Treatment and Outcomes for High-risk and Metastatic Breast Cancer in California: An Inquiry into Disparities and Research Needs

Musa Mayer, M.S., M.F.A.
This paper will discuss issues related to the incidence, mortality, and length of survival of California women with high-risk (locally advanced) and metastatic breast cancer, with regard to access to and utilization of treatment and the impact on outcomes across different racial/ethnic, socio-economic, and age groups.

Musa Mayer, M.S., M.F.A.
Background

In the state of California, over four thousand people will die of breast cancer this year. Some of those who die will have faced locally advanced or metastatic disease when their breast cancer was first diagnosed, while others will have experienced a metastatic recurrence from a few months to many years after their initial diagnosis with earlier stages of breast cancer. Those who die of the disease and their families will have had to deal with the treatments and symptoms of advanced breast cancer in the months and years prior to their deaths. Clearly, the human toll taken by breast cancer in California is immense.

At the same time, most public attention devoted to breast cancer is firmly focused on issues related to the screening, early detection, and treatment of small primary tumors that are still at a curable stage. While commendable, this “pink” focus is limited, for two important reasons. First, not all breast cancers are curable, even if caught early; the paradigm of early detection is clearly limited by biological realities. Second, the needs exist of the many thousands of women already living with high-risk and metastatic breast cancer in California today, and will continue to make demands on us tomorrow. To help these women and men, we must understand more clearly what the barriers and inequities to good breast cancer care are.

In the years that I have been advocating for patients and families dealing with advanced breast cancer, I've observed a strong emphasis on the screening and treatment of early-stage breast cancer. Traveling and consulting around the country, it’s been clear to me that few support organizations have been able to adequately address the needs of patients with advanced breast cancer, despite their obvious concern and willingness to do so. A survey conducted by the National Alliance of Breast Cancer Organizations in 2001 found fewer than 20 support groups across the United States to meet the specific needs of metastatic breast cancer patients, from among the nearly one thousand groups then in existence.1 Most of the breast cancer survivors who run and staff breast cancer organizations are still themselves personally at risk for recurrence. Being long-time members of this “sisterhood,” they have lost many friends and may find this aspect of breast cancer depressing and emotionally threatening.

It is my conviction that these feelings within the breast cancer community and in the public at large must be confronted and overcome if we are to move effectively into researching these most difficult areas of breast cancer. This paper will try to take a positive step in that direction, by focusing on issues that are more difficult to talk about: the needs and experiences of women diagnosed at later stages of the disease, who tend to be disproportionately poor and black.

First, of course, we must define the dimensions and specifics of this population. Who are they? Because length of survival is so variable, no one really knows how many people are living today with locally advanced and metastatic breast cancer. Figures relating to incidence and mortality give us snapshots when the disease is diagnosed and when a patient dies of breast cancer. Cancer registry data offer information about initial treatments. But overall we have neither insight into the actual numbers of people with advanced breast cancer, nor their experiences with access to and utilization of the health care system regarding their treatment.

Between one half and two thirds of American women diagnosed at Stage II and III, an annual figure estimated at 45,000–50,000, will develop metastatic disease within five years of diagnosis. In combination with the estimated 10,000–15,000 women who present with Stage IV disease each year, and the 25 percent whose disease recurs after five years, this means that every year between 73,000 and 86,000 American women discover that they have metastatic breast cancer.2 Once breast cancer metastasizes, it is generally considered incurable. However, it is very often treatable. Average survival following a diagnosis with metastatic disease is still generally estimated to be from two to three and a half years. According to
Dr. Susan Love, 25–35 percent of metastatic patients live at least five years, and about 10 percent live ten years or more.³

While there exists no completely accurate count of the numbers of women living with advanced breast cancer today in the United States, the SEER database documents that 24 years after their diagnoses, nearly half of all women diagnosed with invasive breast cancer during the late 1970s have died of their disease.⁴ While earlier diagnosis and treatment have almost certainly improved on the above-quoted, long-term 48.5 percent mortality figure in recent years, it is clear that a large population of several hundred thousand women at any given time are facing the challenges of metastatic disease. Many more at high risk of recurrence are living daily with the fear their cancer will return.

The general public may have misconceptions about how old breast cancer patients really are. Since it seems that the majority of public figures and advocates who are breast cancer survivors are women in their 40s and 50s, many people are surprised to hear that the median age in new breast cancer diagnoses in the United States is 63, meaning that half of all patients are older. So the population of breast cancer patients is in general older than its public presence would indicate.

In the ever more commercialized flurry of breast cancer charitable galas, sales promotions, walks and runs that saturate the media each October, elderly women, minority women, and women with advanced breast cancer remain largely invisible. For many years, women with high-risk and metastatic breast cancer have complained bitterly that their experiences are not represented in the media or by advocates.⁵

By the same token, the public doesn’t know much about the population of very young breast cancer patients, those women in their 20s and 30s so often diagnosed with aggressive cancers. We do know that this population is not evenly distributed. While only 25 percent of white women are diagnosed with breast cancer prior to the age of 50, fully one-third of female black breast cancer patients are aged less than 50. The age-specific breast cancer incidence for black women under 35 is twice what it is for white women, and the mortality rate is three times higher.⁶

Since only 3 percent of the overwhelmingly white, under 65, breast cancer patient population enrolls in clinical trials, what we know from clinical studies also reflects disparities in race/ethnicity and in age, rather than shedding light on them. Likewise, there are disparities when it comes to access to care, utilization of treatment, and outcomes for people of different ages, races/ethnicities, and socioeconomic status, to be discussed in greater detail later.

Despite many studies on these disparities, much still remains to be learned. In part this is a function of how data are gathered and recorded in not only the California Cancer Registry but also in all cancer registries, where the data gathered are almost entirely bracketed by the beginning and end of the cancer experience, focusing as they do on diagnosis, initial treatment, and mortality. An argument can be made that these data are far more descriptive for the women with early stage breast cancer than they are for women with high-risk and metastatic breast cancer, who continue to interact with the health care system for a period of many years.
High-Risk and Metastatic Breast Cancer: The Basics

There are different ways of describing the diagnostic criteria for high-risk and metastatic breast cancer. The widely used American Joint Committee on Cancer (AJCC) staging system is the accepted method for grouping patients with similar prognoses at first diagnosis. This “TNM” system (for tumor, nodes, metastases) takes into account the tumor size, the status of lymph nodes, and the presence of distant metastasis. Combined with menopausal status, estrogen-receptor (ER) status, tumor grade, and other pathology variables, this classification helps the physician and patient in selecting appropriate treatment. In general, those diagnosed at Stage I with small, localized breast cancers, are least likely to suffer a metastatic recurrence. Those diagnosed at Stage II, with larger tumors and/or invasion of the axillary lymph nodes are at higher risk of recurrence.

More than half of cancers diagnosed at Stage I and II do not recur, but this of course depends upon histology of the tumor as well as the adjuvant treatments selected. A recent text on breast cancer estimates the relapse rate for patients diagnosed with Stage I breast cancer to be 20–30 percent, for Stage II 40–60 percent, and for Stage III, greater than 90 percent. About 75 percent of recurrences will occur within five years of diagnosis; however, more recent figures indicate that widespread adjuvant therapy has pushed back the time of relapse for those who do recur.

With adjuvant tamoxifen, 82 percent of 60-year-old women with estrogen-receptor positive, node negative, grade 2 invasive ductal carcinoma of a centimeter or less will be disease-free at 10 years. With adjuvant Cytoxan and Adriamycin, 71 percent of 45-year-old women with ER-negative grade 3 tumors will be disease free in 10 years, but if one to three lymph nodes are additionally involved, the 10 year disease-free survival drops to 57 percent. As many as 10–20 percent of tumors treated with lumpectomy and radiation will recur in the breast, and of these, one-tenth to one-fifth may be harbingers of distant metastatic disease. The figures are similar for regional recurrence following mastectomy.

Breast cancer that has spread significantly beyond the breast at first diagnosis is described as either “locally advanced” (Stage IIIA or B) or as “distant” metastatic disease (Stage IV). Those diagnosed at Stage III have some combination of the following characteristics: tumors larger than 5 cm, tumors of any size that have grown extensions to the chest wall or the skin, tumors of any size that have spread to axillary nodes that are fixed to each other or to surrounding tissue, or that has spread to internal mammary nodes.

A relatively rare subtype of breast cancer that is unusually aggressive and fast growing, inflammatory breast cancer, is also classified as Stage IIIB. Although it may not have spread beyond the breast, inflammatory breast cancer is more likely to recur than other tumor types. A recent analysis found the 5- and 10-year overall survival rate for inflammatory breast cancer to be 56 percent and 35 percent. In a study of 178 patients with inflammatory breast cancer, disease-free survival was 28 percent at 15 years with combined-modality treatment.

While it has not risen to the level of evidence required for a prognostic indicator, research suggests that tumors that overexpress the growth-promoting protein made by the HER2 gene, present in 25–30 percent of invasive breast cancer tumors, tend to behave aggressively and be more likely to recur.

In general, prognosis can be said to worsen as the cancer more extensively invades surrounding tissue and lymph nodes, although it may not always be clear when the cancer has spread through direct extension into the tissue, or through the lymphatic or blood stream—factors that also affect prognosis.

Treatments for High-Risk and Metastatic Breast Cancer

In recent years, more aggressive treatments for locally advanced breast cancer have come into broad use and have shown significant benefit for some Stage III patients. Neo-adjuvant chemotherapy, where combination chemotherapy is administered prior to surgery, is often followed, in cases of extensive axillary node involvement, with a course of post-mastectomy radiation to the chest wall and underarm area, sometimes extending to the upper chest. More frequent and higher doses of chemotherapy drugs have been made tolerable by several new drugs used in supportive care, including marrow-stimulating drugs like G-CSF (filgrastim) and erythropoietin. In clinical trials, these enhanced treatments have shown somewhat better progression-free survival, and may affect long-term survival as well. This is in part made possible by radiation techniques that do a
better job of sparing the heart, large vessels, and lungs, although longer-term damage cannot be ruled out.

For the woman with locally advanced breast cancer, the best chance for survival or long-term remission will usually lie in immediate, aggressive chemotherapy, followed by surgery and radiation, and then more chemotherapy. For her, time is of the essence, since delays in treatment can lead to higher rates of recurrence. If she is to complete the rigorous chemotherapy regimen that has been recommended, she will need good supportive care, especially the latest in expensive growth-factor support and anti-nausea medications. After her treatment has been completed, she will need to be seen by her oncologist on a regular basis, and symptoms that might herald a recurrence evaluated.

It should be emphasized in this introductory section that such complex, intensive treatments are costly, resource-intensive, and certainly require motivated patients with good support networks.

When breast cancer spreads through the bloodstream to other parts of the body, this is described as “distant metastasis.” Nearly any tissue in the body may be affected, but the bones, liver, lungs, soft tissue (including regional lymph nodes), and brain are the most common sites for breast cancer metastasis. Lobular breast cancer, which has a different pattern of recurrence, with an affinity to spread to the lining of the viscera, can be extremely difficult to detect.

At Stage IV, the disease is no longer considered curable, with the exception of the estimated 1–3 percent of patients who, for unknown reasons, experience long-term survival with stable disease or complete remission following treatment. However, even when the disease does continue to spread, metastatic breast cancer can often be treated as a chronic disease for a number of years. Until very recently, estimated mean survival time for women diagnosed at Stage IV or with distant metastatic recurrence was about one to three years, but with improvements in care, including a number of new non-cross resistant treatment alternatives that have been approved by the FDA since the mid-1990s, survival time with metastatic disease appears to have increased significantly.

A recent study from M.D. Anderson Cancer Center that compared length of survival of metastatic breast cancer patients treated at their institution in five-year increments, found that median survival had doubled to 51 months (range 33–69 months) in 1995–2000 from a median survival of 27 months (range 21–33 months) only five years earlier, 1990–1994. Five years after their diagnosis with metastatic disease, 40 percent of these patients were still alive, as compared with 29 percent during 1990–1994. At the initiation of their study, during the period 1974–79, only 10 percent of patients were still alive at five years and the median survival was only 15 months (range 11–19 months).

The woman whose breast cancer has metastasized or who has been diagnosed initially at Stage IV must live with the reality that her breast cancer can no longer be cured, and that the disease is very likely to take her life. Consequently, the length of the remaining time she has to live, and the quality of that time, become issues of paramount concern. For her, access to the best care can make a significant difference, both in length of survival and in quality of life. With luck, excellent care, family support, personal motivation, and a skillful oncologist, her disease is likely to respond to a number of lines of treatment that can serve to extend her life—many of which may be quite costly. She may join a clinical trial, or try to get compassionate access to experimental drugs prior to their approval through single-patient INDs or expanded access programs.

Whatever path she chooses, she will be in treatment for the rest of her life, and she will require close follow-up, which will include costly scans and other tests. As her disease progresses, she will need pain-management and control of her other symptoms, and she is likely to undergo several hospitalizations to deal with particular crises in the course of the illness. Eventually, she will need hospice care.

It should be emphasized that costly high-quality healthcare resources that can successfully and optimally prolong life in metastatic breast cancer patients are not available to all patients. When there are inequities in treatment access and quality of care, improvements in breast cancer treatments may increase differences in outcomes for different groups. When it comes to advanced and metastatic breast cancer, death rates may not tell the entire story, which should also include length of survival from diagnosis and quality of life during the time.
Typically, newly approved cancer drugs remain on patent for a number of years, providing exclusive sales rights at non-competitive rates for the pharmaceutical company that developed and is marketing the drug. This ensures that the cost of receiving the latest treatments will remain high, not only for patients, but for health management companies, insurers, the Medicare system, and especially for the ever-enlarging percentage of the population who remain uninsured and under-insured, for whom the innovations capable of prolonging life may be completely out of reach. While most pharmaceutical companies do have programs that partially or completely fund some treatment for people who can’t afford it, the potential need for assistance greatly outstrips these resources. Thus, improvements in care during the last decade both in the adjuvant care of high-risk patients and in metastatic treatment to prolong life and improve quality of life for Stage IV and recurrent patients may not reach all those in need.

The Impact of High-risk and Metastatic Breast Cancer

Based on the National Cancer Institute’s SEER data, the American Cancer Society has estimated that in the year 2003, over 211,300 cases of female invasive breast cancer will be newly diagnosed in the United States, and 39,800 women will die of the disease. About 1,300 new cases of breast cancer in men will be diagnosed this year, and 400 will die. While breast cancer is the most common cancer diagnosed in women, it is the second leading cause of cancer death, outstripped only by lung cancer, a number that is now falling in California. A full 15 percent of all cancer deaths in women are from breast cancer.14

Accounting for 10 percent or more of the total cases in the United States, the State of California is home to the largest number of new diagnoses and deaths from breast cancer of any state. In California, 23,711 women were diagnosed with invasive breast cancer and 4,152 women died each year of the disease during the period 1995–1999.15

How can we measure this impact, and put it in the proper context? In early-stage breast cancer, it may be meaningful to consider the impact of surgical interventions and radiation, the other side-effects and costs of adjuvant care, and post-treatment issues, including the fear of possible recurrence. When discussing high-risk and metastatic breast cancer, the more appropriate assessment of impact is clearly the loss of life.

But the actual death rates tell only a part of the story. It is important to note that loss of life is only the final loss to breast cancer patients, their families and their communities. Each breast cancer death is inevitably preceded by years of difficult, painful, and costly treatment, by loss of the ability to fulfill roles within the family and community, and by loss of income and productivity. The sum of all these losses is incalculable.

Stage at Diagnosis

Fortunately, the majority of women with invasive breast cancer are diagnosed at earlier stages and will survive their disease to die of other causes. The most recent data available in the SEER registry indicates that for the period 1992–1999, 63 percent of all invasive breast cancer was localized at diagnosis, meaning that it had not spread beyond the breast, corresponding to Stage I and some Stage IIA patients with larger tumors but no axillary node involvement. Twenty-nine percent were diagnosed with regional disease, a wide spectrum of risk, ranging from a single node with cancer cells to multiple nodes that have grown through the capsule into surrounding tissue. Finally 6 percent of breast cancer is diagnosed as “distant” or Stage IV. In the SEER data, 3 percent of breast cancer is listed as “unstaged.”

It should be noted that these classifications in the SEER Summary Stage system do not take into account tumor size or other pathological features as does the American Joint Committee on Cancer (AJCC) TNM (tumor, node, metastasis) classification used by most physicians and hospitals.16

So the SEER category of “regional” encompasses at least two diagnostic categories in the AJCC TNM staging system, each of which carries a very different prognosis or risk for recurrence. For example, one recent report, using national data from 1,735 hospitals, reported Stage II five-year observed survival at 74.5 percent, while Stage III five-year observed survival was only 48.5 percent.17

These figures also vary significantly when broken down by race and age, as demonstrated by Figures 1 and 2 below. In the United States as a whole, white women are diagnosed at earlier stages, regardless of age. The disparity of later stage disease in black women can be
more readily grasped visually in these two bar charts. Figure 1 illustrates stage at diagnosis for women under the age of 50, while Figure 2 illustrates stage at diagnosis for women over the age of 50. Worthy of note is that regardless of race, women under 50 are diagnosed at a later stage than the over 50 group. This may be a function of earlier detection through mammographic screening in the post-menopausal population. Younger women prior to the age of menopause often have dense, glandular breast tissue that is more difficult to visualize on mammograms. It’s also important to realize that in younger women, tumor biology may be of a more aggressive and hormonally-insensitive type, a factor that may play a role in higher recurrence rates and mortality in young black women.

**Figure 1. Stage at Diagnosis for Women under age 50 (SEER data)**

**Figure 2. Stage at Diagnosis for Women over 50 (SEER data)**
Five-Year Relative Survival

The SEER data further state that five-year relative survival (eliminating other causes of death) for the nine cancer registries including San Francisco-Oakland followed to the year 2000 is as follows: all stages is 86.6 percent, 97.7 percent for localized, 78.7 percent for regional, 23.3 percent for distant, and 56 percent for unstaged. The low five-year relative survival rate for the unstaged cases may suggest that unstaged cases include many of those that are diagnosed late, are poorly compliant with treatment, or receive inferior care, of which lack of staging information may be a component. Further research on this group would be of interest.

Five-year relative survival as a meaningful surrogate or proxy for survival has been widely questioned by breast cancer advocates and others. This is in part because of the slow-growing nature of the disease in general, as well as the delays in recurrences that have become more common now than in the era before widespread adjuvant treatment. For women with regional and distant metastatic disease, however, because they are at higher risk for recurrence and have more aggressive disease, five-year survival is worth discussing.

The five-year relative survival figures vary significantly when broken down by race and age. According to the SEER data, in the United States as a whole, white female breast cancer patients have better five-year survival from breast cancer than black patients.

Five-year survival from breast cancer is lowest for black women under the age of fifty, and highest for white women over the age of fifty. The higher rate of mortality in black women is often ascribed to diagnosis at a later stage, but this table demonstrates that even when women are classified by stage and age alone, a broad disparity exists in survival between white women and black women.

Expressed in graphic terms on the bar chart in Figure 3, below, the disparities between younger black and white women become immediately apparent.

**Figure 3. Five-year Relative Survival by Stage and Race, Women < 50 (US SEER data)**

The meaningfulness of the five-year relative survival statistic as a predictor of ultimate survival is directly related to the stage of the disease at diagnosis. As mentioned above, for early-stage disease, you would *not* expect disparities in treatment or inherent differences between groups to be fully evident at five years, because women in this group are less likely to recur. The early stage of their cancers may reflect inherently indolent disease that would never spread or spread only very slowly, regardless of early detection or treatment. Some women in this five-year relative survival group may be living with recurrence. Others, perhaps as many as 10–30 percent, will eventually have recurrences that have not yet manifested themselves.

So, it is important to note in the bar graph above that the point spread in five-year survival in early-stage localized disease is a minimal 3.1 percent between black and white breast cancer patients under 50. In regional disease,
however, the disparity expands to 14.5 percent, and in distant disease it is an even greater 19.6 percent. This clearly reflects the more aggressive nature of the disease, and may be more likely to point to treatment related issues, like access to standard of care, compliance with treatment and follow-up. These differences persist for older women, as is evident in Figure 4 below, but are somewhat less pronounced, perhaps reflecting the less aggressive, more hormonally-dependent nature of breast cancer in older women, as well as access to treatment under Medicare, which has been suggested as a potential modifying factor of racial disparities in outcome.

**Figure 4. Five-year Relative Survival by Stage and Race, Women over 50  (US SEER data)**
Incidence Data for Locally Advanced and Stage IV Breast Cancer in California, by SES, age, and Race/ethnicity.

Data from the California Cancer Registry between 1988–1999 echo the findings in the US at large, but add more detail about Hispanics and Asian/Pacific Islanders.

Breast cancer falls disproportionately among different groups and ages, however. While it accounts for only 9 percent of invasive cancers in whites, it accounts for nearly a quarter of invasive cancers diagnosed in very young black women, aged 20–29. By age 30–39, breast cancer accounts for nearly half of diagnosed cancers in black women. While breast cancer is largely a disease of older women, with a median age of 63, for women younger than 50, breast cancer accounts for nearly 40 percent of all invasive cancers and is the principle cause of cancer death.

Table 1 displays breast cancer incidence per 100,000 people by age, demonstrating the dramatic increase in numbers of cases in older women, at a rate nearly ten times higher that in younger women, with a disproportionately high incidence in older white women.

Table 1. Female Breast Cancer Age-adjusted Incidence per 100,000 Population by Race/Ethnicity, California, 1995–1999

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>&lt; 50 Years of Age</th>
<th>50+ Years of Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>All races combined</td>
<td>40.1</td>
<td>363.0</td>
</tr>
<tr>
<td>White</td>
<td>43.5</td>
<td>412.7</td>
</tr>
<tr>
<td>Black</td>
<td>41.8</td>
<td>317.9</td>
</tr>
<tr>
<td>Hispanic</td>
<td>30.8</td>
<td>221.9</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>38.1</td>
<td>220.3</td>
</tr>
</tbody>
</table>

From 1988–1999, 258,849 women in California were diagnosed with breast cancer at a combined, age-adjusted rate of 128.8 per 100,000 population. The rate of breast cancer diagnosed at a distant stage was highest among blacks (7.5) and lowest among Asian/Pacific Islanders (3.0). The highest rate of unstaged breast cancer was also among black women (5.2). Asian/Pacific Island women were far more likely than black or Hispanic women to be diagnosed at an early stage.

The California Cancer Registry assesses socio-economic status (SES) not from individual data, but by place of residence, according to census block groups, each representing about 1,000 individuals. A statistically significant association exists between stage at diagnosis and SES as determined in this fashion. Those living in more affluent neighborhoods tended to be diagnosed at an earlier stage, while those living in poorer areas, were more likely to be diagnosed at a later stage. “Black women living in the most affluent areas were 60 percent more likely to be diagnosed at an early stage than those living in the poorest areas.” Interestingly, the association of SES as predictor of later stage diagnosis was most pronounced in black and Hispanic women and less so, though still statistically significant, for white and Asian/Pacific Islanders.

An analysis of California Cancer Registry data from November 2002, based on follow-up through 2000 using SEER 1990 life tables, confirms that in California both race/ethnicity and socio-economic status (SES) have an impact on survival from breast cancer.
Without regard to race, relative survival (excluding death from other causes) improved dramatically as SES increased. As Figure 5 shows, the five-year relative survival was 76.6 percent for the lowest socio-economic group, and 90.1 percent for the highest socio-economic group. As already discussed, a breakdown by race/ethnicity shows similar disparities in five-year relative survival, with 86.8 percent in white women and a low 73 percent in black women. Hispanic women had a five-year relative survival of 81.3 percent, while the figure for Asians was 85.6 percent.

**Figure 5. Five-year Relative Breast Cancer Survival in California by Socio-economic Status**

Table 2 illustrates what happens to five-year relative survival when the two variables of race/ethnicity and SES are combined.

**Table 2. Five-year Relative Survival of Female Breast Cancer, California, 1988–2000 by Race/ethnicity and Socio-economic Status**

An examination of the interaction of the two variables of race/ethnicity and socio-economic status shows poorer five-year survival for black women at all socio-economic levels, as well as poorer survival for white, Hispanic, and Asian women by socio-economic level. It is interesting to note that within each racial/ethnic group, the variable of SES can accurately predict for five-year survival, as is visually evident in the bar chart in Figure 6 (next page over). This clearly shows that class may well be as important an issue—or even more important—as race. In fact, these figures are so compelling that some believe that race/ethnicity is actually a proxy for socio-economic status.
Changes in Breast Cancer Mortality Rates

In the United States as a whole, breast cancer mortality rates have declined somewhat in recent years. That this is a recent trend is evident from the fact that during the twenty years from 1970–1990, death rates showed a small but significant increase for white women of about 0.3 percent per year and a more substantial increase of 1.6 percent for black women.

During the 1990s, however, mortality rates fell in white women by 2.5 percent a year, while they declined more slowly in black women, at a rate of 1.0 percent. The decline in mortality has largely been attributed to broader screening leading to earlier stage at diagnosis, so it is understandable that access to and utilization of screening and treatment has been hypothesized as the major reason for these disparities in mortality. However, as we will see, the data on changes in incidence and mortality suggest that changes in treatment, not early detection, may play a more important role in explaining the recent decline in mortality.

In California, the decline has exceeded the national rate, but again, not for all racial/ethnic groups. For the years 1970 through 1999, the overall decline of 26 percent in mortality from breast cancer in California was seen mostly among white women. Mortality in white women decreased some 24 percent over this period, while it decreased only moderately in Hispanic women (4.8 percent). In black women, the rate stayed the same, with only a 0.4 percent decrease, while in Asian/Pacific islanders an increase in mortality of 78.4 percent was seen. It should be noted in the latter case, however, that even after this dramatic increase, the mortality rate for Asian/Pacific Islanders was 13.7 percent in 1999, far below the rates for other groups: 31.8 percent for black women, 26.8 percent for white women, and 17 percent for Hispanic women. However, this alarming rise in incidence in Asian/Pacific Islanders should be researched to understand which sub-groups are affected, and what factors seem to be involved.

An analysis of more recent changes in mortality rates from breast cancer in California shows declines in all racial/ethnic groups. The annual percent decrease in mortality in the period from 1988–1999, was 2.5 percent for white
women, 1.8 percent for black women, 1.6 percent for Hispanic women, and 1.0 percent for Asian/Pacific Islander women.

In the United States, current thinking appears to lend more weight to mammography screening and earlier diagnosis as the primary cause for decreasing mortality rates, while in the UK and in Europe, where mortality rates have been declining more recently, the predominant current theories seem to favor the wide use of adjuvant tamoxifen as the cause. Since tamoxifen lowers mortality by nearly a third in long term studies of women with ER-positive breast cancers (about 75 percent of those diagnosed) this is certainly a plausible explanation.

Looking at the changes in actual rates of incidence by stage and in mortality rates in breast cancer offers a surprising glimpse at the real impact of screening during the fifteen-year period between 1983 (before widespread screening was adopted) and 1998.

A 2002 article in the New York Times, in which Dr. Barnett Kramer, director of the Office of Disease Prevention at the National Institutes of Health, was interviewed, detailed the dramatic increase in breast cancer incidence, using the numbers in the Table 3, below. “There are very few things that can so dramatically increase the incidence of new disease,” Dr. Kramer said, emphasizing that there is no apparent cause, in the form of a strong new carcinogen, like tobacco, to explain this 27 percent increase in incidence over fifteen years. “That, he said, ‘leaves screening as an explanation’,” Dr. Kramer continues. “Mammography appears to find many cancers that would not otherwise have been found in a woman’s lifetime.”

Indeed, the data on changes in stage at diagnosis and changes in death rates offer an illuminating picture. Looking at the increases and decreases in stage at diagnosis, by comparison with the decrease in death rates, in Table 3, it becomes quite clear that while we may be reducing stage at diagnosis and deaths a modest amount, we are, in the process, diagnosing many more early-stage cancers that are likely never to progress to become life-threatening.

**Table 3. Changes in Stage at Diagnosis and Deaths from Breast Cancer**

*(SEER Data United States, 1983–1998)*

<table>
<thead>
<tr>
<th></th>
<th>Rate per 100,000 population</th>
<th>Change over 5 year period</th>
<th>Rate and percent change per 100,000 population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1983</td>
<td>1998</td>
<td></td>
</tr>
<tr>
<td>DCIS</td>
<td>6</td>
<td>31</td>
<td>+ 25 N 417%</td>
</tr>
<tr>
<td>Small localized tumors</td>
<td>22</td>
<td>60</td>
<td>+ 38 N 172%</td>
</tr>
<tr>
<td>Large localized tumors</td>
<td>27</td>
<td>24</td>
<td>- 3 11%</td>
</tr>
<tr>
<td>Large localized tumors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&gt; 2 cm.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymph node positive</td>
<td>42</td>
<td>38</td>
<td>- 4 9%</td>
</tr>
<tr>
<td>Lymph node positive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tumors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IV (distant</td>
<td>4.3</td>
<td>3.7</td>
<td>No trend (P= .83)</td>
</tr>
<tr>
<td>metastases)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall incidence of</td>
<td>111</td>
<td>140.5</td>
<td>+ 29.5 N 27%</td>
</tr>
<tr>
<td>invasive breast cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths from breast cancer</td>
<td>32</td>
<td>28</td>
<td>- 4 13%</td>
</tr>
</tbody>
</table>
“This phenomenon is largely attributable to mammography,” according to the *New York Times* article: “The number of women with breast cancers with the worst prognosis, those that spread to other organs, had been fairly constant in the years before mammography was introduced, and that trend did not change after the introduction of mammography.”

Clearly, Dr. Kramer was suggesting that early detection had failed to live up to its promise. “If screening worked perfectly,” the article continues, “every cancer found early would correspond to one fewer cancer found later. That, he (Kramer) said, did not happen. Mammography, instead, has resulted in a huge new population of women with early stage cancer but without a corresponding decline in the numbers of women with advanced cancer.” The modest size of the reductions in later stage cancers and the unchanged status of metastatic disease are troubling. It appears that the early-detection approach to reducing cancer mortality fails to take into account the reality that some tumors are so aggressive that even the earliest detection will fail to eradicate them, while others are so indolent that it seems to make little difference if they are found before they become palpable. The burden of advanced breast cancer shows no real sign of abating, and is likely to continue and even increase as treatments prolong life.

In Figure 7 on the facing page, the SEER data for 25-year breast cancer incidence rates by stage, as well as death rates, are presented in graphic form. The top line, representing localized breast cancer clearly shows the precipitous rise begun in the early 1980s, with the dashed reddish line indicating the trend. The other clearly ascending line, accompanied by a dashed reddish line, is for in situ breast cancer, also associated with increased mammography screening. The dashed purplish trendlines for both the regional breast cancer rates and deaths show only slight decreases. There has been no change in the rate of distant (metastatic) breast cancer diagnosed over twenty-five years.

**Disparities in Outcome: Causes and Dilemmas**

Many studies have attempted to definitively explore the causes for disparities in stage at diagnosis and mortality across differing racial and socio-economic groups, both in California and elsewhere in the United States. Not surprisingly, researchers have often come to different conclusions about which possible causative factors are most important. A brief survey of the literature examines some of these factors.

It should be emphasized here that the problem of disparity in outcomes is far more racially and ethnically nuanced than the white-black focus that is the subject of most of the studies referenced in this report. Few studies have attempted to examine the many subpopulations within the larger categories of white, black, Hispanic and Asian.

A 2003 study of the SEER data between 1992–1999 looked at subgroups within the broad categories of Asians and Pacific Islanders, as well as in Hispanic whites: “Relative to non-Hispanic whites,” the study authors found, “blacks, American Indians, South and Central Americans, and Puerto Ricans had a 1.4- to 3.6-fold greater risks of presenting with Stage IV breast cancer.” A disproportionate number of blacks, Mexicans, and Puerto Ricans failed to receive appropriate surgery and radiation that met agreed-upon standards, the authors found. “In addition, blacks, American Indians, Hawaiians, Vietnamese, Mexicans, South and Central Americans, and Puerto Ricans had 20 percent to 200 percent greater risks of mortality after a breast cancer diagnosis.” Further, this study concludes that “for blacks, American Indians, Hawaiians, and Mexicans, these mortality differences persist even after adjusting for stage, ER status, PR status, and primary breast cancer treatments received.”

**Stage of Disease at Diagnosis**

Stage at diagnosis is widely considered a primary determinant of ultimate disease outcome. In the US as a whole, women with localized breast cancer have a five-year relative survival of 96.8 percent, whereas women who are not diagnosed until their disease has already metastasized to distant sites have a five-year relative survival of only 22.5 percent. In his 2002 review published in the journal *Cancer*, Dr. James Dignam maintained that “the benefit obtained from effective treatments is modest compared with the predictive effect that disease stage has on prognosis.”

As established earlier, it is widely known and accepted that in California, and in the United States overall, black breast cancer patients are more likely to be diagnosed at later stages of the disease than are white patients. There are
less pronounced disparities with regard to other racial/ethnic groups, with some notable exceptions. For 1988–1997, American Indian and Alaskan Natives, for example, were diagnosed at even later stages than black women were, with a larger percentage diagnosed with distant disease.26

This repeatedly confirmed observation has led a number of researchers to examine the question of whether black and white women of the same stage have similar outcomes. In other words, does the prevailing factor of stage at diagnosis account for all or most of the disparity in mortality rates?

Examining breast cancer patients from three metropolitan areas, including San Francisco-Oakland, the National Cancer Institute’s Black/White Cancer Survival Study found that after controlling for age and geographic location, the risk of dying of breast cancer was 2.2 times greater for black women than it was for white women.27 In this study, adjusting for the stage at diagnosis lowered this elevated level of risk in black women by comparison with white women (OR= 1.0) from an odds ratio of 2.2 to 1.7. Clearly, other factors are at work.

A large early study conducted with data from the American College of Surgeons in 198228 obtained information on a constellation of characteristics relating to stage at diagnosis. Expectedly, it found that black women tended to have larger tumor size, greater nodal involvement, and more estrogen receptor-negative breast cancers. Even after taking
into account stage, age, and tumor characteristics, outcomes for white women were significantly better. Race was determined to be an independent prognostic factor. Using data from the Black/White Cancer Survival Study group, Hunter et al. systematically examined “multiple explanatory factors” associated with breast cancer staging differences, and found the associated factors to be access to health care, lack of mammograms, and increased body mass index (BMI). In this study, different factors were associated with stage at diagnosis for blacks and whites. Income was associated with stage only for white patients, perhaps expressing the relatively small numbers of blacks with higher socio-economic status.

More recent studies have led to similar findings, and have likewise determined that while time trends over the last decades show that stage at diagnosis is improving over time, much of the improvement in breast cancer outcomes has occurred disproportionately in white women.

**Other Disease Characteristics**

Also using the Black/White Study data, Hunter et al. found that a constellation of factors including nuclear grade and having a clinical breast examination, as well as a history of patient delay, explained about half of the excess risk for Stage III and IV cancer in black women with breast cancer. When these factors were compensated for, it reduced the odds ratio (comparative risk) from 2.19 to 1.68. In other words, most of the excess risk was still unaccounted for.

A 2000 SEER-based study of 135,424 breast cancer patients comparing survival data in black and white women, found that within each stage category, black women had significantly poorer survival, were less likely to have estrogen- or progesterone-receptor positive tumors (as well as other less aggressive tumor types), and were more likely to have inflammatory breast cancer.

Histologic grade in breast cancer is a prognostic factor. A study done in Metropolitan Detroit found that black women were more likely to have tumors of a higher histological grade as well as being hormone receptor-negative. In this study of ten thousand women, even after controlling for age, tumor size, stage, grade, socio-economic status, and quality of care, the relative risk (odds ratio) of mortality for black women was 1.68 that of white women, for women under the age of 50.

Looking at SEER data between 1992 and 1999, a 2003 study examined histologic grade, stage and survival for black and white women. The study found that black women had a significantly higher proportion of Stage III tumors than white women. When the study authors corrected the data, they found that “African American women have a less favorable six-year cause-specific survival than Caucasian women for nearly every combination of stage and grade, regardless of age.” While an argument can be made that lack of screening and/or socio-economic factors lead to later stage diagnosis, the study authors point out, “It is not so obvious that low SES or lack of screening account for the higher-grade tumors seen in African American women compared with Caucasian women.” Further, the presence of higher grade tumors at all stages in black women may mean that early detection may not eliminate survival disparities.

Further research is clearly needed to examine the question of differences between racial and ethnic groups with regard to the histology and natural history of the breast cancers they develop. Perhaps a strategy that emphasizes mammography screening may work less well for women who are prone to more aggressive cancers at an early age. We cannot hope to address the disparities in outcomes for minority women until we understand more fully why it is that black women are more likely to die of breast cancer—or, for that matter, what it is about Japanese women’s breast cancers that makes them more likely to be detected early and have better outcomes. We should not be dissuaded in this quest by decreasing overall mortality rates, or the apparent increase in early stage diagnosis attributable to mammography screening. The serious, continuing problem of high-risk and metastatic breast cancer should not be obscured by the increasing detection of early disease through screening.

Since the breast cancers of younger women often are aggressive and hormone-receptor negative, disproportions in age distribution across racial and socio-economic groups is also important. An analysis of data from the SEER database of women diagnosed with breast cancer between 1988–1995 found that black women diagnosed with breast cancer were younger, overall, than white women. Approximately 33 percent of black women were less than or equal to 50 years of age when diagnosed with breast cancer. By comparison, slightly less than 25 percent of the white women newly diag-
nosed with breast cancer belonged to that younger age group. There are many such studies; however, care must be taken in understanding attempts to identify what has been referred to as a “black breast cancer.” Observed biological differences, whether innate or acquired from exposures and experiences in a person’s lifetime, which may play some contributing role in differing outcomes, can potentially be misused to dismiss important shortcomings in access to care, provider biases, and public education surrounding health behaviors and attitudes.

It’s also important to understand that race and ethnicity are far from the clearly definable constructs we often assume that they are, especially when it comes to genetic differences. “There is more variability in genetic traits within racial groups than across racial groups,” points out Catarina Kiefe, of the University of Alabama.36

“Differences in cancer biology between racial groups are unlikely to be responsible for a substantial portion of the survival discrepancy,” members of the Health Outcomes Research Group at Memorial Sloan-Kettering Cancer Center conclude in their 2002 review of the literature on racial discrepancies in cancer survival.37

“Race is not a category that is based on biology,” agrees Harold Freeman, Director of the NIH Center to Reduce Cancer Health Disparities, who sees race as a social construct that changes over time. “This has been agreed upon by most of the predominant members of the scientific community.”36

Nevertheless, observable differences do exist across racial and ethnic lines, some of which may be the result of differing biology and genetics. An example is of higher breast cancer incidence related to BRCA mutations in Ashkenazi Jewish women—the result not of their being Jewish, but of intermarriage within a single population group. Lower incidence of breast cancers in some Asian populations might be another example, although it is far from a simple matter to distinguish between intrinsic and extrinsic factors.

Age
Age is a well documented factor that may lead to disparities in screening, diagnosis, and treatment. Mammography screening, which typically begins at age 40 or later, has been a somewhat problematic early detection tool for younger women, whose breast tissue is often denser than that of older women. The incidence rate in very young women is so low that breast lumps and nipple discharges may not be properly evaluated, leading to later diagnoses. The combination of delayed diagnoses with typically more aggressive, estrogen receptor-negative disease can be a deadly one.

Elderly patients, like very young patients, have also suffered from inferior care, and have often failed to benefit from treatment innovations. Clinical trials have historically provided little information on women older than 65, and surgeons and medical and radiation oncologists have in the past tended to undertreat such patients, even in the absence of co-morbid conditions, in order to spare them from the rigors of radiation, chemotherapy, and axillary dissection. Recently, however, a number of studies have demonstrated that healthy older women with high-risk breast cancers can benefit as much as younger patients from combination chemotherapy, radiation and other treatments.

“More than half of all new breast cancers in the United States occur in women 65 years old or older, a statistic that has even more impact in a population whose longevity is increasing,” writes Hyman Muss, in his review of the impact of age, race, and socio-economic status on the selection of adjuvant therapy in breast cancer.39 Because of a higher incidence of other health concerns, older women are less likely to be offered chemotherapy and radiation, and they are less likely to participate in clinical trials. The lack of trials information in elderly women about the effects of adjuvant treatment on quality of life and survival must be remedied.

Screening
While the focus of this paper is not on screening, it should be stated that to the extent breast cancer screening has a meaningful impact on stage at diagnosis, it is important in addressing the disparities discussed here. However, the contribution that mammography has made is not clear at this point.

A recent study on cancer screening in California was prepared by the UCLA Center for Health Policy Research.40 While three-fourths of California women now report that they’ve had a mammogram in the past two years, rates are lower among Asians, American Indians, Alaska Natives, and Latinas. Interestingly enough, data from the 2001 California Health Interview Survey show that 78 percent of both white and black women have received mammograms.

A yet-to-be-published report from the Cancer Surveillance Section, Department of Health Services and the
Survey Research Group, Public Health Institute, on utilization of screening mammography from 1987–2000 in California, found that during the most recent period studied, more black women aged 40 and over (93.5 percent) actually reported having had a mammogram, than did white women over 40 (90 percent). This was particularly true among black women aged 40–49, suggesting that the message about younger onset of breast cancer in black women has been effectively communicated. Of course it is important to keep in mind that the debate about screening premenopausal women, who are more likely to have dense breasts, is far from settled. All too frequently, we hear stories about false negatives in these young women, who may be lulled into complacency by a clear mammography report.

If mammography does ensure earlier detection, and if this early detection will lead to lowered mortality for all ages and racial/ethnic groups, then the disparity between black and white outcomes in breast cancer should decrease over time. However, the disparities have not decreased to date. The fact that there has been no noticeable improvement in outcomes for black women, despite the high utilization of screening among black women in California, is striking. If there is no improvement in outcome within the next several years, this will raise some important doubts about the utility of screening in saving lives. This is a fertile area for research.

The UCLA study shows that despite available free testing for lower income women, utilization lags behind that of higher income women. And within the lower income groups, the study found that Latinas, Asians, American Indians, and Alaska Natives are much less likely to seek screening. However, among those covered by Medi-Cal, screening utilization across races is more equivalent, suggesting that access to screening and treatment may play a role in whether women take an active role in their health care by seeking mammographic screening.

**Treatment**

A comprehensive review of patterns of care studies from UCLA researcher Jennifer Malin and colleagues illustrates the difficulty of drawing conclusions about the quality of care, and “found marked variability in the patterns of breast cancer care both in the United States and other countries.”

One reason for this may lie in the poor quality of cancer registry data as a source of information on outpatient treatments. For example, a study comparing patient records with data in the California Cancer Registry found that the registry correctly reported only 72 percent of radiation treatments, 56 percent of chemotherapy treatments, and 36 percent of tamoxifen use. By contrast, the accuracy of registry data was much higher for hospital-based procedures—95 percent for mastectomy and lumpectomy and 96 percent for lymph node dissection.

Studies examining the impact on mortality of access to treatment and utilization of treatment have yielded mixed findings and have usually been limited to the initial treatment of primary breast cancers, for example the four months that SEER data reflect. This points to an obvious need for better ways of looking at the entire dimension of treatment information in breast cancer.

There are at least five areas to consider regarding treatment, and they may often be interwoven. These are:

- Consumer attitudes toward screening, treatment, and health care overall
- Access to treatment, including financial issues, insurance, transportation, etc.
- Provider adherence to standards of care
- Adherence to or compliance with recommended treatments on the part of patients
- Health care provider bias or other inequities in provision of services

Consumer/patient beliefs and attitudes about medical treatment and providers can influence the other variables. Clearly, access to treatment—whether or not a woman can find the resources to receive standard-of-care treatment for breast cancer—does not inevitably lead to treatment adherence and utilization, nor does it reflect the unspoken (and perhaps unconscious) bias that may exist in some health care providers leading to less than optimal treatment and poorer outcomes for patients who are older, obese, minorities—especially non-English-speakers—and those of lower socio-economic status. Any or all of these factors may interact to influence the actual treatment for breast cancer a patient receives—and the outcome of her disease, as a result. Not all women are able to take the time they need from work to travel for time-consuming treatments.

In an attempt to correct for these factors and examine whether or not a racial basis for differences in outcome
exists, several studies have looked at outcomes for patients treated in single institutions, where financial and geographic barriers to access to care are removed or at least thought to be equivalent for different patient groups, and where all patients are offered the same treatments by the same doctors. An examination of survival data in NSABP cooperative group clinical trials found that when stage of disease and treatment were comparable, outcomes were similar for black and white breast cancer patients. However, a 10-year survival study done at M.D. Anderson Cancer Center found that even after correcting for the effects of age, socioeconomic status (SES), stage of disease, and delay in seeking treatment for symptoms, an ethnic difference remained among black, Hispanic, and white women.

A recently published study from the Center to Reduce Health Disparities found that even when correcting for staging, stage-specific six-year survival rates were lower for black women of all ages. But a closer examination of the data further defined the affected groups. It showed that “only black women younger than age 50 years with ER-positive tumors and women younger than age 65 with ER-negative tumors had significantly lower stage-specific survival rates.” The study also found that black women of all ages had lower rates of Stage I breast cancer. The study authors hypothesize that black women over the age of 65 may do better because of access to Medicare services, which may serve to alleviate disparities in cancer treatment.

Survival among Asian/Pacific Island (API) breast cancer patients has generally been found to be either equivalent to or superior overall to that of white women. A 2002 SEER-based study found different stage distributions and five-year outcomes for different subpopulations classified within the API group, finding higher stage-adjusted survival rates for Japanese women, compared to Chinese and Filipinas. The study concluded that “The heterogeneity of cancer outcomes observed within the community classified as Asian reinforces the need for cancer statistics to be reported for disaggregated subgroups.”

Other research points out that long-term compliance with adjuvant breast cancer treatments may be problematic in some patient groups, leading to poorer outcomes. For example, a recent study from the Journal of Clinical Oncology examined utilization of tamoxifen by tracking whether pharmaceutical prescriptions were refilled during the entire recommended five-year course of treatment. Tamoxifen use is important because it represents the most widely-used and effective treatment for hormone-positive breast cancer, representing the majority of cases.

Unlike more recently developed hormonal therapies (principally aromatase inhibitors), tamoxifen is no longer under patent, meaning that few economic barriers to its use persist. This study used prescription records of patients enrolled in New Jersey’s Medicaid or Pharmaceutical Assistance to the Aged and Disabled (PAAD) programs. Analysis of these records over five and a half years found that almost one quarter of patients did not follow the five-year course of tamoxifen prescribed by their oncologists. Further, it found that nonadherence was highest among the youngest, oldest, and non-white patients.

The reasons for this are unknown, but this finding may well underscore the importance of an ongoing relationship with a medical team, an option not open to those with no insurance or means to pay for this level of care. For many people, hospital emergency rooms represent their only contact with health care.

A small study of patients treated for breast cancer in an HMO setting determined that missed appointments and later stage at diagnosis were “key determinants of survival.” After correcting for these variables, the effects of race were “marginal.” The study found that black women were more likely to miss their appointments, however, and concluded that “this measure is an important component of how race affects survival.

Compliance with appointment keeping and alleviating reasons for noncompliance must be considered as factors in breast cancer survival.”

A study of Latinas in Massachusetts looked at the incidence of the attitude of fatalism as a predictor of poor screening behavior in minority women with family histories of breast cancer, and discussed cultural values in which open discussion of a cancer diagnosis was frowned upon, creating a potential for late diagnoses in familial cancers. Other studies have pointed at the low rates of routine regular medical care in minority populations and poor insurance coverage.

Surgery following neoadjuvant treatment for Stage III and surgery on the primary tumor for Stage IV patients may offer another insight into disparities in outcome. A 2000 Arkansas tumor-registry study on residual disease found that black women, who tend to be diagnosed at
later stages, have “a lower incidence of becoming “disease-free” during treatment in Stage III and IV disease appears to be a contributing factor to the decreased survival in those stages.” The authors relate this to a higher rate of Stage IIIB disease combined with less surgical intervention among black women. More recently, research presented in the 2003 5th Annual Lynn Sage Breast Cancer Symposium on nearly 10,000 Stage IV patients in American College of Surgeons’ National Cancer database demonstrated that survival is adversely affected when surgery is not performed on the primary tumor in metastatic breast cancer patients, or when surgery does not obtain tumor-free surgical margins.51

A study in older women, linking Medicare claims data to cases in the SEER database, showed that older women were less likely to receive radiation therapy after lumpectomy, a significant predictor of less favorable outcome. This failure to offer therapy was not found to be due to physician concern over other health issues. The authors concluded that “Between the ages of 65–69 years and 80 years or older, radiation therapy declined from 77 percent to 24 percent among women with no comorbid conditions.”52

Similar findings came from another large SEER-based study that found that black women of all ages were significantly less likely to receive radiation therapy after breast conservation.53

Data from the NCI Black-White Cancer Survival study,54 comparing treatment received in these two populations with standard-of-care treatment in the mid-1980s, found that while only 4 percent of early-stage breast cancer patients were not treated with “minimum expected therapy,” that figure escalated to 36 percent of patients with late stage disease. “Older women and women with no usual source of care were significantly less likely to receive minimum expected therapy,” study authors reported. “Overall, 21 percent of black women did not receive minimum expected therapy compared to 15 percent of white women.”

A study of SEER Patterns of Care data from 1990–1998 in young breast cancer patients under the age of 35 found racial/ethnic disparities in both clinical characteristics and treatment.55 Young black women were less likely to have health insurance, had larger tumor sizes, more ER-negative tumors, and more positive lymph nodes, although fewer black women were offered axillary dissection. More black women and Hispanic women refused chemotherapy than white women. Both Hispanic and black women were less likely to receive radiation after lumpectomy, especially if they were on Medicaid. In this young population, combination chemotherapy was received by 46.5 percent of black women, 52.4 percent of Hispanic women, and 67 percent of white women. Not surprisingly, the study concludes, “African American and Hispanic women experienced poorer outcomes compared with white women. Just over 23 percent of African American and 21.9 percent of Hispanic women, compared with 15.6% of non-Hispanic white women, had breast cancer listed as the underlying cause of death.”

**Socioeconomic Factors**

As previously stated, the California Cancer Registry calculates socioeconomic status by census block group rather than by individuals, and reports it in quintiles, with SES 1 being the poorest and SES 5 being the most affluent. The most recent data from November 2002, show that socio-economic status is a predictor for five-year relative survival, within each racial/ethnic group.

A recent study of socio-economic status and breast cancer survival in the Greater San Francisco Bay area between 1988–1992.56 sought to broaden the understanding of disparities in two other racial/ethnic groups, Hispanics and Asian women. This study found that ten-year unadjusted (all mortality) survival rates for breast cancer patients were 81 percent for whites, 69 percent for blacks, 75 percent for Hispanics, and 79 percent for Asians. When they adjusted the statistics to account for differences in stage, they found that Asians and Hispanics showed no significant difference from whites, while for black women there was still a disparity, with a persistent relative risk of 1.29, down from 1.81 before stage adjustment. While other factors did not further reduce the relative risk, living in a blue-collar neighborhood was found to be independently associated with a 1.16 increase in mortality.

A thoughtful 2002 review of socio-economic factors and breast cancer outcome cites previous research indicating that factors related to socio-economic concerns—such as child/family care, literacy/education levels and lack of transportation may contribute to non-compliance with recommended treatment and poorer outcomes.57

“Most researchers will agree that race is a surrogate measure of factors such as SES, access to health care, and cultural systems,” Sue Joslyn states, citing studies
that show similarities in low-income and high-income survival rates, regardless of race. “Two hypotheses arise from these studies: (1) SES is the true causative factor in racial differences in survival or (2) the health experiences of African American women are different from that of white women.”

The Cost of Treatment

Standard-of-care—and especially state-of-the-art—treatments for high-risk primary and metastatic breast cancer commonly involve different criteria than for early stage primary breast cancer, which is more broadly systematized and easier to characterize.

Because most clinical trials in drug development are done with metastatic patients, treatment for these patients undergoes a process of constant evolution, rather than changing periodically as the product of consensus documents or meetings of experts in the field, as is generally true with adjuvant treatment for early-stage breast cancer.

The sheer complexity of describing how standardized treatment should be offered to address such a widely variable disease is in itself challenging, and often leads to confusion for patients because of differing treatment recommendations when a second opinion or consultation is sought. By contrast, early-stage primary breast cancer seems relatively straightforward, though of course it possesses its own complexities.

In addition, it is in the nature of evolving research that treatment regimens and practices offered in sophisticated research centers may take significant time to filter down into community clinics. Disparities may exist in treatments for high-risk and metastatic disease between the teaching hospitals and major cancer centers which have strong research programs, and the community cancer clinics and hospitals where most patients are still being treated.

Among the many treatment guidelines developed for breast cancer, aspects of high-risk and metastatic disease are sometimes included, but more often are not a focus. Every two years, for example, international cancer researchers and physicians meet in Switzerland for the St. Gallen Consensus Conference on Therapy of Primary Breast Cancer.

The National Comprehensive Cancer Network (NCCN), a cooperative network of 19 leading cancer centers, issues clinical practice guidelines in breast cancer, and in many other cancers. These guidelines rely on evidence from the latest trials, as well as expert consensus opinions. NCCN algorithms or “decision trees” for treatment of various stages of breast cancer are publicly available on their website at http://www.nccn.org58. Their recommended workups and treatment guidelines for high-risk and metastatic breast cancer are reviewed on an ongoing basis.

The NIH Consensus Guideline document for adjuvant treatment, last issued in the year 2000, also includes some recommendations for high-risk, locally advanced disease.59

Certainly, one of the most frequently consulted guidelines sites is PDQ, the National Cancer Institute’s (NCI’s) comprehensive cancer information database, which includes a treatment guideline for health professionals.60 In this peer-reviewed statement, which is updated monthly, the section marked Stage IIIB, IV, Recurrent, and Metastatic Breast Cancer provides a concise narrative review of standard treatment options. Offering an idea of the variability and difficulty of discussing treatment options in the metastatic setting, it concludes with the following summary, which offers a sense of how much has yet to be understood about optimal treatment in advanced breast cancer:

The rate of disease progression, the presence or absence of co-morbid medical conditions, and physician/patient preference will influence the choice of therapy in individual patients. At this time, there are no data supporting the superiority of any particular regimen. Sequential use of single agents or combinations can be used for patients who relapse. Combinations of chemotherapy and hormone therapy have not shown an overall survival advantage over the sequential use of these agents.

Patterns of Care: Metastatic Breast Cancer

For those who have followed breast cancer drug development over the last decade or so, one striking fact is evident: the majority of state-of-the-art treatments for metastatic breast cancer in use today have received accelerated or full FDA approval since the early 1990s. In order of their approval, these include: Aredia (pamidronate,1991), Taxol (paclitaxel,1992), Navelbine (vinorelbine,1994), Arimidex (anastrozole,1995), Taxotere (docetaxel,1996), Gemzar (gemcitabine,1996), Femara (letrozole,1997), Xeloda (capecitabine,1998),
Herceptin (trastuzumab, 1998), Aromasin (exemestane, 1999), Zometa (zoledronic acid, 2001), and Faslodex (fulvestrant, 2002). If past history is an accurate predictor, in time, with further clinical research, most of these treatments will go on to become adjuvant treatments for primary breast cancer. Some, like Taxol and Arimidex, have already begun to do so.

There are many more drugs on the way. The Pharmaceutical Research and Manufacturers of America (PhRMA), issues an annual report on new cancer drugs each year. According to latest report, 2003 Survey: Medicines in Development for Cancer, there are 395 drugs in development for various cancers, including 49 in breast cancer, and 94 in solid tumors, many of which include breast cancer patients in trials. Among the breast cancer drugs in the research pipeline, several are in late stages of clinical trials investigation. The targeted anti-angiogenic therapy Avastin (bevacizumab), reported close to approval in colon cancer, and the growth-inhibitor Iressa (gefitinib), recently approved for non-small-cell lung cancer, both show promise in breast cancer. And there are quite a few others, including targeted and oral versions of existing cancer therapies reformulated to be work better with fewer side effects.

Many of these new drugs have already supplanted or will supplant older, less effective, and more toxic drugs. Some will represent incremental but real steps in patient care. Others are obvious attempts on the part of manufacturers to hold onto their market share by securing approval for newly-patentable reformulations of drugs that have gone off patent. Some of these new drugs possess entirely new mechanisms of action, and represent novel non-cross-resistant treatment options that may extend life for women with metastatic breast cancer. Eventually, with more clinical trials, most of these treatments will move up to become adjuvant treatments for primary breast cancer.

In addition, most of the drugs used in supportive care have been approved in the last decade or so, like the anti-nausea drugs Zofran (ondansetron, 1991), Kytril (granisetron, 1994), and Anzemet (dolasetron, 1997), and growth-factor support like Nupogen (filgrastim, 1991) and Epogen (Epoetin alfa). Approved this year, the new drug Emend (aprepitant) in combination with other anti-emetics, reduces delayed nausea and vomiting from chemotherapy. In the complex area of pain control, there are continuing refinements and newer drug formulations. The list of palliative and supportive agents is extensive.

As we evaluate these treatments, we also need to understand that Western conventional medicine is not the only form of treatment in use by breast cancer patients. It’s important to examine other influences that may pertain to metastatic treatment choices in different populations, taking into account cultural values surrounding life-threatening illness as well as the utilization of alternative and complementary healing practices.

Treatment Costs for Metastatic Breast Cancer

With few exceptions, the newer drugs still under patent are extremely costly to patients, private insurers and Medicare, Medicaid, and public insurance programs like Medi-Cal. Unlike adjuvant treatment for primary breast cancer, metastatic breast cancer patients typically receive continuous treatments throughout their lives. Typically, the drugs that metastatic breast cancer patients use and the tests, doctors visits, and other medical care to administer these life-prolonging treatments run into many thousands of dollars each month for each patient. With new treatments extending lives, the costs, of course, will increase proportionally.

Given the current state of spiraling health care and insurance coverage costs, combined with a larger population of uninsured and underinsured in the United States, it would not be surprising to learn that availability of these expensive new drugs is not equally distributed across all races and classes. In fact, equity in access would be surprising.

These financial realities have serious implications for patients with high-risk and metastatic breast cancer, and may account for many lives lost and shortened. These are areas that cry out for extensive study and research.

These escalating costs may be more problematic for women with metastatic breast cancer, than for primary breast cancer patients currently, and in the future. More and more, oncologists speak of treating metastatic breast cancer as a chronic disease. In the metastatic setting, where the 97 percent mortality figure is still considered accurate, the continuing extension of life in the direction of chronic disease is an important goal. The MD Anderson study, cited previously, offers persuasive evidence that 40 percent of patients optimally treated at their center now live five years or more with distant
metastatic disease. That number is surely growing, as available agents increase and as refinements in treatment are made.

Further evidence comes from a recent Canadian study from the British Columbia Cancer Agency presented at the most recent meeting of the American Society of Clinical Oncology (ASCO) examined the impact of new treatments for metastatic breast cancer on length of survival. Prior to this study, there had been no population-based study that demonstrated that length of survival in 2,151 metastatic patients had improved from the oft-quoted median survival of 12–24 months. The study linked to a pharmacy database to look at the impact on length of survival of drugs approved from 1991–2001, the period during which Taxol, Navelbine, Taxotere, the aromatase inhibitors, Xeloda and Herceptin were approved for use in Canada. During 1991–1992, median survival was 434 days, with 34 percent of patients surviving two years or more. By 1999–2001, median survival had increased to 661 days, and 45 percent of patients were still alive at two years. It seems reasonable to assume that access to these new treatments does prolong life.

During the entire time a patient is being treated, periodic testing should be done to follow the disease and assess treatment response. Tests for this purpose include (but are not limited to) MRI and CT scans, PET and bone scans, X-Ray studies, tumor markers, and liver function tests.

It is common now for women with metastatic breast cancer to have multiple lines of hormonal, chemotherapy, and biologically targeted therapies over a period of years—that is, if they are fortunate enough to have the means, knowledge, and access to these treatments at the hands of skilled oncologists. Knowing what we know about differences in mortality rates between black and white women, this scenario raises certain inevitable questions—questions to which we don’t as yet have answers.

Will a newer, more expensive treatment be offered to an elderly metastatic breast cancer patient, for example, after the second or third or fourth line of treatment has failed her? Will she be able to travel to get her treatments on public transportation, or can special arrangements be made for her to get to her doctor’s appointments if she is ill or disabled? Will someone make sure she has needed family support during the long course of her illness? Will her case be carefully followed with blood tests and scans to assess whether treatments are working or should be discontinued? Will she have access to newer hormonal therapies or targeted biologics in a dedicated attempt to extend her life and offer her good quality of life? Will she be offered supportive medications to ease her pain or nausea? Will her co-morbid conditions and risk/benefit factors be carefully addressed?

All of these interventions are becoming increasingly costly. Documentation of the dollars spent in treating metastatic breast cancer in California, as well as any potential disparities in such expenditures on behalf of different patients across racial/ethnic, socioeconomic and age groups would clearly provide important data for health policymakers. It would be important to understand what treatments are received by women with advanced breast cancer, including any reliance on indigenous healing practices.

**Patterns of Care: High-Risk (Locally Advanced) Breast Cancer**

Lack of treatment compliance and/or failure to provide standard-of-care treatment in high-risk breast cancer can lead to a higher incidence of metastatic cancer and mortality. The benefits of adjuvant treatment for high-risk patients in disease-free survival at ten years in the clinical literature can now easily be estimated by patients and health care providers through an online computer program, known as Adjuvant!, that offers the latest clinical trials information concerning the impact of various forms of treatment on ten-year disease free survival and mortality. Developed by Dr. Peter Ravdin and colleagues at the University of Texas in San Antonio in 2001, this calculator can be found online at [http://www.adjuvantonline.com](http://www.adjuvantonline.com). This tool is “not intended for use by patients in the absence of health professional input,” however. According to the authors, this caveat is necessary due to both the potential emotional impact on a newly diagnosed patient of reading prognostic data and the difficulty of including all the relevant factors which oncologists factor into treatment recommendations. Nevertheless, for our purposes here, Adjuvant! provides a useful way of estimating potential risk and benefit from adjuvant treatment, and illustrating the potential impact inferior adjuvant care can have on outcome.
In general it is true that statistically, the greater the risk of recurrence, the greater the actual benefit of optimal adjuvant therapy to the patient, so that the benefit for patients with high-risk primary breast cancer is proportionally more than for those with early-stage disease. This means that provision of standard-of-care treatments is crucial to obtain the best chance at survival.

Without adjuvant chemotherapy, a 38-year-old black woman with a 3.5 centimeter, ER-negative, grade 2 tumor with four involved lymph nodes faces only a 26 percent chance of being alive and cancer-free ten years later. The standard four cycles of Adriamycin and Cytoxan (CA) can improve her absolute odds of not having recurrence by over 20 percent, but the addition of four cycles of Taxol to the CA can increase her chances of disease-free survival by an additional 8 percent, in absolute terms. With optimal chemotherapy, then, this hypothetical high-risk patient’s chances of disease-free survival at ten years are doubled by aggressive chemotherapy, from 26 percent to 54 percent. If she has more than nine involved lymph nodes at diagnosis, the disease-free survival benefit to her of optimal chemotherapy is actually tripled.

We know that certain patient groups are at greater risk for getting less than optimal care, notably those who are elderly, obese, poor, and those of some minority populations. Questions have also been raised about the relative treatment given at NCI-Designated Comprehensive Cancer Center and teaching hospitals, community cancer centers and private oncology practices. Are there differences in the kind of care that is offered to patients, according to medical setting? Does where breast cancer is treated affect outcome? These are important questions to examine.

We need to understand whether certain patient groups, such as those with inflammatory breast cancer, for whom the usual delays in diagnosis and treatment can be deadly, are receiving optimal care, and whether this care differs by age, racial/ethnic group, and socio-economic status. We need to know if issues of familial predisposition and genetic testing are being adequately addressed in the various communities.

**Clinical Trials**

Any paper addressing research needs and disparities in health care could not conclude without examining the issue of clinical trials enrollment. For women with high-risk and metastatic breast cancer, trials represent an important strategy for optimal care that can offer early access to new treatments prior to FDA approval, as well as to the cooperative group protocols that represent ongoing refinements of already approval treatments. An argument can be made that trial participation is also indicative of a sense of connection to the medical and research communities, as well as showing a commitment to the goal of furthering research and to the patient’s own treatment goals.

Participation in clinical trials among adult cancer patients has long been known to comprise only a small percentage of patients. A National Cancer Institute study found that “more than 70 percent of cancer patients aged 0–19 years are estimated to enter cooperative group clinical trials compared with 4 percent of cancer patients aged 20–49 years and 1.5 percent of patients aged 50 years or older.” The high participation in pediatric clinical trials is often related to the rapid development and relative success treating of childhood cancers. A report prepared by the Minority-Based Community Clinical Oncology Program (MBCCOP) found that “While minority patients are willing to participate in clinical trials, there are profound barriers involving language, logistics, and the appropriateness of available protocols.”

According to the authors of one recent University of California survey done of causative factors for low trial participation, “Low accrual rates clearly have a negative impact, often prolonging the duration of the trials, delaying the analysis of important results, or leading to early close of important studies.” Even in this research institution, clinical trials were not widely offered to patients. One-third of the time physicians didn’t mention clinical trials to their patients, either because of false perceptions about lack of available protocols or the patient’s poor performance status. Nearly half of eligible patients surveyed refused to participate in trials because of travel concerns, fear of experimental therapies and of being randomized, and problems with insurance reimbursement. Reasons given for lack of minority participation cited elsewhere have been lack of opportunity, mistrust of the white-dominated health care system, and lack of information about trials.

Clearly, more needs to be done in California, as elsewhere, in furthering enrollment in clinical trials so that more patients of all ages, socio-economic status, races and ethnic groups can participate. Research must build on existing studies to explore the barriers to trial participation as a necessary step.
It’s a familiar parable, but worthy of repeating in this context:

Under a streetlight, on a very dark night, a man was looking for a set of lost keys. A policeman came by and inquired about the object of his search. After the two had searched diligently for quite some time, the officer finally asked, “Are you sure you lost them here?”

“Oh, no,” said the man, pointing out into the darkness. “I lost the keys somewhere over there.”

“Then why are you looking for them over here?” the officer asked.

“Because this is where the light is!” the man replied.

What lies under the streetlight seems largely to have influenced the focus of studies that have examined disparities in breast cancer outcomes. The data collected by cancer registries has offered much that is of value, but much important data still lies largely unexplored in the outer shadows, particularly in the poorly documented areas of incidence and treatment of locally advanced and metastatic breast cancer. Likewise, when it comes to understanding the experiences and needs of advanced breast cancer patients, we have few other informational resources upon which to draw, outside of clinical trials data.

As mentioned earlier in this paper, the incidence and mortality data captured in the California Cancer Registry (CCR)—as in SEER and other cancer registries—offers specific, detailed information at two points in time only, at diagnosis, initial treatment, and death. What happens between these two points in time is largely unexplored territory. Thus, an accurate picture of the extended treatments received by women undergoing aggressive primary treatment, as well as multiple ongoing treatments for metastatic breast cancer are not reflected in this data. Clearly, there are problems with retrieval, accuracy, and analysis of treatment-related data in the CCR and other databases.

This paper has advanced the thesis that the intense focus of the last 20 years on early detection and screening has yielded limited results in reducing absolute rates of stage at diagnosis and mortality. Further, it is clear that this focus has failed to take into account the needs and experiences of women with high-risk and metastatic breast cancer. Few informational resources exist that accurately document the treatments offered to this group of patients. Many believe that it is advances in treatment, as much as (or more than) screening that is responsible for the lowered death rates seen in the last decade or so.

Like the rest of the United States, California has been hampered by poor quality information on breast cancer treatment, a fact that is particularly meaningful for high-risk and metastatic breast cancer patients, whose treatment is by necessity extensive and ongoing. Without accurate treatment data on these vulnerable populations, we will not be able to fully explain differences in outcomes.

**Documenting the Patient Population**

An important informational gap that exists in cancer registry data is that of the incidence of breast cancer recurrence. Since the database is limited to initial diagnosis, initial treatments and deaths, there is no record of recurrence. This makes it impossible to get a sense of the magnitude of a patient population that includes all patients who ultimately die of breast cancer, except insofar as they can be extrapolated from death rates. Without a clear sense of the numbers and distribution of these patients, and the length of their survival, novel ways to address disparities in the provision of care and other needs are likely to remain elusive.

One subgroup that should be analyzed are those categorized as “unclassified” in the registry data. The outcomes for this group are poor enough that they almost certainly include Stage III and IV patients. It is possible that this group represents a disproportionately underserved and minority population, and that the absence of staging or documentation of staging is an aspect of this lack. An analysis of the reasons why these patients are not staged would be of interest.

**Disparities in Outcomes: Issues**

The research is confusing when it looks at the issue of race/ethnicity as a predictor of outcomes versus socio-

**Directions for Research**
economic status as a predictor. Some studies seem to suggest that race/ethnicity may actually serve as a proxy for SES. A more in-depth understanding of the ways in which these factors play out in California breast cancer populations may provide some important further insight.

Some of the large racial/ethnic subgroupings have very diverse outcomes. Of particular interest are the different races and ethnicities of Asian/Pacific Islanders, whose outcomes vary so widely that larger subgroupings may not be meaningful.

Of particular concern in the Asian/Pacific Islander population, which still overall bears relatively low comparative incidence and mortality rates, are the dramatic recent increases in mortality. While still well under the rates for other groups, the increases have been so rapid that they are worrisome. An investigation of causation, including a comparison of the effects of immigration over time on incidence and mortality, would be crucial.

A number of other issues in understanding disparities in outcome are worthy of further study in the California population. For example, in view of the broad increase in utilization of mammography screening among black women, outstripping that of white women in some subgroups, what role does early detection actually play in explaining the persisting disparities in outcome? If in fact screening and early detection proves to be only marginally effective (or not effective at all) in improving outcomes in certain populations, how well do these current models of intervention actually work? The answers to these important questions will be crucial in allocating scarce funding.

Breast cancer in black women occurs at younger ages, with more aggressive features. Is there a biological difference in the kind of breast cancer that young black women are likely to get? Is there a biological difference in the kinds of breast cancer that certain Asian populations with unusually positive outcomes are likely to get? Are these differences related to inherent factors, to behavioral and environmental differences, or to other factors, as yet undetermined? How do access to treatment, healthcare coverage, patient compliance, and provider biases interact with these differences? These are some of the important research questions that should be examined.

**Looking at Treatment**

Multiple explanatory factors have been proposed to explain disparities in outcome, including stage at diagnosis, disease characteristics, age, screening behaviors, and treatment variables. Those explanatory factors that are easier to document than others, such as stage at diagnosis and mammography screening, have been more widely studied—the “street light syndrome” mentioned above—while little is known about how, whether, and which treatments are actually offered, accepted or undergone.

Most newly diagnosed breast cancers are hormonally driven, so hormonal drugs like tamoxifen and Arimidex are standard adjuvant treatments. Yet the few studies that have been done suggest that compliance with the full five-year prescribed treatment can be very low in some racial and socio-economic groups. What role do factors like consumer and provider attitudes play in treatment compliance? What role does regular health care, follow-up appointments, problems with childcare, transportation, and other financial/social issues play in compliance? The issue of compliance with treatment recommendations must be considered in the context of other health care, economic, and social considerations in minority communities.

Patterns of care studies in California women have the potential of following women from all ages, SES, racial, and ethnic groups through diagnosis, treatment, and follow-up to look at whether differences in care received and/or accepted is meaningful. Comparisons between standard of care recommended and actual treatment received should be instructive. Where there is funding for health care in poor and minority populations, for example in women aged 65 and older, has this impacted outcome in a meaningful way in these populations? It would be especially meaningful to examine the number of lines of metastatic breast cancer treatment offered to various groups of patients, as well as the quality of palliative care offered, and actually received by patients.

Are disparities in outcome related to the attitudes, biases, and values of health care providers toward different populations? Could these factors be addressed by physician training in connection with specific areas deemed worthy of remediation, e.g., failure to diagnose breast cancer in young black women, or failure to
provide full doses of radiation or chemotherapy to elderly or obese patients?

The issue of treatment costs must be addressed in research, particularly as more patented drugs for the high-risk and metastatic population are approved, costs continue to spiral, and issues of universal access to care are deferred. It would be important to have research that documents the actual dollars spent in treating high-risk and metastatic breast cancer in California, as well as any potential disparities in such expenditures on behalf of different patients across racial/ethnic, socio-economic, and age groups. Understanding how these data may relate to outcome data would serve to clarify some of the fundamental questions raised in this paper. These data would clearly provide important data for health policymakers.

A Final Word…

It’s my hope that this report will be of some assistance in bringing into view some of the more challenging needs of California women diagnosed with high-risk and metastatic breast cancer.

As an advocate, I hope one day to see the bright light of evidence shed on even the most difficult social dilemmas—a light so brilliant, with data so clear and persuasive, that we as a people cannot fail to finally address the issues before us, instead of turning away, as we so often do. Clearly, the disparities reflected in the outcome data in breast cancer in California, as elsewhere, point directly to the most difficult social problems we face today: racial and class discrimination, poverty, rising health care costs, diminishing quality in medical care, the continued persistence of life-threatening cancers despite billions of dollars in research, and, of course, the incalculable loss of thousands of women and men each year to breast cancer.

I commend the California Breast Cancer Research Program for your consideration of these challenging issues in breast cancer research. May your program continue to serve as a model, offering support and encouragement to researchers willing to take up this challenge, inspiring them with the dream and the possibility that their research will one day make a difference.
Notes

1 Personal communication with S Cooper, information specialist, NABCO, 2001.


Ibid.


California Cancer Registry, file aug28RSRbreast.xls.


