High-dose radiation to chest/breast Prior benign breast disease
1.1 – 2.0	No full-term pregnancies Late age at first full-term pregnancy (>30 years) Early menarche (<12 years) Late menopause (>55 years) Never breastfed children High alcohol consumption Smoking Recent oral contraceptive use Recent or current use of combined hormone replacement therapy Physical inactivity Obesity or adult weight gain (postmenopausal)

*Note: Interpreting the Magnitude of Relative Risk (RR)—RR > 4.0 is a strong association: 2.1 ≤ RR ≤ 4.0 is a moderate association: 1.1 ≤ RR ≤ 2.0 is a weak association

Table Source: American Cancer Society. Breast Cancer Facts & Figures 2009-2010. Atlanta.

of 10 and 30 years treated for cancers, such as Hodgkin's lymphoma.[24] Studies have demonstrated that women who had their first exposure to medical radiation procedures during childhood, even at lower doses, had a greater increase in the risk of breast cancer than those who were first exposed at older ages.[41] This higher risk begins about eight years after such exposure and continues to be elevated for more than 25 years.[24]

2.9 PREVENTION OF BREAST CANCER

All women are at risk for breast cancer, and though there are a few actions a woman can take to reduce her risk, there is no known single action or intervention that will prevent breast cancer from developing in an individual. Chemoprevention—giving drugs to women who do not have breast cancer—is one approach to risk reduction. There is no current evidence that these drugs "prevent" breast cancer; some studies suggest that they may reduce the chance that a woman will get breast cancer during a certain period of time.[42] As with most drugs, chemoprevention drugs have adverse side effects, and it is important that their benefits outweigh their risks.

The risk/benefit analysis for chemoprevention is different from the risk/benefit analysis for breast cancer treatment. Treatment drugs are given to women who already have breast cancer, while chemoprevention drugs are given to healthy women. Chemoprevention drugs will only benefit a small proportion of healthy women, because most healthy women will never get breast cancer. Therefore, women must have reliable, quality information on all of the risks and benefits of chemoprevention drugs before deciding whether to take them.

All women are at risk for breast cancer, and though there are a few actions a woman can take to reduce her risk, there is no known single action or intervention that will prevent breast cancer from developing in an individual.

THE ADVOCATE PERSPECTIVE

There are a number of seemingly entrenched myths and misunderstandings that surround breast cancer. It is almost easier to start with what we do not know. NBCC believes that in order to make true progress in breast cancer we need to better understand what causes this disease, what puts individual women at risk beyond the known risk factors, how different types of breast cancer behave, and which treatments are appropriate and effective for each type of breast cancer to ensure that women receive quality care.

We need to understand how to prevent breast cancer, how to prevent metastasis, and how to cure the disease. These are just some of the things we do not know.

What we do know is that the breast cancer outcomes that matter most have not changed much over the last 20 years. The rate at which women are diagnosed with metastatic disease has remained constant for more than 40 years, and mortality from the disease has declined only slightly. But statistics often mislead us to believe we have made a great deal of progress in breast cancer. For example, we often hear, "The survival rate for early breast cancer is 98%." What does that mean? Survival rate calculates the number of women diagnosed with breast cancer at five years who are still alive, but it does not tell us anything important about treatment or quality care. Survival rates are skewed by screening. The more women screened, the more cancer is found, the majority of which would never be life-threatening (for example, see Section 2.2). Thus, the survival rate is higher at five years with more screening because we are adding a larger proportion of non-life-threatening cancer into the calculation. But the outcome for most of these women would have been the same without screening.

> NBCC believes that in order to make true progress in breast cancer we need to better understand what causes this disease, what puts individual women at risk beyond the known risk factors, how different types of breast cancer behave, and which treatments are appropriate and effective for each type of breast cancer to ensure that women receive quality care.

Screening often detects cancer earlier than it would have been detected because of symptoms. In many cases, this means that screened people know they have the disease longer than unscreened people, but this doesn't necessarily mean that people diagnosed through screening live longer, counting from the time the disease actually began. Life is not extended, only the amount of time a woman lives knowing the diagnosis.

Campaigns continue to reach out to younger and younger women, even girls, to educate them about breast cancer, though breast cancer is quite rare in young women. The risk increases with age; 50% of breast cancer occurs in women aged

62 and older. Our knowledge and beliefs must be reanalyzed in light of new findings, technology, and better understanding of biology. We want science to advance even if that progress threatens our certainties.

> Campaigns continue to reach out to younger and younger women, even girls, to educate them about breast cancer, though breast cancer is quite rare in young women. The risk increases with age; 50% of breast cancer occurs in women aged 62 and older.

We need more focus on understanding the reality of breast cancer—how to prevent its development, how to stop the aggressive cancers that are not detected with mammography, how to stop breast cancer from recurring, and how to prevent it from metastasizing to other parts of the body and becoming lethal.

2020

2019

2018

2017

2016

2015

2014

2013

2012

2011

3 | BREAST CANCER TREATMENT

3 | BREAST CANCER TREATMENT

Breast cancer was first described by the Egyptians more than 3,500 years ago. In 460 BC, Hippocrates described breast cancer as a systemic malady involving many parts of the body, and believed surgery would be of no benefit. But in the 1700s, physicians began to view breast cancer primarily as a localized disease, leading to the practice of surgery to remove the tumor. In the mid-1800s, William Halstead popularized the radical mastectomy, which doctors performed (with variations) for the next 100 years. By the 1950s, it was thought cancer grew in a very orderly manner. The cancer started very small and gradually grew larger. Doctors believed that if you could remove enough tissue in the area of the tumor, you could cure women.

But surgery was often unsuccessful, and some physicians began to circle back to the view that the disease might be systemic from the beginning—that cancer cells were floating throughout the body in the circulatory system. Chemotherapy, hormonal therapy, and radiation were added to supplement treatment with surgery. This regimen has been the standard of care for the last several decades, with the addition of targeted therapy more recently.

Treatment decisions are based on the stage of disease, and increasingly on the biological tumor subtype. Over the years, we have increased our understanding of breast cancer, and there has been an improvement in slowing or halting disease progression for some women. Many of the advances in recent years have not been discoveries of new treatments, but rather discoveries that less invasive treatments are as effective as more invasive and/or more toxic standard of care. There is a growing recognition that more treatment is not necessarily better treatment. And, in fact, less is often better because of the reduction in long-term side effects, which are sometimes severe and occasionally fatal.

3.1 SURGERY

The type of surgery that is standard care in breast cancer has continued to become less invasive since the 1970s, when the primary treatment for breast cancer was a radical mastectomy, first performed by William Halsted in 1882.[1] In 1976, a clinical trial compared the outcomes of breast-conserving surgery (BCS) (lumpectomy or partial mastectomy) with standard radical mastectomy. Patients were randomly assigned to one of three treatments: total mastectomy, lumpectomy, or lumpectomy with breast irradiation.[2] The cohort was followed for an average of 20 years, and the researchers found no significant differences "among the three groups of women with respect to disease-free survival, distant disease–free survival, or overall survival."[2]

Over time, standard of care included surgery to remove several lymph nodes in the armpits. The nodes are examined for the presence of cancer cells to assess the spread of disease. More recently, study results demonstrated no difference in survival between patients who underwent axillary lymph node dissection (ALND), or removal of over 10 lymph nodes, and those receiving a less invasive sentinel lymph node dissection (SLND), or removal of two to three lymph nodes.[3] And, patients receiving SLND only were less likely to suffer painful and debilitating lymphedema, a condition characterized by fluid retention and swelling in the arm and/or trunk caused by a compromised lymphatic system.

3.2 RADIATION

Radiation therapy (RT) is coupled with breast conserving surgery as a standard of care, in an attempt to destroy remaining cancer cells, or to reduce tumor size before surgery to allow for less invasive surgery.[4] This standard of care is based on the 1976 randomized trial where researchers found no difference with respect to outcomes in lumpectomy versus total mastectomy patients but did observe a 9% (although not statistically significant) decrease in deaths due to breast cancer in patients who received radiation therapy following lumpectomy compared to lumpectomy alone.[2]

Radiation therapy (RT) is coupled with breast conserving surgery as a standard of care, in an attempt to destroy remaining cancer cells, or to reduce tumor size before surgery to allow for less invasive surgery.[4]

The goal of RT is mainly to kill tumor cells while minimizing damage to normal tissue[5] and to minimize or eliminate recurrence. RT is able to kill tumor cells and spare normal tissues because of differences in the tumor cell's ability to repair DNA damage and the fact that tumors are "more frequently in radiosensitive cell-cycle phases, such as mitosis."[5] Furthermore, "division of the radiation dose into a number of treatment fractions provides two important biologic advantages: it allows DNA repair to take place within the normal tissues and allows proliferating tumor cells to redistribute through the cell cycle and move into the more radiosensitive phases."[5]

There are two types of RT: external beam radiation and internal radiation (brachytherapy). External beam radiation is the common form of RT that targets the entire breast, or in some cases, surrounding lymph nodes. Because of the inconvenient nature of external beam radiation (5 days a week for 5-6 weeks), new methods of RT, such as accelerated partial breast irradiations (APBI) are now being explored. APBI shortens treatment to 1-5 days and targets the area of the breast immediately surrounding the lumpectomy site.[6] In contrast, internal radiation involves placing radioactive seeds/pellets directly into the tissue next to the breast cancer.[4] Lumpectomy patients typically receive RT for 5-7 weeks after surgery.

Several studies have affirmed the efficacy of RT, most notably a meta-analysis including more than 7,300 women from 10 trials who underwent BCS with radiotherapy. This study demonstrated a 19% reduction in the five-year local recurrence risk due to radiotherapy, with a five-year recurrence risk of 7% among patients allocated to RT and 26% among those not.[7] Patients in the radiotherapy group had a 30.5% 15-year risk of death from breast cancer, while patients who did not receive radiotherapy had a 35.9% risk, corresponding to a 5% reduction in the 15-year breast cancer mortality risk. While the meta-analysis—which is a type of study that combines results from several trials—found a mortality risk reduction, none of the specific trials found a statistically significant risk reduction.[7]

3.3 NUCLEAR IMAGING

Nuclear imaging is an emerging field under the realm of personalized therapy management. The National Cancer Institute (NCI) explains that "nuclear imaging uses low doses of radioactive substances linked to compounds used by the body's cells or compounds that attach to tumor cells. Using special detection equipment, the radioactive substances can be traced in the body to see where and when they concentrate."[8] For example, often hormone treatments result in acquired resistance to drugs such as tamoxifen,[9] and the subsequent need for chemotherapy.[10] The goal of nuclear imaging is to not only guide treatment, but to develop possible new targeted drugs by monitoring hormone receptor status and drug-receptor interactions.[10]

Nuclear imaging techniques include positron emission tomography (PET) and single photon emission computed tomography (SPECT), both of which are non-invasive and allow monitoring of biochemical and physiological processes.[10] PET can be used as an alternative for invasive biopsies by using a radioactive tracer to acquire 3-D images and monitor the entire body in a single session.[9] These techniques detect and quantify hormone receptor status in breast cancer patients with acquired resistance to treatments, and may allow for discriminating subtypes of resistance and selecting patients likely to respond to therapy—thereby minimizing potentially damaging and unnecessary treatment.[10] Potential applications of these techniques include early prediction of treatment response, individualized dosing, characterization of resistance phenotypes, and monitoring changes in receptor expression during disease progression.[9] These possibilities are still undergoing research and validation, and are not ready for clinical use outside of research protocols.

3.4 CHEMOTHERAPY

Chemotherapy is a systemic drug treatment that is administered intravenously or orally.[11] Chemotherapy acts by killing cells that divide rapidly, one of the main properties of most cancer cells. It is considered "systemic" because once the drugs enter the bloodstream they travel to all parts of the body in order to reach cancer cells that may have spread beyond the breast. However, this means that chemotherapy also harms cells that divide rapidly under normal circumstances, such as cells in the bone marrow, digestive tract, and hair follicles.

Researchers are currently investigating gene-expression profiling to predict responses to chemotherapy, in order to reduce the number of women exposed to unnecessary treatment with chemotherapy.[12] As with surgery, much of the progress may be in establishing that less is more for many breast cancer patients. Clinical trial results that have served as a basis for including chemotherapy as standard treatment for breast cancer show surprisingly modest benefits, and sometimes no benefit, from the toxic treatments.

Modern chemotherapy developed after World War II, and treatments for advanced breast cancer were introduced in the early 1970s. A meta-analysis of studies that began before 1985 for women with early breast cancer found a reduction in mortality with chemotherapy compared to no chemotherapy;[13,14] however, a closer look at the results reveals that although the studies showed a statistically significant reduction in the risk of recurrence with chemotherapy in both younger and older women, it was only in younger women that chemotherapy led to a benefit in survival. Even though more women in the studies were over 50 years of age, there was not a statistically significant benefit in survival for those women over 50 who took chemotherapy compared with those who did not.

Treatments combining more than one drug are considered to be more effective than single-drug therapy in early stage cancer,[15] and trials of metastatic disease have demonstrated that combination regimens showed an 18% lower risk of death compared to monotherapy.[16] Although combination chemotherapy, in general, yields higher response rates, it also has greater toxicities than monotherapy.

Typical combinations include AC (Adriamycin and Cytoxan), AT (Adriamycin and Taxotere), CMF (Cytoxan, methotrexate, and fluorouracil), FAC (fluorouracil, Adriamycin, and Cytoxan), and CAF (Cytoxan, Adriamycin, and fluorouracil). These regimens usually include chemotherapy drugs with different functions. The most common types of chemotherapy drugs are described in Table 2.

Table 2. Chemotherapy Drugs & Their Mode of Action

Drug Type	Examples	Action(s)
Anthracyclines	Doxorubicin, Epirubicin	Interfere with enzymes involved in DNA replication in all phases of the cell cycle.
Alkylating Agents	Cyclophosphamide, Cisplatin, Carboplatin, Oxalaplatin	Damage DNA to prevent the cancer cell from reproducing.
Antimetabolites	Capecitabine, 5-Fluorouracil, Methotrexate, Gemcitabine	Interfere with copying of DNA and RNA by substituting for the normal building blocks of DNA. Damage cells during the S-phase.
Topoisomerase Inhibitors	Mitoxantrone, Topotecan, Irinotecan	Interfere with topoisomerase enzymes, which help separate the strands of DNA so it can be copied.
Taxanes	Paclitaxel, Docetaxel	Prevent cells from dividing, or inhibit enzymes from making the proteins necessary for cell division.

Chemotherapy treatments last 3-6 months and are typically given in 2-3 week cycles with recovery periods between.

Chemotherapy can be administered post-operatively, known as adjuvant chemotherapy, or prior to surgery, known as neoadjuvant therapy. There have been reports indicating a 50% reduction in tumor size in 90% of primary operable tumors after neoadjuvant chemotherapy.[17] This allows for the possibility of a lumpectomy for women with large tumors who might have required a mastectomy.[17] However, because neoadjuvant therapy alone does not improve survival,[18] it is not usually offered as a sole form of treatment.

During the 1990s, chemotherapy regimens containing the anthracycline Doxorubicin (Adriamycin), such as CAF, largely replaced CMF regimens for the treatment of breast cancer after studies suggested that the addition of an anthracycline to adjuvant systemic therapy was associated with a 16% reduction in relative risk of breast cancer mortality when compared with CMF alone.[15] However, recent studies have shown that for the vast majority of women with breast cancer, anthracycline-based chemotherapy is no more effective and has the potential for more serious toxicities than other known regimens, such as CMF.[19] Evidence suggests that only a small subset of HER-2-postive breast cancer patients derive benefit from anthracycline chemotherapy, and that those patients could derive equal benefit from a less toxic, targeted treatment.[20] Nonetheless, many oncologists still prescribe anthracyclines as part of a first-line treatment regime for the majority of breast cancer patients.[21]

While chemotherapy agents continue to be added onto regimens, researchers often do not study the impact of subtracting agents that may no longer be necessary.

In the mid-1990s, taxanes were tacked onto the anthracyline backbone after several large studies suggested a 17% reduction in the risk of recurrence in lymph node-positive patients receiving a taxane compared to non-taxane regimens.[22,23] Only one of those trials observed a statistically significant survival benefit with the addition of taxanes, and trials remained contradictory in terms of a survival benefit. The toxicity associated with adding taxanes was considered "modest"[22] and "acceptable"[23] by the researchers, though the most common adverse events for patients receiving taxanes included neurosensory toxicity, neuromotor toxicity, and muscle and joint pain.[23]

While adjuvant combination chemotherapy (with CMF or an anthracycline-containing regimen) has been shown to produce an absolute improvement of about 7-11% in 10-year survival for younger women diagnosed with breast cancer, an absolute benefit of 2-3% was observed in women ages 50-69.[24] The majority of breast cancers are diagnosed in women over age 50.

While chemotherapy agents continue to be added onto regimens, researchers often do not study the impact of subtracting agents that may no longer be necessary.

3.5 HORMONAL THERAPY

An estimated three quarters of breast cancers are estrogen receptor (ER) positive, and are treated with hormonal therapy, such as aromatase inhibitors (AIs) or selective estrogen receptor modulators (SERMs). The goal of hormonal therapy is to block estrogen receptors with antagonists or inhibit the synthesis of estrogen.[25] The hormonal dependence of breast cancer cells was first discovered by Charles Huggins in 1941.[26] The following years led to more discoveries, notably the identification of the estrogen receptor (1966) and the approval of the hormone-blocking drug tamoxifen. AIs work through a mechanism that reduces the amount of estrogen in the body.

Women taking tamoxifen for five years had a risk of death from thromboembolic disease and endometrial cancer of about 0.2% per decade.[27] In terms of benefits, for ER-positive women taking tamoxifen, the annual rate of recurrence and death were reduced by 40% and 34%, respectively, compared to women who did not receive tamoxifen after surgery.[27] In a recent study, women who took tamoxifen for five years after initial breast cancer treatment had a lower chance of recurrence than women who took the drug for two years.[28] Forty percent of patients who took the recommended five-year course had recurrences compared to 46% who took tamoxifen for two years, resulting in a 6% difference in the absolute risk of recurrence.[28]

3.6 TARGETED BREAST CANCER TREATMENT

An advancement in breast cancer has been the discovery that not all breast cancers are the same, and that treatment in some cases can be targeted to a particular tumor subtype.

Targeted therapies narrow treatment delivery based on cancer biology, and promise less toxicity by avoiding action against normal cells. An example is trastuzumab (Herceptin), a monoclonal antibody that has been used to treat more than 420,000 women with HER-2-positive breast cancer worldwide.[29] Heralded as the first biologic for breast cancer and a major advance in targeted cancer therapies when first introduced, the drug has been included in breast cancer treatment protocols in the US since receiving approval for use by the FDA in 1998. Despite widespread use and extensive research, however, the mechanism by which trastuzumab acts is not completely understood. And many questions about which patients will get the most benefit from trastuzumab and the optimal treatment protocols remain unanswered. Furthermore, the promise that targeted treatment with trastuzumab would lead to less toxicity has not been realized. Following studies demonstrating that trastuzumab was more effective in combination with chemotherapy,[30] the standard of care has continued to include toxic agents in combination with targeted trastuzumab.

> An estimated three quarters of breast cancers are estrogen receptor positive, and are treated with hormonal therapy...

There are significant limitations with targeted therapies. For example, cancer cells often develop resistance to even these sophisticated targeted approaches. There are two types of resistance: *de novo* resistance and acquired resistance. *De novo* resistance occurs when patients do not respond to initial treatment, whereas the latter develops after continuous treatment.[31] While trastuzumab is considered a success story as targeted breast cancer therapy, about half of HER-2-positive patients do not respond to trastuzumab therapies due to various resistance mechanisms,[31] and those who do often build up resistance within a year or two.[32,33]

3.7 DRUG DEVELOPMENT, EVALUATION & APPROVAL

There are currently 887 drugs being evaluated in clinical trials or under FDA review for the treatment of cancer, including 91 specific for breast cancer, according to the Pharmaceutical Research & Manufacturers of America.[34] Along with studies of these new agents, there are many clinical trials evaluating existing drugs in new combinations or at different stages of disease. A recent search of ClinicalTrials.gov shows 2,643 clinical trials are currently ongoing or recruiting for the evaluation of drug interventions for breast cancer.[35]

In evaluating new interventions for breast cancer, it is critically important to use outcome measures that will allow meaningful conclusions about the effect of an intervention. Because survival is the most important outcome for patients, mortality is most often the major or primary outcome of interest. However, in order to

shorten the time needed to reach conclusions about an intervention under study, and to collect additional information that might be used to help interpret the primary outcome, many cancer clinical trials also measure interim or secondary outcomes such as disease-free survival or tumor response rate, and sometimes these secondary outcomes are used as the basis for accelerated approval. These are termed surrogate endpoints. It is important to understand, however, that the validity of this approach relies on the assumption that a favorable interim outcome actually correlates with (is a "surrogate" for) lower mortality. That is not always the case. For example, during 2010, the FDA took action to withdraw approval of bevacizumab (Avastin®) for the treatment of breast cancer because improvements in secondary outcomes have not translated into improvements in overall survival, and at the same time the drug increased serious side effects.[36]

An intervention that has a beneficial effect on the interim outcome might ultimately be proven to have no effect or a negative effect on survival, or vice-versa. Interim endpoints can be important, but survival data must be collected in order to fully assess the ultimate usefulness of the intervention. If not, the overall effectiveness of the intervention would be misunderstood. Interventions must provide meaningful benefits for breast cancer patients that outweigh risks of harm or reductions in quality of life.

3.8 PERSONALIZED TREATMENT FOR BREAST CANCER

Breast cancer treatment decisions were traditionally based on the size of the tumor and the degree to which it had spread, and more recently on the presence of excess estrogen receptors. Each woman's breast cancer is different with respect to unique molecular signatures or patterns, and this information is increasingly being used to make treatment decisions. Ongoing research seeks to further understand what the patterns mean, how they relate to whether a woman's cancer will return, and which treatment would be most beneficial to the patient. Gene expression profiling looks for patterns among many genes in a tumor cell to understand the heterogeneous nature and behavior of breast cancers. Researchers have assessed relationships between the gene expression patterns and information from the woman's medical records (i.e., cancer recurrence and whether the woman benefited from treatment such as chemotherapy) to predict how likely cancer will come back or how likely a woman would benefit from treatment.

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MammaPrint® and Oncotype DX® are two well-known gene expression profiling tests for breast cancer.[37,38] These tests measure gene expression levels within the tumor to produce number scores associated with the risk of distant disease recurrence. The tests can be used together with information such as a woman's age, whether her cancer has spread, and whether the tumor tests positive for hormone receptors to guide individualized treatment decisions.

Both Oncotype DX® and MammaPrint® are meant for women who have hormone receptor-positive early breast cancer. These two tests have only one gene in common. Because the two tests have not been directly compared

to each other in the most rigorous way, the issue remains unresolved as to which test is better than the other at predicting what the best treatment will be or whether a breast cancer will return.

While the two tests are widely available for use by physicians, more evidence is needed to understand how clinically useful the tests are. Other assays are also being tested, one of which, the PAM50 assay, separates tumors into intrinsic subtypes (luminal A and B, basal-like, HER-2-positive) and is both prognostic and predictive of response to hormone therapy.[39] Yet another test, the RS-pathologic-clinical (RSPC) Index, combines pathologic and clinical factors with the Oncotype DX® recurrence score to predict risk of relapse.[40]

3.9 ISSUES WITH MOLECULAR PROFILING

Accurately testing tumors for their genetic and molecular make-up continues to present significant challenges. In order to benefit from our understanding of the different types of breast cancer and their response to different interventions, we must be able to accurately determine tumor characteristics. For example, accurate testing of HER-2 is important, not only for correctly identifying patients who would benefit from treatment, but also identifying those who would not, and preventing unnecessary exposure to drugs that can have serious side effects.

Testing for HER-2 has long been an issue of debate and controversy. At the heart of the debate is the issue of which specific testing method is better for the prediction of response to treatment. The two most commonly used methods of testing include: immunohistochemistry (IHC), which looks for abnormalities in protein (receptor) overexpression, and fluorescence in situ hybridization (FISH), which looks for abnormalities in gene amplification. The FDA has approved a third test more recently, chromogenic in situ hybridization (CISH). CISH is similar to FISH but lacks some of the more sophisticated testing features of the FISH method.

The three types of tests—IHC, FISH, and CISH—are well regarded for their ability to accurately identify abnormalities, but they are nonetheless subject to errors and inconsistencies in specimen handling, testing procedures, and analyses. One of the significant problems encountered is poor agreement between HER-2 test results from local laboratories and those from large-volume central laboratories whether using either IHC or FISH methods.[41,42] Another drawback is that the scoring system used to determine HER-2 status is considered subjective.

A major issue is determining the best strategy for results that are borderline or inconclusive. When results show that HER-2 status is strongly negative or positive, clinical guidelines concerning the course of treatment are fairly certain, but when results are inconclusive or borderline, the best course of treatment is not clear.

3.10 TUMOR DORMANCY & LATE RECURRENCES

After treatment of cancer, some tumors will reappear to grow and spread, sometimes many years later. The period of time before the tumor resurfaces is called tumor dormancy. Tumor dormancy is more likely to be observed with certain types of cancer, including breast cancer. Unfortunately, we know very little about tumor dormancy, and why or how late recurrences happen.

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3.11 TUMOR MICROENVIRONMENT

In the past, cancer research was mainly focused on the cancer cell itself. Recently, scientists have begun to investigate how the rest of our body influences the cancer cell. The tumor microenvironment consists of normal cells and molecules that surround cancer cells; scientists now think that the communication between the tumor cells and the surrounding cells helps drive the tumor growth process.[43]

The process by which normal cells become benign tumor cells, benign tumor cells are transformed to malignant cells, and malignant cells turn metastatic may depend on the molecular signals between the cells and the surrounding area.[44] Contained within the tumor microenvironment are normal epithelial cells, stromal cells such as fibroblasts, cells that make up the blood vessels, immune cells that come from the blood stream, strands of fibers that hold the cell together also known as extracellular matrix, molecules important for cell signaling and growth, and chemicals like oxygen.[45,46] The cancer cell may be dependent on the microenvironment for its proliferation, progression, and metastasis; an example includes the role of the inflammatory response in tumor cell proliferation, angiogenesis, invasion and metastasis.[47,48] Also, research has suggested that chemical signals coming from cells surrounding a tumor (stromal cells) along with signals from within the tumor (epithelial cells) together may lead to key events that cause DCIS to progress to invasive breast cancer.[49]

As researchers study and investigate the molecular pathways by which a tumor progresses and is metastasized, targeting the tumor microenvironment is a promising avenue for creating new therapeutic agents for breast cancer.

Not only does the microenvironment play a significant role in tumor evolution and progression, but it also has an impact on the efficacy of cancer therapy. For example, tissue organization and interactions with the extracellular matrix may impact the cell's response to chemotherapy—if the cell is resistant to the drugs or if it dies.[50] For this reason, the cell-cell and cell-matrix interactions that influence the behavior of cancer cells are targets with as much potential for the development of effective therapies as the tumor cells themselves. As researchers study and investigate the molecular pathways by which a tumor progresses and is metastasized, targeting the tumor microenvironment is a promising avenue for creating new therapeutic agents for breast cancer.

Most studies analyzing the relevance of the microenvironment in cancer formation and progression have been performed in mice and in other animals.[43] However, numerous observations obtained from human patients support the hypothesis that the tumor microenvironment is important in the cancer process. For example, polymorphisms, or variants, in genes encoding the extracellular proteins have been found to influence the risk of breast cancer metastasis.[51] Researchers have also hypothesized that the differences in cancer incidence and mortality between various ethnic groups may be due to genetic polymorphisms in genes that regulate the tumor microenvironment.[43]

The exact role of different cell types in the tumor microenvironment, interacting with each other and with the cancer cell, in the progression of breast cancer, has not been fully delineated.

3.12 COST OF TREATMENT

The cost of treating breast cancer continues to soar. Trastuzumab can cost up to $40,000 for a year of treatment, according to manufacturer Genentech.[29] Newer cancer drugs cost even more. For example, bevacizumab, an antiangiogenic approved through accelerated approval, sells for $55,000 a year.[52] Prescription drug spending was $249.9 billion in 2009, which accounted for 10% of the total health care expenditures that year.[53] Cancer drug costs continue to rise and the list of therapeutics continues to lengthen without accompanying decreases in breast cancer mortality. From 1991 to 2002, Medicare breast cancer chemotherapy costs increased an average of $6,160 per person treated, reaching $12,802 per person in 2002.[54] Hospitalizations, cancer-related surgery, and radiation therapy, among other things, add to the cost of cancer treatment.

Expenditures associated with cancer care can be broken down into the following three distinct phases of care: 1) initial phase following diagnosis, 2) the last year of life, and 3) the continuing phase or the period between the

The national cost of cancer care in 2010 was estimated to be $124.6 billion, with female breast leading all cancer sites at an estimated $16.5 billion.[57]

initial phase and the last year of life.[55] In 2006, an estimated $13.9 billion was spent on breast cancer care in the US, with about $11 billion divided almost equally between initial and continuing care, and the remainder spent on the last year of life.[55] Each year about $3.3 billion is spent on mammograms.[56] In terms of lost productivity, breast cancer costs the country $12.1 billion.[55] The national cost of cancer care in 2010 was estimated to be $124.6 billion, with female breast leading all cancer sites at an estimated $16.5 billion.[57] By 2020, a 32% increase in the cost of continuing phase care is expected for breast cancer.[57]

3.13 QUALITY OF CARE

The publication of the Institute of Medicine's 2001 report, *Crossing the Quality Chasm: A New Health System for the 21st Century*,[58] defined quality in health care, laid out a vision for a patient-centered health care system, and highlighted the quality gaps in the United States. Despite the spotlight shone and the alarm sounded on this national problem, progress in measuring and attaining quality care has remained slow and uneven.

Research suggests that on average, the quality of health care received by all patients in the US, including breast cancer patients is less than ideal and costs far more than elsewhere. According to the Kaiser Family Foundation, "the United States not only spends much more per capita on health care than any other country, but also has had one of the fastest growth rates in health spending among developed countries. Despite this higher level of spending, the United States does not achieve better outcomes on many important health measures."[59]

A person with a new diagnosis of cancer has approximately a one in five chance of failing to receive elements of cancer care that are evidence-based and consistent with practice standards.[60] The Agency for Health Care Research and Quality (AHRQ) provides a succinct definition of quality of care as "getting the right care, in the right way, at the right time, for all Americans."[61] Measuring the extent to which quality care is the standard and quantifying quality improvement has been a challenge in the US. For example, the only breast cancer care related measure required by the national Health Care Effectiveness Data and Information Set (HEDIS) measures of the accrediting body, the National Committee for Quality Assurance (NCQA), is for mammography usage—hardly a measure of breast cancer care. Many professional and quasi-governmental groups have developed breast cancer quality measures, from the National Quality Forum (NQF) to the American Society for Clinical Oncology (ASCO) to AHRQ's Consumer Assessment of Healthcare Providers and Systems (CAHPS) surveys, but most are not mandatory and there is no harmonization among them so progress is difficult to assess—both for the health care community as well as for the public.

The effort to measure quality is also contingent on established, recognized and evidence-based guidelines that would help determine baseline and progress measures. There are many organizations which develop and promote breast cancer guidelines both nationally and internationally including the National Comprehensive Cancer Network (NCCN), ASCO, the American Cancer Society and others. However, as with measures themselves, these guidelines vary from each other and cover different practices and aspects of care. They are often produced by groups with inherent conflicts of interest.[62] Adherence to guidelines remains an issue with geographic variations and variations for different populations such as the uninsured, the elderly and communities of color. According to a recent AHRQ report, "Health care quality and access are suboptimal, especially for minority and low-income groups."[61]

The racial differences in breast cancer mortality observed over the years have been attributed in part to African American women having more delays between diagnosis and the beginning of treatment than white women.[63] Additionally, studies have shown that African American women are more likely than white women to discontinue treatment and miss appointments.[64] Furthermore, "national data to assess performance and the

presence of disparities in health care are unavailable for several key measures of quality. In many cases, these data are simply not being collected."[61]

Often, the quality of guidelines themselves, the deviations from high-level evidence-based guidelines, and our inability to measure and mandate quality care have led to overdiagnosis, overtreatment, undertreatment, and mistreatment resulting in unnecessary morbidity and mortality.

Overdiagnosis & Overtreatment

An estimated 30% of all breast cancer cases (both invasive and DCIS) are considered to be overdiagnosed and overtreated.[65] Overdiagnosis, a downside of screening, is diagnosis of cancers that would not have presented within the life of the patient. Overdiagnosis is likely to increase with technological developments, including digital mammography, computer-aided detection and improved biopsy techniques. Overtreatment can occur in two ways—either in overdiagnosis, where any treatment is unnecessary, or with the administration of more aggressive therapies than is necessary.[66,67]

For every 2,000 women invited for screening over a 10-year period, one will have her life prolonged and 10 healthy women, who would not have been diagnosed if they had not been screened, will be treated unnecessarily.[65] The evidence of a mortality reduction from screening is conflicting and continues to be questioned by some advocates, scientists, policy makers and members of the public. In fact, the absolute risk of a woman dying from breast cancer is less than 1% without any screening. Looking at this another way, 995.6 out of 1,000 50-year-old women will not die of breast cancer within the next ten years. This number rises to 996 out of 1,000 with regular mammography screening.[68]

History has shown that once a treatment regimen is in place and becomes standard, it can take a long time to remove it from practice, even when scientific evidence no longer supports its use.[69,70] Patient-centered care requires that removing a treatment from standard care should happen as quickly and routinely as adding a new one, once the evidence supports a change.

For example, the evidence-based recommendation is not to provide any adjuvant systemic treatment for women with node-negative, low risk breast cancer,[71,72] but published estimates of adherence to this recommendation range from 52.2% to 84.9%.[73-75] Once evidence began to suggest that, for the vast majority of women, anthracycline-based chemotherapy is no more effective and has the potential for more serious toxicities than other known regimens, many oncologists continued to prescribe anthracyclines as part of a first-line treatment regime.[21,76]

An estimated 30% of all breast cancer cases (both invasive and DCIS) are considered to be overdiagnosed and overtreated.[65] Overdiagnosis, a downside of screening, is diagnosis of cancers that would not have presented within the life of the patient.

Morbidity & Mortality Caused by Treatments

Breast cancer treatments do carry risks of morbidity and even mortality. Common morbidities reported with breast cancer treatment include cardiac complications, wound infections, lymphedema, impaired range of shoulder motion, and psychological distress. Of these, the morbidity of greatest incidence is lymphedema (swelling of lymph vessels as a result of fluid buildup). The morbidity rates for lymphedema appear to range from 7-80%, with SLNB generally associated with lower morbidity than ALNB.[77] The true incidence of lymphedema is difficult to measure, due to lack of a standard definition, choice of measurement instruments, timing of assessment, and variances in onset.[77,78]

A recent study demonstrated that in patients with a limited spread of breast cancer to the lymph nodes, removal of additional lymph nodes through axillary lymph node dissection had no impact on five year survival.[3]

Immediate morbidity from radiation therapy is typically reported in the form of dermal reactions, but long-term consequences can include new cancers. Consequences of chemotherapy can include cardiovascular damage, peripheral neuropathy, and other cancers, too.[79] Morbidity from the hormonal therapy tamoxifen includes endometrial cancer, thromboembolic disease, and ocular toxicity.[80] Tamoxifen increases the risk of endometrial cancer nearly threefold[81] and 1.5-7.1 fold for venous thromboembolism.[82] Ocular toxicity is less common, with one study reporting 0.9% (45 of 4,948) morbidity in patients after hormone therapy alone.[83]

THE ADVOCATE PERSPECTIVE

Progress in the treatment of breast cancer has been incremental, at best, over the last two decades. Surgery, chemotherapy, radiation therapy, hormonal therapy, and targeted therapy provide slight additive benefits, though we still do not know which individuals need to be treated, and with how much, and which individuals would do fine without any disfiguring or toxic treatments. As the reviewers of the meta-analysis providing the most often cited evidence in favor of combination chemotherapy stated, "Treatment decisions involve consideration not only of improvements in cancer recurrence and survival, but also of adverse side-effects of treatment, and this report makes no recommendations as to who should or should not be treated."[24]

We do not know how to cure lethal breast cancer. We cannot tell any individual woman that she will be cured of her breast cancer if she follows any particular course of treatment. There are benefits to much of what we do to treat breast cancer and there are also risks, sometimes life-threatening. It is important to understand how to interpret the messages given around treatment benefit and risk. For example, we may hear that Drug X works better than Drug Y. What is the evidence for that statement? What does "works" mean? Does it prolong life? Does it mean that a new technology can measure if a tumor grows more slowly with one drug over another, yet neither prolongs life or gives better quality of life? If Drug X slows tumor growth but results in deaths from side effects, does the benefit outweigh the risks?

Our understanding of breast cancer has increased dramatically, but for people facing breast cancer, very little has changed. Researchers and the media often celebrate

small accomplishments. We have been conditioned to believe that a drug that may extend life a few months is a breakthrough, that a 2% reduction in mortality is promising, that tumor regression or stabilization are cause for celebration, even though at that point there is no way to determine if anyone's life was actually prolonged.

NBCC advocates want to see treatments that prolong life or significantly increase quality of life.

NBCC advocates want to see treatments that prolong life or significantly increase quality of life. The push to approve drugs more quickly can be at odds with this goal. The evidence of benefit and risk must be based on high-level studies upon which patients can rely. How well is the study designed? What is the endpoint of a study? That is, what are the outcomes that are measured, and what are the risks that were observed?

While the selection of a less definitive endpoint, such as measurement of tumor progression, may allow for shorter trials and easier measurement, it may not yield useful information about how well an intervention saves or prolongs lives. Whenever less-than-ideal endpoints are selected, important questions will be left unanswered. This means that further trials will be necessary—requiring more time, more money, and more patient participation. It also may result in a treatment in the clinic that is exceedingly expensive, yet gives little benefit and perhaps increased harm.

How those outcomes are interpreted is also important to understand. When discussing interventions that purport to decrease the risk of breast cancer, the risk of recurrence, or the risk of death, we must understand absolute versus relative risk. Study results are often reported, particularly in the popular media, in terms of relative risk, making results sound more significant than they may in fact be.

Absolute risk is the chance or probability that something will happen, and is not compared to anything, while relative risk is comparing two different risks. For example, the absolute risk of dying from breast cancer for a typical 50-year-old woman in the US is 0.4%. or 4 in 1,000. If a pill lowered this woman's chance of dying to 0.2%, or 2 in 1,000, this would be a 50% relative reduction in risk. Explaining these results in relative terms makes the effect of the pill sound pretty significant,

when in reality, and in absolute terms, the pill caused a small change in risk for someone with a fairly small risk to begin with.

Data or no data, quality improvement will be impeded as long as millions of Americans are uninsured and face barriers to quality health care.[84,85] Time and time again, insurance status has been shown to affect access to quality care. In 2006, uninsured women under age 65 were less likely than women with private insurance to receive radiation therapy following BCS.[86,87]

Data or no data, quality improvement will be impeded as long as millions of Americans are uninsured and face barriers to quality health care.[84,85]

IOM quality aims published in 2001 and NBCC quality core values developed in 1999 both envision a system of quality care that is patient-centered and evidence-based. NBCC's vision includes six overlapping core values: Access to all the care you need when you need it; Information that is complete and correct; Choice about your doctors and your treatment; Respect from everyone in the health care system; Accountability so there is a way to fix problems; and Improvement in the system so breast cancer care continues to get better.[88] In 2005, NBCC convened a focused workshop, Measuring What Matters, to evaluate established measures for breast cancer using the NQF and NCQA criteria: importance, scientific soundness, feasibility and usefulness. Recommendations were developed to help guide this work from a patient perspective. Organizations devoted to quality care such as AHRQ, IOM and NQF are including advocates in their ongoing work to assure that this perspective continues to guide the process.

4 | BREAST CANCER PUBLIC POLICY: RESOLUTIONS, LAWS & EXECUTIVE ACTIONS

4 | BREAST CANCER PUBLIC POLICY: RESOLUTIONS, LAWS & EXECUTIVE ACTIONS

Since NBCC was founded in 1991, over 830 resolutions and bills related to breast cancer have been introduced in the United States House of Representatives and Senate.[1] This is the number that contain the words "breast cancer." There are others that have an effect on but do not specifically reference breast cancer. Of the hundreds of resolutions and bills introduced, 11 resolutions were agreed to by the House and Senate, and 42 bills became law.

Since NBCC was founded in 1991, over 830 resolutions and bills related to breast cancer have been introduced in the United States House of Representatives and Senate.[1]

The breakdown of resolutions, laws and executive actions related to breast cancer since 1991 is depicted in Figure 5.

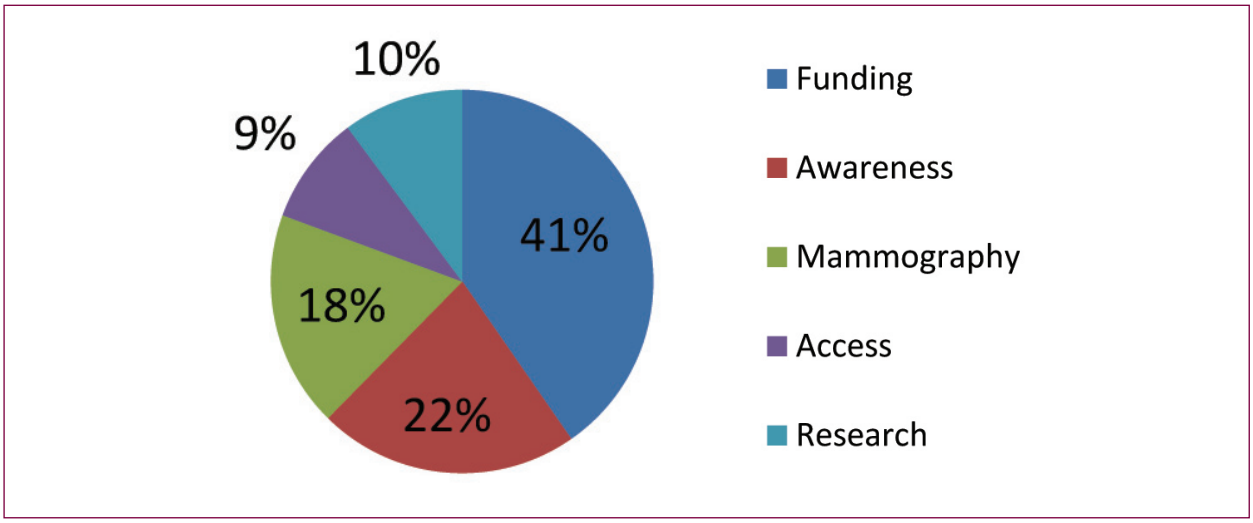


Figure 5. Laws & Executive Actions Related to Breast Cancer Since 1991

Data source: The Library of Congress. THOMAS. ONLINE. 2011. Library of Congress. Available from: http://thomas.loc.gov/home/multicongress/multicongress.html [breast cancer] (Accessed March 24, 2011).

About 40%....focus on the intertwined topics of breast cancer awareness and mammography.

About 40% of the resolutions, laws, and executive actions focus on the intertwined topics of breast cancer awareness and mammography. Another 41% focus on breast cancer specific research funding, mainly through the Department of Defense Breast Cancer Research Program (DOD BCRP). The remaining percentage are laws in the areas of access, and research.

4.1 BREAST CANCER AWARENESS

Over 20% of the breast cancer laws and executive actions since 1991 have dealt with some aspect of breast cancer awareness. These were mainly Congressional Resolutions, designated by H.J. Res. /S. J. Res. or H. Con. Res. or S. Con. Res., which are typically used by Congress for expressing facts, principles, opinions, and purposes of the House of Representatives and the Senate. For example, four of the 55 laws and executive orders related to breast cancer were resolutions to designate October as "National Breast Cancer Awareness Month."

4.2 MAMMOGRAPHY

An additional 18% focused on mammography. These laws ranged from the reauthorization of the Mammography Quality Standards Act, which allows women to be assured that the mammogram they received was properly administered and analyzed, to Congressional Resolutions designating a national mammography day.

4.3 BREAST CANCER SPECIFIC RESEARCH FUNDING

Laws appropriating specific funding to support breast cancer research through the DOD BCRP accounted for a significant portion of the 41% of the laws passed related to funding.

Laws appropriating specific funding to support breast cancer research through the DOD BCRP accounted for a significant portion of the 41% of the laws passed related to funding. The DOD BCRP was created in 1992 as a result of NBCC's "$300 Million More" campaign to increase federal funding for breast cancer research. In FY1993, Congress appropriated $210 million in the DOD research and development budget for a breast cancer peer-reviewed research program administered by the Department of the Army. The Program's mission is to "eradicate breast cancer by funding innovative, high-impact research through a partnership of scientists and consumers."[2] Since 1992, Congress has approved more than $2.5 billion in funding for the DOD BCRP.[2]

Laws concerning the creation and continuation of a first-class stamp, the Breast Cancer Research Semipostal, which can be purchased on a voluntary basis by the public, accounted for 18% the laws related to specific research funding. Net revenues from sales of the stamp are provided to two designated funding agencies, the DOD BCRP and the National Institutes of Health, to support breast cancer research.

4.4 ACCESS

While accounting for less than 10% of the total, the laws and two executive actions which can be categorized as improving access to health care for breast cancer survivors are significant. They include the Breast and

Cervical Cancer Prevention and Treatment Act of 2000, designed and successfully advocated for by NBCC. This Act guarantees treatment to low-income uninsured women screened and diagnosed with breast and cervical cancer through the CDC's National Breast and Cervical Cancer Early Detection Program; the Native American Breast and Cervical Treatment and Technical Amendment Act of 2002 was then passed to help correct the unintended exclusion of American Indian and Native Alaskan women from the Breast and Cervical Cancer Prevention and Treatment Act.[3]

In 2000, President Clinton undertook two important executive actions. In February 2000, he signed an Executive Order that banned genetic discrimination in the federal workplace, an issue important for breast cancer survivors and their families, as genetic predisposition to breast cancer became better understood and tests were available and accessible.

In June 2000, the President issued an Executive Memorandum which ensured those participating in clinical trials, including breast cancer patients, would have access to Medicare coverage for routine patient care associated with participation in these trials.

4.5 RESEARCH

Laws specifying the quantity and conduct of research on breast cancer comprised 10% of the laws related to breast cancer passed during this period. The focus of these laws includes areas to be prioritized, exposures examined and population subgroups defined. Among the laws included in this category are those reauthorizing the National Institutes of Health, and a law requiring research on exposure to the drug diethylstilbestrol (DES).

THE ADVOCATE PERSPECTIVE

Not all laws that affect breast cancer are created equal. The absolute number of resolutions agreed to by the House and Senate, bills that became law, or executive actions issued or signed by a President, taken alone, do not tell us much about the impact of public policy on breast cancer. However, taken together they do provide a useful snapshot of what the conversation around breast cancer has been on Capitol Hill and in various Administrations for the past 20 years.

Some of these laws, such as the Breast and Cervical Cancer

Not all laws that affect breast cancer are created equal.

Prevention and Treatment Act, which guarantees treatment to low-income, uninsured women screened and diagnosed with breast and cervical cancer through the Centers for Disease Control and Prevention's (CDC) National Breast and Cervical Cancer Early Detection Program, are significant. Many are not, such as a law passed in 2004 to authorize illumination of the Gateway Arch in St. Louis, Missouri with pink lights in honor of breast cancer awareness month. In addition, there are multiple laws included in the total to fund the Department of Defense Breast Cancer Research Program (DOD BCRP), as the program must receive appropriations each year to continue. Also significant for women and men living with breast cancer were the two referenced executive actions taken by President Clinton in 2000.

Breast cancer is a political issue. The federal government is the largest funder of biomedical research. Laws regulate and support access to care and health care systems. Third party payors are subject to state and federal regulations. In fact, every aspect of breast cancer is touched by public policy.

Breast cancer is a political issue. The federal government is the largest funder of biomedical research. Laws regulate and support access to care and health care systems. Third party payors are subject to state and federal regulations. In fact, every aspect of breast cancer is touched by public policy. It is key that those who influence that policy are educated and trained and have no agenda other than to save lives, and to end breast cancer.

While we can assume that every member of Congress, of the Administration, and of state and local governmental entities wants to see an end to breast cancer, the question is, "What are they willing to do to get there?" Resolutions will not get us far. Expanding support for meaningful research and access to quality care is more likely to have a real impact.

Advocates understand that the causes and cures for breast cancer will not be found only in test tubes. They must be fought for in public policy forums, at research conferences, in drug company boardrooms, and in the voting booth.

Each year the National Breast Cancer Coalition's Board of grassroots advocates sets a public policy and legislative agenda and publishes a Congressional Record of Support[4] that contains information about that agenda.

Advocates understand that the causes and cures for breast cancer will not be found only in test tubes. They must be fought for in public policy forums, at research conferences, in drug company boardrooms, and in the voting booth.

2020

2019

2018

2017

2016

2015

2014

2013

2012

2011

5 | BREAST CACNER RESEARCH

5 | BREAST CANCER RESEARCH

Since President Nixon declared the "War on Cancer" 40 years ago, billions in public funding, private investment and charitable contributions have been directed toward decreasing the burden of cancer, including breast cancer. However, as outlined above, this investment has not resulted in dramatic gains in lives saved. Investment is only the first step—the funds must be well managed, well spent, and directed to maximize results. What are the elements of the research process that would maximize that investment? We know that individual investigator-initiated research is important, and many discoveries are serendipitous; but there must be investment in all aspects—and discoveries must be applied to people. This section outlines sources of breast cancer research funding and The Advocate Perspective discusses existing barriers that prevent or slow significant results from the extensive investments being made.

5.1 FEDERALLY FUNDED RESEARCH

The US Government is the largest funder of breast cancer research in the US. In 2009, the National Cancer Institute (NCI), within the National Institutes of Health (NIH), spent $599,500,000 on breast cancer research, which was 12.1% of their budget that year (Figure 6). Projects included in this estimate were those that were coded, or had a portion of their project coded, to the breast organ site through the NCI's system of scientific coding.[1]

Other institutes within the NIH fund breast cancer research as well. According to the NIH RePORTER, in fiscal year 2010, the NIH spent $763 million (non-American Recovery & Reinvestment Act) funding breast cancer research projects across its various institutes and centers (including the NCI), and this number is estimated to increase to $778 million in fiscal year 2012.[2]

The National Institute of Environmental Health Sciences (NIEHS) is another sector of the NIH that contributes to the field of breast cancer research. In 2003, the NIEHS and NCI established the Breast Cancer and the Environment Research Centers (BCERC) Network followed by the Breast Cancer and Environmental Research Program (BCERP) to "promote research that would characterize environmental exposures over the lifetime that could alter the risk of breast cancer development."[3]

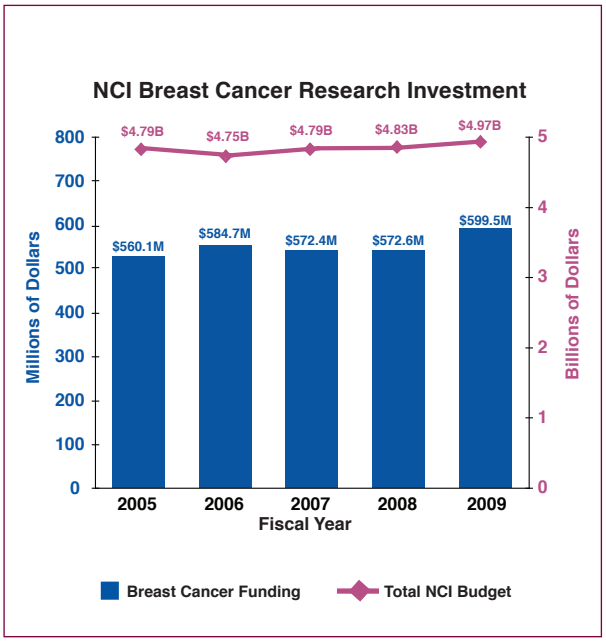


Figure 6. NCI Breast Cancer Research Investment

Graphic source: NCI. September 2010. NCI Breast Cancer Research Investment. [graphic]. A Snapshot of Breast Cancer. Accessed February 20, 2011, from http://www.cancer.gov/aboutnci/servingpeople/snapshots/breast.pdf

Other federal agencies that fund breast cancer research include the Centers for Disease Control and Prevention (CDC), the Environmental Protection Agency (EPA), the Department of Energy (DOE), the National Aeronautics and Space Administration (NASA), the National Science Foundation (NSF), the Department of Agriculture (USDA) and the Department of Defense (DOD).

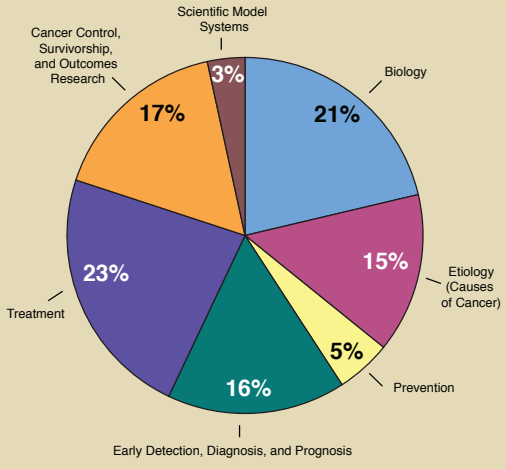
The DOD Breast Cancer Research Program (DOD BCRP) was established and is maintained as a direct result of NBCC grassroots efforts and has allocated over $2.5 billion to peer-reviewed breast cancer research since 1992.[4] The program includes consumer advocates at all levels of decision making, including the establishment of programmatic goals each year.

5.2 COMPARATIVE EFFECTIVENESS RESEARCH

The federal government is increasing its investment in Comparative Effectiveness Research (CER) as a means of improving the health care system in the US. CER compares the benefits and harms of interventions, and assesses outcomes for a diversity of patient populations. If effectively carried out, CER can improve quality care and outcomes by ensuring patients are receiving the best, evidence-based care, while lowering health care costs by removing treatments that are not effective.

5.3 NON-FEDERALLY FUNDED RESEARCH

In addition to the federal government, state and local governments, private organizations, private institutions, and industry also invest substantial amounts of money on breast cancer-related research.



Percentage of Total Dollars by Scientific Area Fiscal Year 2009

Data sources: NCI's Division of Extramural Activities and the NCI Funded Research Portfolio. Only projects with assigned scientific area codes are included. A description of relevant research projects can be found on the NCI Funded Research Portfolio Web site at http://fundedresearch.cancer.gov

Figure 7. NCI Breast Cancer Research

Graphic source: NCI. September 2010. NCI Breast Cancer Research Portfolio. [graphic]. A Snapshot of Breast Cancer. Accessed February 20, 2011, from http://www.cancer.gov/aboutnci/servingpeople/snapshots/breast.pdf

State Governments: Texas & California

Two of the most notable state-funded breast cancer research programs are located in Texas and California. The two are organized quite differently, with the California Breast Cancer Research Program (CBCRP) dedicated to breast cancer research, and Texas's program, titled Cancer Prevention & Research Institute of Texas (CPRIT), encompassing all cancers. In addition, funding of the programs differs, in that CBCRP is tax funded whereas CPRIT is funded by state bonds.[5,6]

CBCRP has provided over $215 million since 1993 and $17 million in 2010 for breast cancer research.[5] The program includes patient advocates in all levels of decision-making: from which projects receive funding to research priorities.[5]

Texas also houses a multibillion-dollar cancer program. CPRIT was established in 2007 with funding from $3 billion of state bonds for research and prevention programs.[7] Funding in 2010 for research, commercialization, and prevention products totaled $40.4 million for breast cancer, higher than any other cancer type, with gastrointestinal funding following at $31.7 million. As a rule, CPRIT does not allocate budgets towards specific cancers; rather, review panels disburse funds based on merit and promise.[6] A significant amount of funding is awarded for secondary prevention programs such as screening, healthy lifestyles, and reducing disparities in the Mexican American and Latino populations.[6]

Non-Profit Organizations

Private organizations also provide significant levels of support for breast cancer research in the US (Table 3). While there are numerous organizations across the country and in other countries that raise funds to invest in breast cancer research, this report highlights those that fund in excess of $1 million annually. The largest among them is The Susan G. Komen Breast Cancer Foundation, Inc. (Komen), which has invested close to $450 million on research since 1982.[8] In 2010, 20% of the Komen budget was dedicated to research.[9]

Table 3. Summary of Private Organizations Funding Breast Cancer Research

Organization	Fiscal Year End	Research expenses (a subset of program expenses)†
The Entertainment Industry Foundation[1] (includes Stand Up To Cancer‡)	12/2009	$51,227,417: Grants program to charities for all cancers, not just breast cancer
	12/2008	$16,867,808: Grants program to charities for all cancers, not just breast cancer
Breast Cancer Research Foundation[2,3]	6/2009	$28,447,757: Grants awarded for research
	6/2008	$34,336,801: Grants awarded for research
Avon Products Foundation[4,5]	12/2009	$26,267,664: Grants awarded through Breast Cancer Crusade
The Susan G. Komen Breast Cancer Foundation, Inc.[6,7]	3/2010	$75,407,069: Of this, $62,691,301 went to awards & grants
	3/2009	$70,146,688: Of this, $59,179,051 went to awards & grants
American Cancer Society[8]	12/2009	$280,179,000: Total Extramural and Intramural Funding awarded for all research areas; of this, $30,357,000 was awarded to breast cancer

† Amounts as reported by each organization in financial reports or IRS Form 990.
‡ Stand Up To Cancer is a program of The Entertainment Industry Foundation.
[1] The Entertainment Industry Foundation. 2009 Audited Financial Statement. 2009; http://c0208372.cdn.cloudfiles.rackspacecloud.com/FS-EIF-123109-final-signed20audit.pdf. Accessed March 10, 2011.
[2] Breast Cancer Research Foundation. Financials and State Disclosures. 2009; http://www.bcrfcure.org/pdf/inv_disclosure_financials09.pdf. Accessed March 10, 2011.
[3] Breast Cancer Research Foundation. Financials and State Disclosures. 2008; http://www.bcrfcure.org/pdf/inv_disclosure_financials08.pdf. Accessed March 10, 2011.
[4] Avon Products Foundation. 2010 Financial Reports. 2010; http://www.avonfoundation.org/financials.html. Accessed March 10, 2011.
[5] Avon Products Foundation. 2010 Avon Foundation Grants; http://www.avonfoundation.org/assets/2010-approved-foundation-grants-website-final-1.pdf. Accessed March 10, 2011.
[6] Susan G. Komen Foundation, Inc. 2009-2010 Final Audited Financial Statements. 2010; http://ww5.komen.org/uploadedFiles/Content/AboutUs/Financial/AUDIT_FINAL_FY2010.pdf. Accessed March 10, 2011.
[7] Susan G. Komen Foundation, Inc. 2008-2009 Final Audited Financial Statements. 2009 http://ww5.komen.org/uploadedFiles/Content_Binaries/2008-2009_AuditedFinancialStatements.pdf. Accessed March 10, 2011.
[8] American Cancer Society. Extramural and Intramural Funding in Selected Priority Areas. 2009; http://www.cancer.org/Research/ResearchProgramsFunding/CurrentlyFundedProjects/extramural-and-intramural-funding-in-selected-priority-areas. Accessed March 10, 2011.

The current breast cancer research portfolio of the American Cancer Society (ACS) is $121.2 million.[10] Overall, ACS spends 39% of its $391 million budget on research programs across all cancers.[11] Between 1992 and 2010, the Avon Breast Cancer Crusade raised $700 million.[12] Based on 2009 figures, approximately 23% of total Avon Breast Cancer Crusade expenditures are for research grants.[13,14] And, since 1993 the Breast Cancer Research Foundation (BCRF) has raised more than $300 million[15] with 88% of its annual budget dedicated to research.[16]

Private Gifts to Academic Institutions

There are private institutions in the United States that conduct breast cancer research. These institutions receive funding from the federal, state and non-profit sources described above. In addition, these institutions receive funding from individuals, family foundations, and local fundraising efforts such as walks, galas, sporting events and the like. One example is Cure Breast Cancer Foundation—a small, family foundation that raises funds through selling keychains and sponsoring golf events. All of their proceeds go to the Memorial Sloan-Kettering Cancer Center in New York, which received over $234 million in cash gifts from individuals and foundations in 2009.[17] The University of Texas MD Anderson Cancer Center has a number of private donor supported research programs as well. For example, the Red and Charline McCombs Institute for the Early Detection and Treatment of Cancer was supported by a gift of $20 million from the Mays family in 2005.[18] Another example is the event, Boston Bakes for Breast Cancer, which has raised $500,000 since 2000 for breast cancer research at Dana-Farber Institute. For both private and academic institutions, many of the benefactors give at levels in the hundreds of thousands. However, there are instances where wealthy individuals give hundreds of millions of dollars towards cancer research. Billionaire David Koch and Nike's Phil Knight each gave $100 million to cancer centers, while retired banker T. Denny Sanford donated $100 million specifically to his namesake, Sanford Health, to establish a national institute for breast cancer. With the diversity of supporters and vast number of donations given every year, it is simply not possible to determine the amount of funding that falls into this category.

Pharmaceutical Industry

There is very little information publicly available on how much pharmaceutical industry money is directed specifically towards breast cancer research (Table 4). Private industries are not required to report expenditure on specific diseases, and reporting is entirely voluntary. The funding that is reported is often vague and collectively referred to as "research and development" (R&D). A National Cancer Policy Board review over ten years ago was the first and it is believed, only review to look at the sources of industry funding for cancer. The study confirmed the lack of a centralized repository for data on industry expenditure for specific diseases.[19] Additionally, the review found that the main reason for private companies' lack of disclosure of funding for specific diseases was due to proprietary concerns.[19]

Table 4. Pharmaceutical Breast Cancer Research

Company	Examples of Research Areas	Examples of Drugs in pipeline/on market	Amount spent on R&D (in billions)	Clinical Trials for Breast Cancer[2,3]
Novartis[1]	HER-2+ , ER+, postmenopausal women	femara afinitor zometa	$8.1 (2010)	125
Sanofi-Aventis[4,5]	Operable node-positive breast cancer, metastatic breast cancer whose tumors over-express the HER-2 gene	taxotere, iniparib	$6.4 (2009)	70
J&J[2,6]	Metastatic breast cancer, lymph node+/node-, early stage breast cancer, combination chemotherapy	nuvoSelect, eRx, doxil	$4.4 (2010)	96
Bristol-Myers Squibb[7,8,9,10]	Metastasis, ER+/PR+	paclitaxel, ixempra, sprycel	$3.6 (2010)	66
Amgen[11,12]	First-line breast cancer, bone metastasis	motesanib, xgeva	$2.9 (2009)	48
Merck[13,14,15]	Vaccine, metastatic breast cancer, early stage	zolinza, caelyx	$11.0 (2010)	32
Pfizer[16,17,18]	Metastatic breast cancer, luminal-B	aromasin, neratinib	$9.4 (2010)	107
Eli Lilly[19,20]	Reduce risk of invasive breast cancer, metastatic cancer, post-menopausal ER+	evista, gemzar	$4.8 (2010)	52

[1] http://www.novartis.com/investors/company-information/fact-sheet.shtml
[2] http://clinicaltrials.gov/ct2/home
[3] Number includes all trials regardless of status
[4] http://www.sanofi-aventis.us/l/us/en/layout.jsp?scat=9B96D94E-A79B-4908-83B0-50B41E34DC00
[5] http://www.sanofi-aventis.us/l/us/en/index.jsp
[6] http://www.jnj.com/connect/healthcare-products/prescription/?flash=true
[7] www.fda.gov/ohrms/dockets/ac/99/slides/3540S2_02_TUCK.ppt
[8] http://ctr.bms.com/OneBmsCtd/InitTrialAction.do?linkname=Cancer&type=pharma&sortby=default
[9] http://packageinserts.bms.com/pi/pi_ixempra.pdf
[10] http://packageinserts.bms.com/pi/pi_sprycel.pdf
[11] http://www.amgen.com/science/pipe.html
[12] http://www.amgen.com/pdfs/Fact_Sheet_Amgen.pdf
[13] http://www.merck.com/investors/financials/form-10-k-2011.pdf
[14] http://www.merck.com/investors/financials/home.html#
[15] http://www.merck.com/product/prescription-products/home.html
[16] http://www.pfizer.com/products/rx/rx_product_aromasin.jsp
[17] http://www.pfizer.com/files/investors/presentations/barclays_capital_031711.pdf
[18] http://www.pfizer.com/files/annualreport/2010/form10k_2010.pdf
[19] http://lilly.com/about/facts/
[20] http://newsroom.lilly.com/ReleaseDetail.cfm?releaseid=470329

Still it is clear that private industry is a powerful stakeholder and has had a significant influence in breast cancer research, specifically the development of new drugs. A 2007 study on the magnitude of private industry involvement in the field found that pharmaceutical involvement in published research has increased significantly: 58% of studies published in 2003 in prestigious journals reported pharmaceutical involvement, compared with 44% ten years earlier.[20] Furthermore, studies that had pharmaceutical involvement were more likely to report positive results (84% vs. 54%). The findings from this paper raised serious concerns about industry influence on research and outcomes.[20]

THE ADVOCATE PERSPECTIVE

Billions have been invested in breast cancer research over the past several decades. But it is not about how much money is raised for breast cancer research; it is about how those dollars are spent. Who oversees the research? Who determines how to allocate those funds? Who makes certain the research is well designed, asks important questions, and is focused on saving lives? NBCC launched unprecedented programs to train advocates to understand the language and concepts of science and to sit at tables where these decisions are made.

We will never learn how to prevent breast cancer or the lethal metastatic spread of the disease without a focus on research and evidence. And yet, despite the significant resources directed at breast cancer research from both public and private sectors for over 40 years, we are not much closer to an understanding. Simply funding breast cancer research has not been enough.

Many aspects of the current system of breast cancer research funding and allocation ensure that only incremental progress is made at best. Incentives are in place that discourage bold, new ideas and encourage safe research with predictable results.

Furthermore, the discoveries that have been made in the laboratory are not rapidly translated to the clinic, if at all. We are told that the lack of focus on producing meaningful interventions for women and men versus pursuing interesting scientific questions is one impediment to progress. As Professor Mitch Dowsett

at the Royal Marsden Hospital and Institute of Cancer Research wrote in a recent publication, "Translational research frequently reflects the immediate scientific interests of the investigators and the specimens available to them as opposed to a specific attempt to address a question that has been identified as having the potential to advance the management of patients."[21]

More than 40 years and billions of dollars have not ended breast cancer. It has, however, created a robust cancer industry that thrives on raising awareness and producing drugs, screening devices, and genetic tests. It has also created an academic system that generates hundreds of thousands of articles about breast cancer. Although there is no doubt individual researchers sincerely want to end breast cancer, the current system is perfectly designed to be cautious and incremental.

"Translational research frequently reflects the immediate scientific interests of the investigators and the specimens available to them as opposed to a specific attempt to address a question that has been identified as having the potential to advance the management of patients."[21]

These obstacles are not scientific challenges but rather organizational and systematic dysfunctions. These are problems with solutions.

We now have the tools, information, resources, and wisdom to create a global strategy to end breast cancer; setting a deadline is the essential first step to starting a revolution in breast cancer. Since the war on cancer was declared in 1971, our understanding of the biology, etiology, and genetics of breast cancer has increased dramatically. New disciplines have shed light on the process of innovation and how organizational systems evolve. And of course, our capacity to gather, synthesize, and analyze information is beyond anything even conceivable 40 years ago.

These developments create opportunities to conduct breast cancer research differently. By leveraging all available resources in a collaborative and rapid research process, it will be possible to cultivate the development of innovative ideas that will ultimately end breast cancer. The goal is not to create better tools to identify breast cancer or better mechanisms for managing it. The goal is to take

what is already known and build upon that knowledge for the sole purpose of ending the disease.

A new approach to breast cancer research is required, including incentives for more than incremental progress, a look at new approaches, collaboration among different disciplines, application of research findings to people, and a focus on the end results in terms of lives saved.

> By leveraging all available resources in a collaborative and rapid research process, it will be possible to cultivate the development of innovative ideas that will ultimately end breast cancer.

2020

2019

2018

2017

2016

2015

2014

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2012

2011

6 | BREAST CANCER ADVOCACY

6 | BREAST CANCER ADVOCACY

In 1978, when first lady Betty Ford announced to the world her breast cancer diagnosis and mastectomy at the age of 56, her openness increased public awareness of breast cancer, prompting women to begin discussing the disease, and helped to remove the stigma associated with it.[1] The 1980s were marked by increasing grassroots efforts to bring breast cancer to the national agenda,[2] accompanied by additional voices of those affected by the disease such as that of another First Lady, Nancy Reagan.[3] The Susan G. Komen Breast Cancer Foundation was founded in 1982, just after widespread mammography had been introduced, and the organization began promoting awareness and early detection as the primary tools for preventing breast cancer deaths.

The 1980s were marked by increasing grassroots efforts to bring breast cancer to the national agenda.[2]

In 1991, a small group of women sought to go beyond awareness and mammography to end the disease. At the time, there was no organized advocacy arm of the movement, and no organization interested in taking on this controversial and challenging role. The National Breast Cancer Coalition (NBCC) grew out of this movement and as a result of NBCC efforts, funding for breast cancer research and care increased dramatically during that decade. Breast cancer was no longer a problem of individual women; it was a public health crisis (see more about the history of NBCC below).

6.1 BREAST CANCER ADVOCACY ORGANIZATIONS

There are hundreds—probably thousands—of non-profit groups in this country that focus on breast cancer. For purposes of this discussion, all of these groups are referred to as advocacy groups. Advocates are involved in a wide range of activities. They can help shape the breast cancer research agenda, the federal drug approval process, and federal and state legislation.[4] They can serve as liaisons between patients and physicians, as well as patients and the scientific community. Some groups provide direct services such as hotlines, support groups, counseling, educational materials, financial aid, and community presentations. Many groups welcome any individual diagnosed with breast cancer, while others such as Nueva Vida, Pink Ribbon Advocacy, and The Triple Negative Breast Cancer Foundation are devoted to patients of specific ethnicities or with particular subtypes of breast cancer.

Breast cancer advocacy efforts are starting to spread across the globe, "capturing more attention and respect from regional policymakers and healthcare providers than anyone thought possible just 15 years ago."[5] International collaborative efforts have facilitated this effort, overcoming social, economic, and cultural circumstances.[6] In Europe, affiliates from 30 countries have joined to form EUROPA DONNA, an advocacy coalition working to increase research funding, raise awareness, and educate women about treatment options. Bangkok, Jamaica, the Philippines, and Singapore are just a few of the many countries which have advocacy and support groups for breast cancer survivors. Current projections show that by 2020, 70% of all breast cancer cases worldwide will be in developing countries.[7] Despite cultural taboos in many developing nations, such as Nigeria and Egypt, the work of grassroots advocates has spurred government and religious officials to speak out on breast cancer issues.[7]

There are hundreds—probably thousands—of non-profit groups in this country that focus on breast cancer.

6.2 HISTORY OF NBCC

NBCC is a grassroots organization dedicated to ending breast cancer through the power of action and advocacy. Founded in 1991 by a small group of women with a mission to end the disease, NBCC has a long history of taking on big issues in breast cancer, challenging business as usual, facing controversy head on and achieving success. NBCC's goals are: 1) to increase federal funding for breast cancer research and collaborate with the scientific community to implement new models of research; 2) to improve all women's access to high-quality health care and breast cancer clinical trials; and 3) to expand the influence of breast cancer advocates in all decisions that affect breast cancer.[8] Today, NBCC's membership includes hundreds of member organizations and tens of thousands of individuals. The member organizations include cancer information, support, and service groups, as well as women's health and provider groups.[8]

Over the years, NBCC has identified challenges, conducted thorough research, collaborated with creative thinkers in a wide range of disciplines, and then developed innovative solutions. For example, in 1991 when NBCC saw that breast cancer research was underfunded, the organization did not simply advocate for "more money." It researched how much was actually needed and could be well spent by the scientific community, and determined that number to be $300 million. Told that it would be impossible to bring about that kind of increase, NBCC did just that through the "$300 Million More" campaign the following year.

NBCC has always known that money alone will not bring an end to breast cancer. Breast cancer advocates bring a unique and powerful perspective to the research process. Educated patient advocates can inspire and aid scientists in formulating novel ideas and hypotheses. As the people directly affected by the disease, advocates can assess a proposal's ethical implications and its potential relevance to their concerns."[9] They can also help improve study design and conduct.[8]

NBCC has always known that money alone will not bring an end to breast cancer. Breast cancer advocates bring a unique and powerful perspective to the research process. Educated patient advocates can inspire and aid scientists in formulating novel ideas and hypotheses.

This concept—advocate involvement in the peer-review, priority setting and scientific research processes—was initially shocking to many in the research community. Despite that skepticism, NBCC went on to conceive and spearhead an unprecedented model of consumer involvement and innovative research in the Department of Defense Breast Cancer Research Program (DOD BCRP).[10]

To prepare advocates for meaningful involvement in the research process, NBCC created Project LEAD®, an intensive science course covering the basics of cancer biology, genetics, epidemiology, research design, and advocacy. Now in its 16th year, Project LEAD® has prepared more than 1,500 graduates to engage in a wide range of local and national forums where breast cancer decisions are made, bringing an educated consumer perspective and critical analysis skills to the table. NBCC offers several different Project LEAD® training courses each year. Each course focuses on preparing advocates to engage and effectively influence breast cancer decision-making within different types of forums.

Since 1991, NBCC has developed and mobilized a powerful, effective, and diverse network of trained grassroots activists, giving breast cancer a meaningful voice in Washington, DC and state capitals, in laboratories and health care institutions. Breast cancer activism is now seen as a model that other disease groups seek to emulate. It is certainly true that the concerns of women and their families living with breast cancer have been increasingly heard by policy makers and researchers.

NBCC knows that clinical trials are essential to finding a way to end breast cancer. But it is not simply more clinical trials, but better trials, that are needed. The NBCC Clinical Trials Initiative was launched to make certain that the right research gets done correctly and quickly; that trained breast cancer survivors are included in trial design and accrual; and that policies encourage access to trials. NBCC collaborates with the scientific community to improve the quality and efficiency of trials. NBCC partnered with investigators and a biotechnology company to design and implement a Phase III clinical trial of the now well-known drug trastuzumab (Herceptin®).

NBCC has also employed its strategies in the crucial area of access to health care. An NBCC advocate saw the pain and injustice of women in a federal health program receiving a diagnosis of breast cancer, but then no treatment. NBCC created a strategy for solving that problem, which involved expanding a federal program. After many years of relentless NBCC grassroots advocacy, the Breast and Cervical Cancer Treatment Act was enacted.[11] It provides enhanced matching Medicaid funds to states so low-income women diagnosed with breast or cervical cancer through the federal screening program get coverage for treatment, and not just screening.

Since 1991, NBCC has developed and mobilized a powerful, effective, and diverse network of trained grassroots activists, giving breast cancer a meaningful voice in Washington, DC and state capitals, in laboratories and health care institutions. Breast cancer activism is now seen as a model that other disease groups seek to emulate. It is certainly true that the concerns of women and their families living with breast cancer have been increasingly heard by policy makers and researchers.

6.3 BREAST CANCER & CAUSE MARKETING

The line between business and breast cancer advocacy became blurred over the years, beginning with the establishment of National Breast Cancer Awareness Month (NBCAM) by the American Academy of Family Physicians and the pharmaceutical company, AstraZeneca Healthcare Foundation and CancerCare, Inc, in 1985.[11] Criticism of NBCAM began from the very beginning because of a pharmaceutical company's lead sponsorship of the annual event. The original goal of NBCAM was to promote mammography as the best weapon to fight breast cancer.

In 1992, the pink ribbon was linked to NBCAM and quickly became an international representation of breast cancer awareness.[12] Companies discovered that adding a pink ribbon to a product would increase sales, and breast cancer became a model for all other cause marketing. From a 2008 report, "As the term 'cause-related marketing' reaches its 25th anniversary and a sea of pink ribbons washes over the US this month, a

new consumer behavior study confirms that cause-related marketing can exponentially increase sales, in one case as much as 74%, resulting in millions of dollars in potential revenue for brands."[13] However, what the pink ribbon on a product means and how it contributes to the "cause" varies wildly. Unfortunately the pinking of America has had little impact on the morbidity or mortality of the disease.

In 2011, thousands of companies are expected to participate in NBCAM to market products and raise funds for various breast cancer groups.

THE ADVOCATE PERSPECTIVE

Almost everyone has been touched by breast cancer in some way—if not personally or through a family member, then through a teacher, neighbor, or work colleague. Millions of individuals in this country alone have lent their support to finding a cure by participating in a walk, giving a donation, or wearing a pink ribbon. But after decades of this support, we are frustrated to still hear of the hundreds of thousands of women diagnosed with the disease each year, and to hear of mothers, grandmothers, young women and even men dying from the disease and leaving their families to mourn.

We want to know—after so many decades of attention paid to this disease—why has there not been more progress? Looking at systems of resource allocation and research are key, but what about breast cancer organizations and advocacy? Has progress been hindered or promoted by these groups over the years?

To advocate means "to speak, plead, or argue in favor of," according to the American Heritage dictionary. Hundreds of breast cancer advocacy organizations exist in our country, and thousands of breast cancer advocates are finding opportunities within health care offices, government, academic institutions, and private organizations to speak where decisions are being made regarding breast cancer. It is important to examine what advocates are arguing for. A spouse, a friend, or a patient advocate who attends doctor visits with a newly diagnosed woman provides a valuable service when helping to advocate for the best breast cancer care and treatment possible. This individual advocacy is extremely important. But what about those who advocate on a larger scale, who serve as representatives of the population of breast cancer patients to government and institutions? Are they pleading for the

changes that will bring an end to the disease, or are they comfortable with the status quo? Are they speaking in favor of what they personally believe in, what industries may be encouraging, or what the evidence tells us? Are they part of collaborations to simply provide a "face" of breast cancer to the scientists, or are they educated and trained and there to speak in favor of what is necessary to end this disease?

> We want to know—after so many decades of attention paid to this disease—why has there not been more progress?

NBCC continues to educate advocates in the science of breast cancer and to train them to change the status quo, focusing on access to quality care and research that will answer the key questions necessary to end the disease. It is crucial that advocates who have the opportunity to influence decisions are not simply a "face" of breast cancer, but speak up and argue for what we all want, an end to breast cancer by January 1, 2020.

What if advocates fail at achieving the deadline? We already have. Hundreds of thousands of lost lives show us we couldn't possibly do worse. The question we ought to be asking ourselves is, "How do we succeed, and what must we do differently in order to succeed?"

7 | PROGRESS TOWARD BREAST CANCER DEADLINE 2020®

2011 2012 2013 2014 2015 2016 2017 2018 2019 2020

7 | PROGRESS TOWARD BREAST CANCER DEADLINE 2020®

Despite the achievements in increasing breast cancer research funds, access to care, and the influence of breast cancer advocates, NBCC advocates have felt increasing frustration at the lack of progress in preventing morbidity and mortality from the disease. As this report has outlined, significant resources have been dedicated to breast cancer research, access to care has expanded, and more has been learned about the biology of the disease. But we have not made significant progress in decreasing the morbidity and mortality from the disease.

....significant resources have been dedicated to breast cancer research, access to care has expanded, and more has been learned about the biology of the disease. But we have not made significant progress in decreasing the morbidity and mortality from the disease.

There are many barriers to progress that must be overcome, but the largest barrier may be the lack of focus on the end result. NBCC took a bold step in September 2010 to refocus resources and efforts and set a deadline for ending the disease—January 1, 2020. In the eight months since **Breast Cancer Deadline 2020®** was declared, NBCC and its advocates have begun to catalyze a shift in focus on several fronts.

7.1 THE STRATEGY

The strategy involves a paradigm shift in the breast cancer world—in government, the media, research, and advocacy—to refocus resources and efforts to the areas that could have the most significant impact in eradicating the disease. The plan is to disrupt the status quo on all fronts with the sole purpose of focusing attention and resources to achieve **Breast Cancer Deadline 2020®**. Scientists, regulators, industry representatives, legislators, health care providers, advocates, and all who care about ending breast cancer have been and will continue to be involved in the plan. NBCC advocates believe that ending the disease requires focusing efforts on two key areas: learning the causes of and how to prevent metastasis, and learning how to prevent development of primary disease. Achieving this paradigm shift involves efforts directed at public policy, the scientific and health care communities, and the media.

7.2 PUBLIC POLICY—BREAST CANCER DEADLINE 2020® LEGISLATION

In order to achieve the goal of **Breast Cancer Deadline 2020®**, NBCC knows that it must change the conversation about breast cancer wherever it is happening, including in Congress and the Administration. In January 2011, NBCC convened a small group of individuals who think innovatively about how governments should work and what role they play in research and health care. The outcome of this public policy roundtable, the Accelerating the End of Breast Cancer Act, will promote the goals of **Breast Cancer Deadline 2020®**. The Act will support the role that the federal government must play in this effort.

7.3 SCIENTIFIC SUMMITS & WORKSHOPS

To focus and aggregate scientific efforts on meeting **Breast Cancer Deadline 2020®**, NBCC will host two strategic Summits in 2011—one on the topic of the causes and prevention of metastasis and one on the topic of primary

prevention—bringing together 30-45 representatives from academia, industry, government, regulators and advocates. Collaborative summit planning committees were formed in early 2011 and have been working to identify and interview key leaders in science, government, industry, and advocacy. The information is being gathered, synthesized and analyzed to shape the format and discussions for the Summits.

Metastasis Summit

Eradicating breast cancer will require that we understand how to prevent metastatic spreading of the disease. To bring resources to this understudied area, NBCC is planning a Summit, to be held in August 2011. The Summit will bring together stakeholders to develop a strategic plan to answer the question:

> ....what must be done to determine, by 2020, the cause of and how to prevent breast cancer metastasis and save women's lives?

what must be done to determine, by 2020, the cause of and how to prevent breast cancer metastasis and save women's lives? The goal of the Summit will be to identify the key questions to carry into catalytic workshops in 2012 and beyond, in order to move research and translate it to the clinic as quickly as possible.

Primary Prevention Summit

Though preventing breast cancer metastasis is crucial to decreasing the mortality from breast cancer, the ultimate goal is to prevent breast cancer development all together, to avoid not only the mortality from the disease, but also the mortality and morbidity from treatments for the disease.

Though the increasing focus on the development of targeted treatments may lead to more efficacious and less toxic treatments, we will not make more than incremental progress over the next ten years unless we shift some resources to understanding the causes of breast cancer and learning how to prevent development of the disease. To bring resources to this understudied area, NBCC is planning a Prevention Summit, to be held in October 2011. This Summit will bring together stakeholders to develop a strategic plan to answer the question: what must be done to determine, by 2020, how to prevent breast cancer and save women's lives? The goal of the Prevention Summit will be to identify the key questions to carry into catalytic workshops in 2012 and beyond, in order to move research and translate it to the clinic as quickly as possible.

Though the increasing focus on the development of targeted treatments may lead to more efficacious and less toxic treatments, we will not make more than incremental progress over the next ten years unless we shift some resources to understanding the causes of breast cancer and learning how to prevent development of the disease.

Catalytic Workshops

NBCC has developed an innovative, advocate-led model to catalyze research in an area that has promise for contributing to the end of breast cancer, which will be adapted to further the key issues identified at the Summits. The model is currently being piloted with the Artemis Project®.

Artemis Project®

NBCC's Artemis Project® brings together a collaborative group of advocates and scientists to take a strategic, systematic approach to the development of a breast cancer preventive vaccine within five years. Current systems of research and resource allocation do not allow for the development of a preventive vaccine as rapidly as is possible given our current state of knowledge. Therefore, NBCC has created an innovative, mission-driven model which ensures appropriate focus on the end result. The Artemis Project® is not simply facilitating work in progress, but actually creating the infrastructure for collaboration around development of the vaccine. This will be the model for future catalytic work that arises out of the Summit process—creating the infrastructure and collaboration around key research questions that do not currently exist. Advocates are the conveners and leaders of the project, ensuring focus on the end results.

NBCC has created an innovative, mission-driven model which ensures appropriate focus on the end result. The Artemis Project® is not simply facilitating work in progress, but actually creating the infrastructure for collaboration around development of the vaccine.

The Artemis Project®—Progress

In March 2010, NBCC convened a meeting to determine whether a strategic approach to the development of a preventive breast cancer vaccine is feasible given the state of knowledge. The 17 participants reflected a broad range of expertise, including breast cancer advocacy, epidemiology, immunology, clinical cancer care, biotechnology product development, and the federal regulatory drug approval process. The group gathered for two days of roundtable discussions in Calistoga, California. A few themes emerged:

- The field of immunology has progressed rapidly in the last ten years, and pursuing development of a breast cancer preventive vaccine is now feasible.
- No scientific or technical obstacles exist that would make the creation of a preventive vaccine impossible.
- The current research environment is not conducive for the collaborative, focused efforts that are necessary for the development of a vaccine.
- There is no overall framework or infrastructure for preventive vaccine research activities—no oversight, conceptual development, prioritization, or responsibility for evaluation.
- The challenges are significant: identifying the most promising antigens, determining the target population, designing quality clinical trials, and navigating uncharted regulatory territory.
- Strong and focused leadership to oversee and coordinate the research is needed to accomplish the development of a preventive vaccine.

In August 2010, NBCC brought together a smaller group of individuals to identify the key issues that must be addressed to move forward with the project. The group identified four key issues:

1. Identification of Targets of Prevention through a Genomic Approach to Prioritizing Preventive Vaccine Candidates
2. Immune System—Variations in Breast Cancer
3. Development Plan for Efficacy
4. Development Plan for Safety

The four areas will be addressed simultaneously, with interaction and conversation among teams. Investigators and advocates are working together within and among the teams, responding to issues as they arise. A steering committee oversees the process, and a group of advisors contributes expertise. NBCC is facilitating interaction within and across teams by creating an infrastructure for communication and collaboration.

Artemis Project®: Annual Meetings

The Artemis Project® Steering Committee, Advisory Committee, Team Leaders and working group members gather each spring in Calistoga, California for annual meetings to assess progress, and to adjust teams, projects, and focus as necessary. At the first annual meeting in 2011, initial outlines were developed and reviewed. In an iterative process, teams adjusted plans in response to critiques from the entire group of scientists and advocates. This process will be followed at each annual meeting as projects are adjusted and refocused as necessary.

7.4 THE DEADLINE: IS IT IMPOSSIBLE?

It is. The same way curing polio was impossible. The same way a 4-minute mile was impossible. The same way a man on the moon in nine years was impossible. They are called impossible dreams. They are the most difficult challenges known to humanity. That's why most people stay away from them. And that is exactly why we will not. Our love for our daughters demands that we seek and engage the most difficult battle available to us. This will be daunting, grueling, and intimidating. It will be difficult on a scale no one can possibly imagine. But it is time we ended our addiction to easy. When President Kennedy launched the Apollo program, he said that, "We seek to go to the moon and do other things. Not because they are easy, but because they are hard…because that goal will measure the best of our abilities." We have set this deadline to measure the best of ours.

It will be difficult on a scale no one can possibly imagine. But it is time we ended our addiction to easy.

There's a difference between what appears impossible and what actually is.

"More of the same" will not be effective; additional funding and time can only be used fruitfully if efforts are part of a larger strategic plan focused exclusively on the one goal of eradicating breast cancer.

This effort will require a critical look at research and health care priorities, financial incentives, funding mechanisms and advocacy efforts. It will require a concentrated strategy to expand quality, evidence-based care. It must embrace unprecedented coordination, information sharing and accountability. It will require individuals and institutions to cooperate in new ways and to an extent never before considered.

It will require individuals and institutions to cooperate in new ways and to an extent never before considered. Vision, urgency, unwavering focus and creative collaboration under true leadership will be the key ingredients for success.

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A collaborative deadline-driven mission approach to breast cancer has never been attempted. But examples of success in other fields suggest that often it is the lack of vision, willpower, accountability and leadership—not level of knowledge or the science itself—that stymies progress.

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8 | CONCLUSION

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The current system of breast cancer research and advocacy, and existing public policy, have not led to significant progress in ending breast cancer or in preventing deaths. And yet it is not for a lack of attention or resources that we have failed to make progress. Billions of dollars in funding have been allocated to research in both the public and private sectors, and hundreds of advocacy organizations have brought attention to the disease. But myths and misunderstandings about breast cancer are widespread and promoted in the media and through industry marketing every day. Feel-good messages and beliefs abound.

The reality of the disease is much harder to accept. The reality is that the emphasis in our country on early detection of breast cancer through mammography and breast self-examinations has led to significant increases in the incidence of DCIS, significant overdiagnoses and overtreatment, without a compensating drop in breast cancer mortality. The rate of diagnoses of breast cancer that has metastasized has remained stable since 1975. The slight drop in breast cancer mortality after the 1990s may be in part a result of changes in women's use of hormone replacement therapy and not only improvements in treatment for breast cancer. The stark reality is that 39,840 women and 390 men continue to die from breast cancer each year in this country alone. And the scientific and health care communities continue to focus on the issues that will lead to no more than incremental progress for these women and men in the future.

What we do know is that more of the same will not produce different results. NBCC advocates are leading a new approach—a new strategy—to change the conversation and to get answers to the key questions in breast cancer that must be answered to ultimately end the disease by January 1, 2020. Resources must be redirected to understanding how to prevent the development of breast cancer and understanding the causes and prevention of breast cancer metastasis in order to save women's lives. By calling for an end to breast cancer by 2020, NBCC is calling for a change in course. We owe it to all of our daughters and sons, and grandaughters and grandsons, to try something new. Indeed, our ultimate goal is to close the doors of NBCC by the end of the decade because the mission to end breast cancer has been accomplished.

> It is time, once again, for us to launch a revolution in how we think about breast cancer and how to eradicate the disease.

Breast Cancer Deadline 2020® is a call to all of us who care about breast cancer to push toward the goal. We are calling for a global campaign to end breast cancer by 2020. This bold and radical goal is rooted in our sense of urgency, tenacity, and focus. It is time, once again, for us to launch a revolution in how we think about breast cancer and how to eradicate the disease. **Breast Cancer Deadline 2020®**. The end of breast cancer by January 1, 2020. It is time.

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