

## Race/Ethnicity

### Introduction

This chapter provides an overview of research aimed at elucidating disparities across racial/ethnic groups in breast cancer incidence and outcomes. Following a discussion of race and ethnicity, their conceptual frameworks, and some general issues surrounding how these concepts are typically categorized for health research, the review of the literature is organized according to the continuum in breast cancer burden, from incidence to mortality.<sup>1</sup>

### **Historical and Political Conceptualization of Race and Ethnicity**

The concept of race in this country is interwoven with a contentious sociopolitical history. Probably no other health research concept has generated so much passionate debate.<sup>2-4</sup> Freeman states that race is “perhaps the single most defining issue in the history of American society,” despite the fact that there is no genetic basis for racial classification.<sup>5</sup> Views in this debate range from calling for the elimination of race and its commonly-used categories altogether from health research, as continuing their use perpetuates racism in society;<sup>6,7</sup> to viewing race as strictly a sociocultural construct with no biological basis;<sup>3,4,8</sup> to affirming that the modern concept of race and its categorization indeed have biological significance and ramifications in biomedical science.<sup>2</sup>

Categories of race and ethnicity have been used inconsistently across research efforts.<sup>9</sup> The classification scheme established by the Office of

Management and Budget (OMB; Executive Office of the President) is used for federal reporting purposes, including the U.S. Census. In 1997, and in preparation for Census 2000, OMB revised its Statistical Policy Directive No. 15 by modifying its established categories for race and ethnicity to include five race groups: “White”, “Black or African American”, “Asian”, “American Indian and Alaska Native”, and “Native Hawaiian and Other Pacific Islander.”<sup>10</sup> This classification scheme appears to emphasize ancestry.<sup>2, 11, 12</sup> Ethnicity is a concept based more on cultural traditions, reflecting commonalities in history and possibly genetic heritage,<sup>2, 11, 12</sup> and is addressed by OMB in reference to “Hispanic origin” in two categories: “Hispanic or Latino” or “Not Hispanic or Latino”. According to the OMB, race and ethnicity are not mutually-exclusive categories; individuals of any race can be “Hispanic or Latino.”<sup>10</sup>

The definitions for race and ethnicity commonly used in epidemiologic research appear to be fairly similar to the OMB definitions, with race reflecting more on ancestry and geographical origins, and ethnicity emphasizing shared cultural heritage.<sup>11, 13</sup> By law, federally-funded research (including collection and reporting of data) must use OMB classifications and definitions.<sup>10</sup> In epidemiologic studies, however, it is fairly common for Hispanic or Latino to be considered a separate race category. Relatedly, ethnicity is often used in reference to subpopulations within the major race categories. For example, Chinese, Cambodian and Sri Lankan are three of more than 30 ethnic subpopulations that fall under the rubric of “Asian”; Samoan, Chamorro and Fijian are three of more than 30 ethnicities within the

“Native Hawaiian and Other Pacific Islander” rubric.<sup>14</sup> Furthermore, due to their relatively small census (in comparison with larger race groups), epidemiologists often combine Asians and Pacific Islanders into a single category – “Asian/Pacific Islander” (API) – for strengthened statistical significance.<sup>14</sup> American Indian/Alaska Native populations are often combined into a potpourri category of ‘Other,’ if referenced at all. These federally-used broad categories of race and ethnicity are described below.

**Hispanic or Latino:** OMB defines Hispanic or Latino as “a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin regardless of race.”<sup>10</sup> Persons from the Dominican Republic are also considered Hispanic. Of over 40 million “Hispanics or Latinos” responding to Census 2000, 49 percent identified their race/ethnicity combination as “Hispanic White”, 48.2 percent as “Hispanic-Hispanic”, and 3 percent as “Hispanic Black.” The term Latino is preferred by the American Public Health Association because it reflects the integration of Spanish, indigenous, and African cultures among the people of Latin America.<sup>15</sup>

**White:** White is commonly used to describe persons of lighter skin hue with origins in the populations of Europe (except Spain) and Caucasia. The U.S. Census Bureau defines the “White race” as “people having origins in any of the original peoples of Europe, the Middle East, or North Africa”<sup>10</sup> and includes people who checked the box “White” on the census form or wrote in entries like Irish, German, Italian, Israeli, Lebanese, or Scottish.

**Black or African American:** Black is commonly used for persons of darker skin color with origins in sub-Saharan African populations. The Census Bureau describes “Black or African American” people as having “origins in any of the Black racial groups of Africa”<sup>10</sup> and includes people who checked the “Black, African American, or Negro” box on the census form or provided write-ins of African American, Afro-American, Haitian, or Nigerian when asked to describe their race/ethnicity.

**American Indian and Alaska Native (AIAN):** The Census Bureau defines American Indians and Alaska Natives as persons “having origins in any of the original peoples of North and South America (including Central America) who maintain tribal affiliation or community attachment.”<sup>10, 16</sup> They also include those who report their race as American Indian/Alaska Native or who wrote in their tribal affiliation for the U.S. Census. American Indian/Alaska Native populations are heterogeneous, with many distinct cultures and languages. As Cobb points out, American Indian/Alaska Natives “live in environments ranging from the deserts of the Southwest to the Alaskan tundra.”<sup>17</sup> Currently, there are 562 federally-recognized tribal entities in the U.S. and many more recognized by individual states. One-hundred and seventy-five Native American languages are still spoken in the U.S.

**Asian or Pacific Islander (API):** Beginning with Census 2000, the U.S. Census Bureau collected and reported its decennial census data using new and separate definitions for “Asians” and “Native Hawaiians or Other Pacific Islanders.” “Asians” are defined as “people having origins in any of the

original peoples of the Far East, Southeast Asia, or the Indian subcontinent,” including, but not limited to, people from China, Japan, Korea (Far East); Cambodia, Thailand, Vietnam (Southeast Asia); and India, Pakistan, Sri Lanka (Indian subcontinent).<sup>10</sup>

### **Native Hawaiians or Other Pacific Islanders**

(**NHOPI**) are defined as “people having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.”<sup>10</sup> Although OMB classified Native Hawaiian and other Pacific Islanders in their own race category in 1997, the National Cancer Institute (NCI), and other cancer research entities; e.g., the American Cancer Society (ACS), continue to collect and report national cancer surveillance data for these two distinct population groups in the “Asian/Pacific Islander” aggregate, and most research studies do not distinguish between the two broad categories.

### ***The Need for Disaggregated Racial/Ethnic Data***

The practice of collecting and reporting health data in the broad and heterogeneous categories “Asian/Pacific Islander” and “American Indian/Alaska Native” is motivated by the desire for sufficient number of health outcomes to achieve statistical significance when evaluating the data. Unfortunately, this may result in obfuscating important health disparities among subpopulations within these groups.

Unaware of (or perhaps insensitive to) the complexity of heterogeneity of the more than 60 distinct population subgroups contained within the “Asian/Pacific Islander” rubric, the policy and practice of collecting and reporting aggregate

Asian/Pacific Islander breast cancer rates serves to obscure those Asian/Pacific Islander subgroups with high incidence and/or mortality rates.

Additionally, breast cancer control, research and funding decisions based on aggregate Asian/Pacific Islander data serve to further perpetuate the myth that breast cancer incidence and mortality rates remain low across all Asian and Pacific Islander populations; ultimately, these practices will result in even greater breast cancer disparities among some Asian and Pacific Islander women.

For example, in “Cancer Incidence and Mortality in California: Trends by Race/Ethnicity, 1988 – 2001,” the California Cancer Registry (CCR) reports that invasive female breast cancer incidence rates for Asian women remain lower than other groups.<sup>18</sup> However, disaggregation of Asian/Pacific Islander breast cancer data reveal substantial increases in breast cancer incidence rates for Japanese, South Asian, Chinese and Korean women. Since 1988, California breast cancer mortality rates have either decreased or exhibited minimal change, while mortality rates among the state’s South Asian women and Filipinas rose slightly during this period. However, in a recent joint ACS/CCR report,<sup>19</sup> trend tables of breast cancer incidence and mortality showing aggregate Asian/Pacific Islander breast cancer rates over the same time period all but obscure rate increases seen in specific Asian populations when such data are disaggregated.

Key to understanding critical breast cancer surveillance data for U.S. Asian, Native Hawaiian and other Pacific Islander women is knowledge of

their U.S. census and demographics, and the impact of nativity, immigration, and generation in the U.S. for Asian/Pacific Islander subpopulations on reported cancer surveillance data.<sup>14</sup> Nationally, the Asian/Pacific Islander census has doubled each decade since 1970, from 1.5 million to nearly 13 million for Census 2000. Since 1990, the Asian/Pacific Islander population has grown 41 percent – faster than any other U.S. race or ethnic group. In 2005, the aggregate Asian/Pacific Islander census was 15,366,331, of which 989,673 were Native Hawaiian and other Pacific Islander (6.4 percent) and 14,376,658 were Asians (93.6 percent). Comprised within the aggregate “Asian/Pacific Islander” rubric are more than 30 different Pacific Islander subpopulations and more than 30 diverse Asian ethnic groups. Globally, more than 2,000 distinct Asian and Pacific Island languages and dialects are spoken, of which ~100 are commonly spoken in the U.S.<sup>20</sup>

In Census 2000, 69 percent of Asians and ~20 percent of Pacific Islanders reported nativity outside the U.S. Research reveals immigrant populations are more likely to experience significant language barriers and social isolation, and to be socioeconomically disadvantaged.<sup>21</sup> An important but often-overlooked factor in Asian/Pacific Islander heterogeneity is the bimodal distribution of socioeconomic status between subpopulation groups.<sup>22</sup> Spanning the socioeconomic status continuum, within the Asian/Pacific Islander rubric exist those groups with the highest and lowest levels of English language proficiency, educational attainment, income, coverage and quality of medical insurance, and numerous other markers of social class in the U.S. Although Census 2000 reports

Asian/Pacific Islander (aggregate) populations to have the lowest (11 percent) poverty rate in the U.S., second only to non-Hispanic whites (8 percent), only three Asian American subgroups (Filipino, Japanese and Asian Indian) and no Pacific Islander subgroup had poverty rates at or below the U.S. national average (12 percent). Hmong (38 percent) and Cambodian (29 percent) populations had the highest poverty rates. Despite the number and extent of poor and medically underserved subgroups within the Asian/Pacific Islander rubric, aggregate collection and reporting of demographic and health data continue to obscure troubling health disparities.

Of course, there are valid situations in which aggregate data reporting is useful and desired. The ability to track trends over time and between major population groups are examples of such situations; the advent of health disparity research has relied heavily on these important contributions to the literature. Nonetheless, it is important to recognize the adverse impact aggregate reporting of data has had on communities. Advances in detailed, population-specific research aside, studies reporting aggregated race/ethnicity data continue to dominate the biomedical literature. Thus, for our review of the literature, we will try to highlight studies that provide detailed race and ethnicity data as much as possible. Where the research limits our efforts, we will cite the available literature, cautioning the reader regarding the reliability (or lack thereof) of aggregate data across all or most Asian and Pacific Islander populations.

## **Genetics and Race/Ethnicity**

The degree to which health disparities are the result of genetically-driven biologic differences between racial/ethnic groups has long been a source of contention. The recent advent of bioinformatics has given researchers new tools to evaluate this issue. Some researchers argue that genetic clustering generally corresponds with the continental groups described above, while others find that genetic groupings diverge from traditional racial/ethnic categories.<sup>12, 23</sup> In addition, relatively little is known about the interaction of environmental and genetic factors.

The initial analysis of human genome commonalities between individuals and racial/ethnic groups has yielded complicated results. There are no “African,” “Caucasian” or “Hispanic” genes, but a differential proportionate distribution of alleles across populations. There is greater variation between individuals than between groups (no matter how they are defined), even though individuals with the same geographic ancestry are more similar to each other on average than to individuals with different geographic ancestries.<sup>24</sup> Some researchers report that they find good correlation between the self-reported race and racial groupings based on continental origins.<sup>12</sup> However, others warn that the groupings may not be as clear-cut as they first appear, because of possible overclustering<sup>25</sup> and a lack of true diversity in the sample population.<sup>24</sup> Additionally, there is disagreement about whether the broad continental groupings will be predictive of the presence of specific variants in individuals based on their group membership. The admixture of populations, particularly in the U.S., could

require genetic assignment on the individual level according to a continuum, rather than discrete separations into categories. This debate becomes important when trying to determine whether this method of grouping populations can ultimately be used to inform individuals about biological risks and whether it could be used to predict drug responses.<sup>12, 26, 27</sup> However, it is still unknown whether race categories and/or the continuum of race groupings are biomedically useful or predictive of treatment response, independent of genetic factors.

Efforts to characterize the magnitude and impacts of these issues as well as strategies for addressing them have been attempted, and more have been proposed and are underway. The National Institutes of Health (NIH) has released at least two relatively recent program announcements to address these broader methodological issues, and resources such as the International HapMap database<sup>28</sup> and the Human Genome Diversity Cell Line panel<sup>29</sup> are being developed to investigate the relationship between genetic clustering in populations and race. While acknowledging the need for these methodological efforts that are necessary to improve research on race/ethnicity,<sup>30, 31</sup> we focus this section on documenting the breast cancer disparities across the standard OMB racial/ethnic groups, with attention to identifying gaps and future directions for moving beyond these categories to better understand underlying factors responsible for the disparities.

**Overview of the literature, by outcomes in breast cancer continuum**

**Incidence**

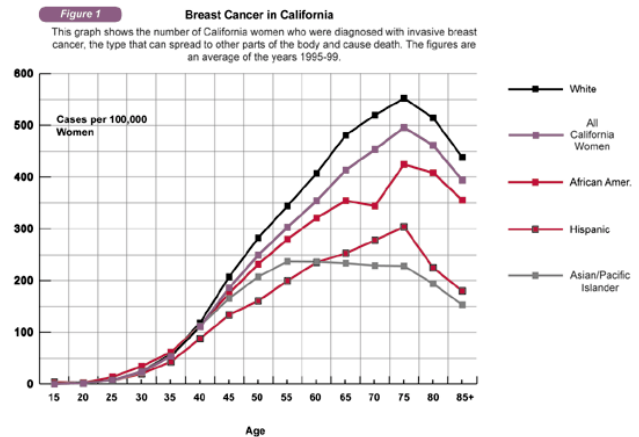
Breast cancer incidence varies markedly by race/ethnicity in the U.S., with the highest age-adjusted rates (130-140 per 100,000) in non-Hispanic white and Native Hawaiian women, intermediate rates in African American, Japanese and Filipina women (80–120 per 100,000), and lower rates in Hispanic, Chinese, South Asian, Vietnamese, and Korean women (50–79 per 100,000).<sup>18</sup> Thus, among women living in the same country, breast cancer rates can have up to a three-fold variance solely on the basis of racial/ethnic classification.

Racial/ethnic differences in age-specific incidence of breast cancer are well-described for the broad OMB-defined racial/ethnic groups. For example, Figure 1 below summarizes age-specific incidence of invasive breast cancer in California (1995–1999) as described in a recent report from the California Cancer Registry.<sup>32</sup> It illustrates the high rates among non-Hispanic white women and the relatively low rates among Asian/Pacific Islander and Hispanic women. It also illustrates the long-recognized ‘cross-over’ phenomena where the rates for young women are higher for black than for non-Hispanic white women but then reverse in older women, such that non-Hispanic white women have the higher rates.<sup>33</sup>

The presentation of aggregate data such as these, however, masks the high incidence rates among certain Asian/Pacific Islander subpopulations, such as Native Hawaiians and Japanese Americans.<sup>34</sup> Furthermore, it suggests that age-specific incidence rates among Asian/Pacific

Islander women level off after menopause. Disaggregated California data, reported by National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) program (although for a slightly earlier time period), paints a very different picture, with increasing age-specific rates after age 55 for Chinese, Filipina, Japanese, and Native Hawaiian women.<sup>34</sup>

Temporal trends in breast cancer incidence also vary by racial/ethnic group. However, because of historical constraints in the level of detail collected by population-based registries, most of this evidence has been limited to the last decade or so, and much of it has been limited to the broad



aggregate racial/ethnic groups. Interestingly, incidence rates in women age 50 and under have been stable in most racial/ethnic groups, but have been significantly decreasing in African American women,<sup>19</sup> to the point where the previously observed higher rate among younger African American women relative to white women<sup>33, 35</sup> may no longer exist.<sup>19, 36</sup>

An interesting phenomenon in breast cancer incidence for black and white women is what has been labeled the “crossover” effect. While breast

cancer incidence is highest in non-Hispanic white women, African American women under the age of menopause (approximately 40 – 50) have higher breast cancer incidence rates compared to white women, but have lower rates in older ages.<sup>33,37</sup> Studies have suggested a relationship between the crossover effect and reproductive factors related to socioeconomic status, although previous research is not conclusive.<sup>33, 38, 39</sup> This shifting disparity of the crossover to lower incidence rate in older women differs by stage at diagnosis. The crossover occurs at age 35–39 years for localized stage, and at ages 55–59 for regional stage. For distant stage, black women of all ages experienced higher incidence compared with white women. Similar crossover effects do not exist for American Indians or Asians/Pacific Islanders compared to white women, or for Hispanic women compared to non-Hispanic women.<sup>37</sup>

Another relevant age-related phenomenon is Clemmenson’s Hook, which describes a shift in the slope of breast cancer incidence rates around the time of menopause. Incidence rates continue to increase following menopause for women of all race and ethnic groups in the U.S., although at a much slower rate of increase compared to pre-menopause increases. The rate of increased incidence following menopause for Asian/Pacific Islander women in the U.S. is even lower than that of whites and blacks, but is important to note, because for at least one subpopulation of Asians/Pacific Islanders, Japanese women born in Japan, incidence rates decline following menopause.<sup>40, 41</sup> This significant difference indicates the impact of environment on breast cancer incidence.

While incidence rates appear to be stable in most of the broad racial ethnic groups from 1988-2001, a more detailed examination of the disaggregated statewide data reveals some alarming trends. Most notably, incidence rates increased among Japanese, South Asian, Chinese, and Korean women.<sup>18</sup> Furthermore, in a detailed study of breast cancer diagnosed in Los Angeles (L.A.) County, California, significant differences were noted among the more detailed subgroups of Asian/Pacific Islander women, with a greater than two-fold difference in the 1997 incidence rates for Filipinas over Korean women, and for Japanese over Chinese women.<sup>42</sup> This study also reported a very sharp rise in incidence rates for Japanese American women, such that continuance of this trend may result in Japanese American breast cancer incidence rates in L.A. County exceeding those of non-Hispanic-white women in the near future.<sup>42</sup>

Breast cancer incidence among American Indians and Alaska Natives has been challenging to monitor, owing mostly to difficulties in accurate identification of these groups in cancer registry settings, lack of reliable denominator data, and unstable rate estimates due to small numbers. This misclassification bias is a significant problem with no easy solution. Misclassification could explain the particularly low incidence rates for American Indian and Hispanic women. Prior to expansion of SEER, the only American Indian data came out of the relatively healthy American Indian groups in New Mexico, thus limiting the numbers and reliability of the data. Often rate estimates are so unstable that they are not presented separately for American Indians/Alaska Natives. Historically, it has been reported that American Indian/Alaska

Native women have low breast cancer incidence rates.<sup>43</sup> Recently, however, it has been argued that data are really inadequate for fully ascertaining the breast cancer experience in this group of women. Most data on American Indians/Alaska Natives come from either SEER or the Indian Health Services (IHS).<sup>44</sup> Approximately 75 percent of the American Indian population in the SEER data come from Arizona and New Mexico, but only 19 percent of the American Indian population live in these states.<sup>45</sup> Furthermore, breast cancer rates may be lower among southwestern American Indians than other American Indians/Alaska Natives. Data from the IHS also potentially undercount breast cancer cases because they are based on hospital discharges only and because many American Indians/Alaska Natives do not receive care at the IHS.<sup>44</sup> Linkages with the IHS have improved classification. However, over half of all American Indians/Alaska Natives live in urban areas, are part of unrecognized tribes, or otherwise may not have access to IHS. Regardless, IHS-enhanced estimates of incidence rates for American Indians in New Mexico and Alaska Natives in Alaska suggest that rates for American Indians/Alaska Natives may be substantially higher, perhaps as much as four-fold higher, than rates in U.S. white women.<sup>46</sup>

By virtue of their close interrelationships, it is difficult to interpret racial/ethnic differences in breast cancer incidence without consideration of socioeconomic status and immigration status. However, joint relationships among these factors are difficult to study using population-based cancer registry data, owing to deficiencies in available numerator and denominator data. Several studies<sup>47, 48</sup> have documented that

racial/ethnic differences in invasive breast cancer incidence persist after adjustment for area-level socioeconomic status. For example, among Californians living in areas of the highest socioeconomic quintile, rates were 87 percent higher in non-Hispanic whites, 52 percent higher in African Americans, and 31 percent higher in Hispanics, compared to Asian women.<sup>47</sup>

While there appear to be few recent studies assessing racial/ethnic differences according to immigration status, there is a well-established body of literature documenting differentials in breast cancer risk among Asian women according to acculturation status. These studies show that breast cancer risk increases with generational status in the U.S., and with time since migration, even within a woman's lifetime.<sup>49</sup> In women under age 54, risk almost doubled in foreign-born women who lived in the U.S. for 18 years or longer, compared to those who lived in the U.S. for two-seven years.<sup>50</sup> However, even among long-term foreign-born residents, risk remained lower than in U.S.-born Asian Americans. As with Asians, the incidence of breast cancer in Hispanic women is strongly influenced by migration patterns and acculturation. Incidence rates are twice as high in U.S.-born Hispanics as in foreign-born Hispanics, and increase with increasing duration of residence in the U.S. and over successive generations.<sup>51</sup>

Certain racial/ethnic groups in California are markedly heterogeneous with respect to immigration status. Higher breast cancer incidence rates in acculturated subgroups may be masked by very low rates in recent immigrants. The changing associations of incidence rates with

socioeconomic status over time observed by Krieger support an interactive role of acculturation and socioeconomic status having an impact on incidence among Asians, Pacific Islanders, and Hispanics.<sup>48</sup>

### ***Breast cancer subtypes***

Potential racial/ethnic disparities in the incidence of specific subtypes of breast cancer generally have not been explored at the population level. A recent study, however, suggests that substantial differences in tumor characteristics exist across racial/ethnic groups in the U.S.<sup>52</sup> This study reported that relative to non-Hispanic whites, the risks for estrogen/progesterone receptor-negative breast cancers were elevated for African Americans, American Indians, Filipinos, Chinese, Koreans, Vietnamese, Indians/Pakistanis, Mexicans, South/Central Americans, and Puerto Ricans, with risk estimates ranging from 1.4 to 3.1. The investigators' analysis of rates by histologic subtype confirmed previously documented reports of higher rates of lobular cancers among non-Hispanic white women compared to all other groups.<sup>32</sup> and revealed significantly different risks across racial/ethnic groups for five of the seven histological subtypes examined. Similar racial/ethnic differences in tumor characteristics have been documented in California populations as well.<sup>53, 54</sup>

DNA microarray analysis of breast tumor characteristics has led to a new classification scheme.<sup>55</sup> Tumors can be divided into clinically relevant subcategories (luminal A, luminal B, basal-like and erb-B2) that have biologically distinct mechanisms.<sup>56, 57</sup> Using this classification, a recent study has found that the basal-like

subtype, which correlates with the worst prognosis, was more prevalent in pre-menopausal African Americans than in any other population examined.<sup>58</sup>

Differences in tumor biology may reflect differential genetic susceptibilities and/or differential exposures to environmental contaminants or established risk factors (e.g., association of HRT use with lobular subtype), and may relate to certain clinical differences in breast cancer observed among racial/ethnic groups, including later stage at diagnosis and poorer outcomes. The California Cancer Registry now routinely collects information on tumor hormone responsiveness, histologic subtype, and Her-2-neu status. More studies similar to the one conducted by Li and colleagues,<sup>52</sup> including those in younger women, may help elucidate the degree to which such differences in tumor biology may play a role in racial/ethnic disparities in breast cancer treatment, survival, and mortality.

### ***Incidence: Conclusions and future directions:***

Overall, non-Hispanic white women bear the greatest burden of breast cancer incidence. An important area for future research is to identify groups with possibly under-recognized risk. This most certainly should involve examination of racial/ethnic differences in breast cancer incidence by detailed racial/ethnic subgroup, socioeconomic status and immigration status. Racial/ethnic disparities in the incidence of breast cancer by histologic subtype and tumor hormone responsiveness generally have not been well documented and warrant further attention. Because it appears that recent temporal trends in

breast cancer incidence rates vary by racial/ethnic group, it is important to continue to monitor these patterns of incidence, both to generate hypotheses related to etiology and to target prevention and cancer control strategies.

The very limited data on American Indians and Alaska Natives suggesting potentially high rates of breast cancer incidence<sup>46</sup> warrants further attention and underscores the need to develop better data ascertainment methods to document the cancer experience of this population in the U.S.

Population-based cancer registry data represent the major source for measuring and tracking racial/ethnic disparities in breast cancer incidence. Cancer registry data, however, are narrow in scope, consistent with mandates to broadly collect information for all cancers diagnosed in defined geographic areas, and the data are based on medical records. They do not include important information available from other sources on personal risk factors for breast (e.g., pregnancy history, hormone replacement therapy use) or on potential exposures to chemical contaminants in the environment or occupational settings. Supplementing CCR data--through linkages to administrative data from Medicare, Medicaid and large health maintenance organizations such as Kaiser--could greatly enhance the use of these data to evaluate cancer disparities. While tumor registries have limitations for assessing etiology, their use has been increasing in evaluating treatment patterns and quality of care.

## Etiology

The reasons for the pronounced racial/ethnic disparities in breast cancer incidence are only partially understood, because until recently, relatively few epidemiologic studies have been conducted in non-white populations. Several large cohort and case-control studies that include non-white women were initiated in the 1990s and have started to produce important data towards a better understanding of breast cancer risk factors in African American, Hispanic, and Asian American women. Examples include the Multiethnic Cohort Study,<sup>59</sup> Women's Health Initiative,<sup>60</sup> Black Women's Health Study,<sup>61</sup> WISH Study,<sup>62</sup> New Mexico Women's Health Study,<sup>63</sup> Carolina Breast Cancer Study,<sup>64</sup> CARE Study,<sup>65</sup> San Francisco Bay Area Breast Cancer Study,<sup>66</sup> Northern California Family Registry for Breast Cancer,<sup>67</sup> Los Angeles Breast Cancer Study in Asian Americans,<sup>68</sup> and the Four Corners Breast Cancer Study.<sup>69</sup> For American Indian and Alaska Native women, information on breast cancer risk factors is still very limited.<sup>70</sup>

Differences in the *prevalence* of known risk factors (hormonal and lifestyle factors) are likely to contribute to racial/ethnic disparities in incidence. It remains uncertain whether the *magnitude* and *direction* of associations with known risk factors differ between racial/ethnic groups. Few studies have examined the contribution of environmental exposures to the observed racial/ethnic disparities in breast cancer incidence. Differences in genetic susceptibility and in combined effects of genetic and hormonal/lifestyle/environmental factors may also

influence breast cancer incidence and contribute to disparities.

### **Racial/ethnic differences in hormonal and lifestyle factors**

Most research to date aimed at elucidating etiologic factors underpinning the noted racial/ethnic disparities in incidence has focused on the degree to which racial/ethnic differences in the *prevalence* of established risk factors are likely to contribute to racial/ethnic differences in incidence. Epidemiologic studies that reported on breast cancer risk factors in African Americans,<sup>35, 59-62, 64-66, 71-79</sup> Hispanic,<sup>59, 60, 63, 66, 69, 80, 81</sup> or Asian Americans<sup>50, 59, 60, 68, 77, 82</sup> demonstrate wide variation in the prevalence of risk factors between racial/ethnic groups in the U.S. The prevalence has been shown to vary by place of birth (U.S.-born versus foreign born)<sup>59, 81, 83</sup> and acculturation<sup>81</sup> and to change over time.<sup>84</sup> While in general, the prevalence of factors that increase or decrease risk tend to parallel incidence rates, there are numerous exceptions and inconsistencies, suggesting a complex interplay of multiple factors and the likely importance of yet-to-be identified factors that underlie the risk in specific racial/ethnic groups.

There is some evidence that the relationship of breast cancer risk with known risk factors may not be the same (in *direction* and/or *magnitude*) across all racial/ethnic groups. For example, in non-Hispanic white women, it has been well established that breast cancer risk increases with decreasing age at menarche.<sup>85, 86</sup> This relationship, however, has not been as consistently documented among African American women, with some studies reporting an inverse

association<sup>64, 72</sup> and others reporting a positive or no association.<sup>62, 75, 79, 87</sup> Likewise, studies in Hispanic women have produced mixed results. Later menarche has been associated with increased risk in some studies,<sup>63, 80</sup> and decreased risk among foreign-born, but not U.S.-born, Hispanics.<sup>87</sup> For Asian/Pacific Islander women, an inverse association has been reported that is similar to that seen in white women.<sup>83</sup>

Similar inconsistencies across racial/ethnic groups in either the *magnitude* and/or *direction* of the risk relationship have been reported for several other risk factors, including parity, age at first full-term birth, breast-feeding, and oral contraceptive use.<sup>61-65, 79, 87</sup> These inconsistencies may in part be due to the relatively small numbers of non-white women included in the above studies and heterogeneity in risk due to immigration status. Differences in underlying biologic mechanisms may also play a role, as has been suggested, for example, for the effect of body size.<sup>69</sup>

### **Racial/ethnic differences in genetic/biologic factors**

There is emerging evidence that genetic factors that contribute to the development of breast cancer may also differ by race/ethnicity and may contribute to racial/ethnic differences in incidence. For example, deleterious mutations in BRCA1 and BRCA2 are more common in Ashkenazi Jewish women than non-Jewish white women and non-whites, and African Americans appear to have a different spectrum of BRCA1 and BRCA2 variants than white women. Few studies to date, however, have investigated BRCA1 and BRCA2 mutations in non-white populations. The prevalence of common genetic variants, such as

single nucleotide polymorphisms (SNPs), also varies by race/ethnicity, as documented in various HuGE reviews.<sup>88</sup>

Researchers have linked risk disparities to germ line mutations such as BRCA1/2 and/or differential gene/environment interactions in culturally-shared behavior or geography.<sup>89, 90</sup> Fewer studies have been performed looking at differences in epigenetic changes,<sup>91, 92</sup> but studies in this area may give more clues to differential gene/environment interactions.

Increasingly, molecular epidemiologic studies assess breast cancer risk in relation to genetic variants in specific pathways, primarily comparing Caucasians and African Americans. Porter et al.<sup>93</sup> conducted a study looking at the expression of cell cycle regulatory genes, among other factors, in grade-matched tumors from African American and Caucasian women. They found reduced levels of cyclin D and elevated levels of cyclin E and p21 in the tumors of African American women, which are all hallmarks of tumors with poor prognosis. Other studies have reported that the ethnic disparity in genetic mutation may lie in the types of mutations rather than the frequency. For example, Shiao et al.<sup>94</sup> found similar rates of p53 mutation rates in African Americans and Caucasians, but observed that African Americans had more G:C to A:T mutations and Caucasians had more A:T to G:C mutations. This variation in mutations may indicate a difference in carcinogen exposures.

Many associations are based on small sample sizes, and often not replicated in larger studies. Several studies in non-white populations cited above have collected blood samples (e.g., the

Multiethnic Cohort Study, Carolina Breast Cancer Study, CARE Study, San Francisco Bay Area Women's Health Study, Northern California Family Registry for Breast Cancer) and have begun assessing breast cancer risk in non-white populations in relation to genetic variants in different pathways, as well as the modifying effect of lifestyle and environmental factors.<sup>95-101</sup>

There has been speculation that racial/ethnic differences in endogenous hormone levels may partially explain some of the racial/ethnic disparities in breast cancer incidence, particularly with respect to the high rates among Native Hawaiians and young African American women, both of whom have been reported to have high levels of pre-menopausal estrogen and progesterone. Pike et al.<sup>59</sup> speculated that the strikingly high incidence of breast cancer seen among Native Hawaiians in the Multiethnic Cohort Study may be due to a) higher endogenous pre-menopausal serum estrogen and/or progesterone levels, which may have a carryover effect on post-menopausal breast cancer risk; b) elevated post-menopausal serum estrogen levels and differences in the distribution of genetic polymorphisms in the sex steroid and gonadotropin metabolism pathways; c) elevated insulin-like growth factor levels; or d) dietary factors.

### ***Interactions of Genetics, Lifestyle/Environment, Socioeconomic Status, and Race/Ethnicity***

Differences in proportions of tumor markers by specific race/ethnic group are most likely due to variables other than race for women diagnosed with breast cancer in the U.S., where it is widely

known that race is strongly correlated with socioeconomic status. In addition, several significant lifestyle/environmental etiologic factors for breast cancer are strongly correlated with race and socioeconomic status. These known and suspected etiologic factors include lactation history, patterns of oral contraceptive use and menopausal hormone use, age at first birth, parity, BMI/obesity, physical activity, and alcohol use.

The impact of the interaction of these factors with genetics, race, and socioeconomic status is mostly unknown, but hypotheses are beginning to emerge from the literature. For example, studies show that increased parity and younger age at first birth are associated with decreased risk of breast cancer. These protective factors are more prevalent among African American women and women of low socioeconomic status.<sup>102, 103</sup> However, these factors that reduce the risk of breast cancer are associated with poor prognostic markers and breast cancer subtypes.<sup>104</sup> It is hypothesized that these risk factors are partially responsible for African American women diagnosed with breast cancer presenting with disease characteristics associated with poor prognosis, such as younger age, advanced stage, and biologically aggressive tumors, as found in several studies including.<sup>105-108</sup>

Results of studies that examine the combined effect of race and socioeconomic status have been mixed in determining whether race is an independent significant predictor of breast cancer prognosis apart from socioeconomic status.<sup>105-107, 109-114</sup> However, the majority of well-done studies have concluded that if socioeconomic status, treatment, prognostic tumor markers, and comorbidity are equivalent--or are all controlled in

multivariate statistical analyses--race is not a factor in breast cancer outcome. Studies show these confounders are not equally distributed by race and/or socioeconomic status in women diagnosed with breast cancer.<sup>108, 115, 116</sup>

### ***Etiology: Conclusions and future directions***

We have yet to fully understand the etiologic factors underpinning the observed racial/ethnic disparities in breast cancer risk. Much of the research to date has been aimed at comparing the prevalence of known risk factors across racial/ethnic groups. Several studies have concluded that known risk factors do not fully explain the differences in incidence<sup>59</sup> or risk<sup>51, 60</sup> between racial/ethnic or migrant groups.<sup>51, 59</sup> These studies generally have focused on reproductive and menstrual factors, while dietary and other behavioral risk factors, such as physical activity and smoking, have received comparatively less attention. Almost completely ignored in the literature to date is an examination of the degree to which exposures to environmental contaminants play a role in racial/ethnic disparities in risk. The currently known breast cancer risk factors, which were primarily identified by studying white women, explain only about half of all breast cancers in white women.<sup>62, 117-121</sup> Furthermore, it is not entirely clear that these factors impart the same risk in other racial/ethnic groups. Thus by limiting our evaluation of racial/ethnic differences to these factors, we are inherently hindering our ability to fully explain racial/ethnic disparities in breast cancer.

One of the fundamental challenges in studying racial/ethnic disparities in breast cancer is

disentangling the effects of genetics, socioeconomic status, immigration status, and potential exposures to environmental contaminants. There is evidence that racial/ethnic disparities persist after adjustment for socioeconomic status and vice versa. While difficult to conduct, research focused on women that are discordant for these factors may help tease out the independent effects of these highly correlated factors.

Consideration of exposures to chemical contaminants through the workplace or ambient environment generally has not been considered in the body of literature on racial/ethnic differences in breast cancer incidence and risk. The strong regional variations observed in breast cancer incidence, with rates highest in urban and industrialized areas, suggest a potential role for these types of exposures. While overall, non-white populations (who tend to have lower rates of breast cancer incidence), are more likely to live in highly polluted areas, there may be some specific exposures more common to white women that have yet to be identified. Furthermore, the potential role of environmental contaminants in explaining the modestly higher rates of breast cancer incidence among young African American women largely has been ignored. Future research aimed at elucidating factors responsible for racial/ethnic disparities in incidence needs to move beyond considering solely the known breast cancer risk factors to identify and include occupational, environmental, and social factors.

## Screening

Historically, non-white women have had lower rates of mammography screening than have white

women in the U.S. After nearly two decades of health promotion efforts to improve mammography screening rates, racial/ethnic disparities have been greatly reduced, especially in California. In its publication Healthy People 2010 (HP2010), the CDC set out as a national objective to achieve 70 percent of women age 40 and older having received a mammogram in the previous two years.<sup>122</sup> Most recent data reported by the 2001 California Health Interview Survey (CHIS),<sup>123</sup> indicate this goal has been reached in nearly all racial/ethnic groups in California, with the rate exceeding the HP2010 goal in white and African American women, and lagging slightly among Native Hawaiians and Pacific Islanders (Table 1).

Table 1. Women in California age 40+ who reported having a mammogram during the last two years by race/ethnicity, 2001.\*

Race/Ethnicity	Mammography use	
	% Screened in past 2 years	% Never Screened
White	78.1	8.1
African American	78.5	9.4
Hispanic	69.9	17.7
Asian	67.2	17.2
Native Hawaiian/other Pacific Islander	63.4	§
American Indian/Alaska Native	68.8	10.0
All Women age 40 and older	75.5	10.7

\* Source: 2001 California Health Interview Survey<sup>123</sup>

While the increases in mammography utilization over the last twenty years can be counted as one of the great successes of health promotion efforts within the public health community, these summary data mask some important pockets of remaining disparities in utilization. Specifically, an examination of screening rates by age indicates that screening rates among women age 40-49

## Identifying Gaps in Breast Cancer Research

years of age still fall short of the HP2010 goal for all racial/ethnic groups except African Americans.<sup>32</sup> Additionally, disparities in mammography utilization among subpopulations within these broad racial/ethnic groups persist.

A recent analysis of the 2001 CHIS data with a more detailed categorization of Asians revealed significant differences in mammography screening among specific Asian ethnic subgroups, with Cambodians and Koreans having significantly lower rates of utilization (Table 2).<sup>124</sup> Although no recent California data has been published by specific subgroups within Hispanic women, there is evidence that screening rates within the Hispanic population are likely to vary by country of origin, socioeconomic status, and level of acculturation.<sup>125</sup>

**Table 2. Women in California age 40+ who reported having a mammogram during the last two years by detailed Asian ethnicity, 2001.\***

Population subgroup	% Reporting mammogram in past 2 years
Chinese	64.6
Filipino	71.5
Japanese	76.4
Vietnamese	71.3
Korean	53.1
South Asian	69.6
Cambodian	56.6

\* Source: 2001 California Health Interview Survey<sup>124</sup>

Major research efforts have sought to explain the factors underlying the well-documented underutilization among some Asian and Pacific Islander women. Asian/Pacific Islander women often share many of the structural barriers with other minority women, including lack of

insurance, lack of health care access, low socioeconomic status, lack of a usual source of care,<sup>90, 126-129</sup> and lack of encouragement by physicians.<sup>90, 130</sup> Sociocultural factors, including low level of education,<sup>127, 131</sup> limited knowledge of breast cancer,<sup>130</sup> and low English proficiency<sup>90, 132</sup> have been found to be associated with low mammography utilization among Asian/Pacific Islander women. Furthermore, level of cultural assimilation, often measured by length of U.S. residency and English proficiency, has also been a critical determinant of mammography.<sup>90, 132</sup> Additionally, some qualitative studies using focus groups and key informant interviews have explored cultural beliefs that underlie health-seeking behaviors.<sup>129, 130, 133</sup> These studies have identified other perceived barriers to utilization, including having a male physician, fear of being exposed unnecessarily to radiation,<sup>90</sup> and the lack of sensitivity from hospital staff regarding their embarrassment of having to undress for a mammogram, which often discouraged them from returning for subsequent visits.<sup>133</sup> Similarly, other studies have shown a potential interaction between immigration status, cultural beliefs, and income (or other socioeconomic status-related variables) for perceived barriers to breast cancer screening.<sup>134, 135</sup> Unfortunately, many of these variables overlap with one another and are hard to measure quantitatively. Regardless, these studies illustrate the complexity with which the structural and sociocultural barriers operate in this heterogeneous population.

### **Screening: Conclusions and future directions**

Health promotion efforts in the last few decades have greatly increased mammography screening rates and have helped reduce racial/ethnic disparities in mammography utilization. With the few notable exceptions discussed above, mammography rates in California have generally reached HP2010 goals across all broad racial/ethnic groups. More detailed analyses suggest that sociodemographic characteristics beyond race/ethnicity may be more important predictors of mammography utilization. Recent data from both CHIS and the California Women's Health Survey (CWHS) suggest that lack of health insurance may be one of the largest contributors to underutilization of screening mammography among all racial/ethnic groups.<sup>123, 136</sup> Only half of uninsured California women ages 40-64 report having a mammogram in the past two years, with uninsured Asians reporting the lowest screening rate (39.5 percent).<sup>123</sup> Having a usual source of care also appears to be an important predictor of mammography utilization, with women who have no usual source of health care reporting screening rates below 45 percent, regardless of race/ethnicity.<sup>123, 137</sup> (For more, see Section II, Chapter E.) These data suggest that rather than targeting specific racial/ethnic groups, it may be more effective to target interventions towards lower-socioeconomic-status women, particularly recent immigrants, and women with no health insurance and/or usual source of health care.

The ultimate goal of increasing screening rates and reducing racial/ethnic disparities in screening is to reduce the corresponding mortality associated with

late-stage diagnoses. Controversy remains as to whether further efforts to increase screening will significantly improve racial/ethnic disparities in survival.<sup>138</sup> As discussed later in this chapter, despite having the highest mammography screening rates, African American women continue to be diagnosed at later stages and have worse survival rates than all other groups. This begs the question in terms of both the biology and post-diagnostic treatment of these cancers.

It may be that the HP2010 goal of 70 percent having had a mammogram in the last two years is not the yardstick by which to measure success. Debate persists over the ideal interval between screening mammograms, especially among women age 40-49.<sup>139</sup> Some consider 'full breast cancer screening' to also include annual clinical breast exams.<sup>136</sup> The American Cancer Society (ACS) and the California Department of Health Services recommend that women age 40 years and older receive both an annual mammogram and annual clinical breast exam.<sup>140, 141</sup> Recent California survey data suggest that only a little more than half of women 40 years of age and older meet this guideline, with similar racial/ethnic patterns as those seen for mammography usage within the last two years.<sup>136</sup> However, the efficacy of mammography screening in women under age 50 years remains a source of debate.<sup>142</sup> Breast tissue in younger women is more sensitive to radiation and is denser, making mammograms less effective.<sup>143</sup>

Finally, while the relatively small differences in screening rates seem to suggest that racial/ethnic differences in stage and survival are not due to disparities in screening, others would argue such a

conclusion is premature.<sup>144</sup> Dr. Smith-Bindman recently noted that these observations have been largely based on surveys of mammography use that are self reported, only consider recent use, and do not take into account reasons for mammography and frequency of use.<sup>144</sup> In her linkage-based study utilizing mammography registry data, in which she took these other aspects of mammography use into account, Dr. Smith-Bindman and colleagues found that compared to white women, African American, Hispanic, Asian, and Native American women were more likely to receive inadequate mammography screening.<sup>144</sup> Furthermore, this study reported that the higher rates of late-stage, high-grade tumors among African Americans disappeared when the data were stratified by screening interval. The results from this study underscore the need to firmly identify the optimal level and components of screening necessary to minimize late-stage diagnoses and ultimately maximize reductions in breast cancer mortality.

## **Diagnosis**

Stage of disease at diagnosis is one of the strongest predictors of survival. Among women diagnosed with localized disease (tumor is confined to the breast tissue), the five-year survival rate is 97 percent, but it falls to 26 percent among women diagnosed with late-stage disease (when the tumor has spread to distant organs).<sup>145</sup> Known factors that contribute to later stage at diagnosis include infrequent mammography, delays in follow-up after abnormal mammographic findings, limited access to health care, and more aggressive tumor characteristics.<sup>19, 60</sup>

Tumor size is often used as an indicator of delayed detection, because tumors smaller than one centimeter are primarily found by screening mammography, whereas larger tumors are often detected by additional modalities such as clinical examination. Both stage at diagnosis and tumor size are used as surrogate indicators of screening utilization and to evaluate potential inequities in quality and timeliness of follow-up.<sup>146</sup>

In California in situ and localized breast cancer incidence rates are highest in non-Hispanic white women and lowest in Hispanics, while the rates of late-stage disease are highest among black women and lowest among Asians/Pacific Islanders.<sup>32</sup> In a recent analysis of national cancer registry data, African Americans, American Indians, and Hispanic whites were all about twice as likely to be diagnosed with stage IV breast cancer as non-Hispanic white women.<sup>147</sup> This same study found that African Americans and Hispanics were somewhat more likely to be diagnosed with larger-sized tumors.<sup>147</sup> In these analyses, Latinas and Asians were also disaggregated into specific ancestry groups. Some variation in the likelihood of advanced-stage disease was seen across Hispanic ancestry groups (Mexican, South/Central American, Puerto Rican, and other Hispanic) with the highest risk in Puerto Ricans (OR = 3.6 compared to non-Hispanic whites), though the risk in all Hispanic sub-groups was statistically significantly elevated. Among Asians and Pacific Islanders, Hawaiians (OR = 1.4 compared to non-Hispanic whites), South Asian Indians/Pakistanis (OR = 2.3) and “other Asians” (OR = 1.7), were more likely to present with late-stage cancer, while Japanese women were less likely to present with late-stage disease (OR = 0.7).<sup>147</sup>

Potential risk for advanced-stage disease and larger tumor size among Asian Americans and Pacific Islanders by specific ancestry groups has been reported in several other studies.<sup>147-152</sup> The risk for larger tumors among Asian women appears to vary by both birthplace and place of ancestry.<sup>153</sup> Hedeem et al. reported that the risk for tumor size greater than one centimeter was significantly increased for all Asian-born Asian American women relative to white women (OR = 1.6), yet no elevated risk was observed for U.S.-born Asian American women, except for U.S.-born Filipinas.<sup>153</sup> These researchers also observed increased risk for advanced-stage diagnosis among U.S.-born Filipino women and Korean women, compared to U.S. white women. These results suggest that acculturation may influence beliefs and behavior with regard to accessing preventive services. However, approximately a quarter of the women in this analysis were missing information on place of birth, which could have biased the estimates of association between birthplace and risk of more advanced disease.<sup>154, 155</sup>

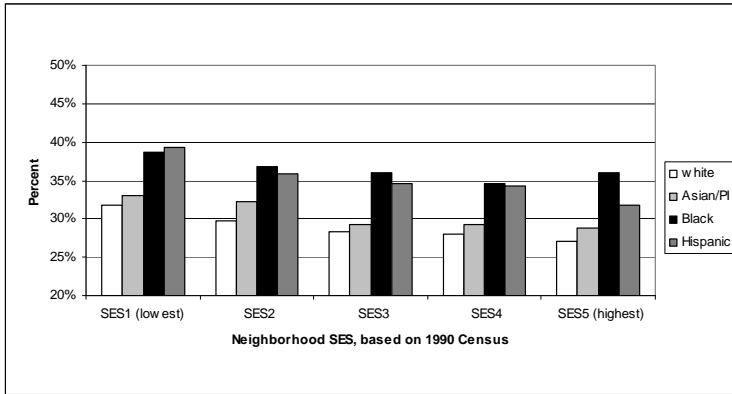
Birthplace and acculturation may also be important issues to consider when examining the differences in stage and tumor size among Hispanic women. A study based on SEER data found that Hispanic women born in Latin America had an increased risk for tumors larger than two centimeters, compared to their U.S.-born counterparts (OR = 1.72)<sup>156</sup> However, there was no significant difference in risk of advanced-stage disease by birthplace in this study (OR = 1.09).

Most studies have found that American Indian women are diagnosed at a later stage than white

women.<sup>147, 157-159</sup> Several of these studies have used data from the New Mexico Tumor Registry.<sup>157-159</sup> However, a study in Washington state found that the distribution of breast cancer stage at diagnosis for American Indians was not significantly different from the distribution for whites.<sup>160</sup> These disparate results could be due in part to misclassification of American Indians, a frequent problem with cancer data, or because of heterogeneity between American Indians living in New Mexico and Washington State.<sup>157</sup> There are very little California-specific data on stage of breast cancer diagnosis in American Indians.

Differences in socioeconomic status do not fully explain the differences in breast cancer stage. At all levels of socioeconomic status in California, the disparities by race/ethnicity exist. As shown in Figure 1, in every socioeconomic status group, Blacks and Hispanics have the highest proportion of cases diagnosed at late stage (regional and remote) while whites and Asian/Pacific Islander women have the lowest percentage.

**Figure 1. Percentage of breast cancer cases diagnosed at late stage (regional and remote) by neighborhood socioeconomic status (SES) and race/ethnicity, California, 1995-1999.\***



\*Source: California Cancer Registry Data, 1995–1999

**Diagnosis: Conclusions and Future Directions**

Disparities exist in staging and tumor size across racial/ethnic groups in all socioeconomic groups in California. These differences remain despite relatively small differences in rates of screening mammography, as previously noted. Determining the underlying reasons for these disparities will require the consideration of factors in addition to mammography. Several other possible reasons for delayed detection could include less frequent clinical breast exams, lag-time in follow-up on abnormal results, rapid tumor growth, or other biological factors. In addition, there may be more complex reasons for these disparities that relate to acculturation and other social and physical aspects of the environment.

**Treatment**

A number of studies have noted systematic differences in patterns of treatment between racial/ethnic groups of women presenting at comparable stages of disease. This section briefly summarizes the current evidence regarding these differences, with a focus on recommended treatment modalities thought to have a proven impact on breast cancer outcomes, particularly for quality of life and survival: 1) surgical treatment (vs. none); 2) breast conserving surgery for in-situ and invasive stage I and II breast cancers; 3) adjuvant radiation following breast conserving surgery and 4) use of adjuvant systemic therapy, such as chemotherapy and hormonal therapy. This section relies heavily on a recently-conducted comprehensive review of 23 studies of racial/ethnic patterns in cancer treatment by Shavers and Brown,<sup>161</sup> with additional information from a few studies that were not included or have been published since that article.

**Brief overview of treatment options**

The treatment regimen for an individual patient is determined by a complex series of clinical, demographic, and personal factors influencing both the treating physician(s) and the patient. Standard tumor-specific factors include stage, axillary lymph node status, histologic and nuclear grade, presence of lymphovascular space invasion, estrogen receptor and progesterone receptor status, and Her-2-neu status. Additional factors that also influence clinical treatment options are patient age, menopausal status, presence of comorbid conditions, presence of multifocal disease, and access to treatment. The specific standard treatment for given patient and tumor

characteristics are detailed in the Physician Data Query.<sup>162</sup> The social, cultural, and fiscal situation of the patient further influences the initial treatment plan.

In the late 1980s, clinical trial results established that survival following breast-conserving surgery with radiation therapy was equivalent to survival following mastectomy for women diagnosed with early-stage breast cancer. In 1990, the National Institutes of Health Consensus Panel recommended breast conserving surgery and radiation therapy to be preferable to mastectomy for early-stage breast cancer because of the potential for better quality of life. However, there continues to be substantial geographic, socioeconomic, and racial/ethnic variation in the use of breast conserving surgery in the U.S.,<sup>163-165</sup> raising concerns about “over-treatment” in some groups.<sup>166</sup> Radiation adjuvant to lumpectomy results in lower local recurrence rates, and possibly better survival, compared to lumpectomy alone.<sup>167-171</sup> Adjuvant chemotherapy or hormonal therapy (e.g., Tamoxifen) is also recommended for some women diagnosed with early-stage breast cancer. For advanced-stage cancer (stage IV), treatment usually involves chemotherapy and/or hormone therapy, and is given for palliation instead of cure.

### **Breast conserving surgery**

The use of breast conserving surgery has increased in all race groups since the issuance of the 1990 NIH Consensus recommendation,<sup>163-165, 172</sup> but racial/ethnic differences in breast conserving surgery persist. Studies of patients diagnosed in the 1980s suggest that breast conserving surgery was less often used among blacks than whites.<sup>161</sup>

However, more recent studies demonstrate few differences between blacks and whites in the utilization of breast conserving surgery, with some more recent studies.<sup>112, 154, 164</sup> showing slightly higher utilization among blacks. In an analysis of California Cancer Registry (CCR) data for stages 0-II breast cancer cases diagnosed from 1988-1995, Hispanics and Asians were approximately half as likely to have breast conserving surgery, while blacks were 16 percent more likely to have breast conserving surgery, compared to whites.<sup>164</sup> Lower rates of breast conserving surgery among Hispanic women were also recently noted among a population of Florida women diagnosed with early-stage breast cancer.<sup>173</sup>

A small but interesting analysis is based on 1996–1997 Detroit cancer registry diagnoses which were linked to Medicaid data and 1990 Census tract poverty information<sup>112</sup> considered the relative effects of black race and poor individual- and neighborhood-level socioeconomic status (as represented by Medicaid enrollment status and census tract poverty, respectively) on breast cancer stage at diagnosis, treatment, and survival. They found that blacks were 63 percent *more* likely than were whites to have breast-conserving surgery. However, patients who were on Medicaid fee-for-service and those who lived in census tracts with five percent or more below poverty were significantly *less* likely to have breast-conserving surgery. This suggests that in this population, blacks are receiving breast-conserving surgery at a higher level than are whites with comparable sociodemographic and clinical characteristics, but the most economically disenfranchised segments of the population, irrespective of race, are not. Lack of access to modern radiation therapy

facilities is a contributor. However, radiation treatment facilities are most often found in larger urban areas, where racial and ethnic diversity is greatest.

Lower utilization of breast conserving surgery among Asians has been consistently documented. In the study based on CCR data from 1988-1995, the proportion receiving breast conserving surgery was not only lowest among Asians/Pacific Islanders, but they also experienced the smallest increase in breast conserving surgery over the eight-year time period.<sup>164</sup> Studies that have considered Asian subgroups separately have found that certain subgroups, including Chinese, Filipinos, and Vietnamese, are more likely to undergo mastectomy for their early-stage tumors, a pattern not completely explained by the sociodemographics of the patient or clinical characteristics of the tumor.<sup>53, 154, 174</sup> Similarly, in a California interview study of 379 women residing in the greater Bay Area, Chinese women were more than three times more likely than non-Hispanic whites to have mastectomy (OR = 3.3; 95% CI = 1.5–7.1), attributable in part to language, education, and recency of immigration.<sup>154</sup> Linkage of Hawaii Tumor Registry data with health claims data determined that Japanese and Filipinas were 25 percent and 50 percent less likely than whites to have breast conserving surgery, respectively.<sup>175</sup>

In a recent large and comprehensive analysis of SEER data from five registries (Hawaii, Los Angeles, San Francisco/Oakland, San Jose/Monterey, and Seattle), comprising over 66,000 stage I and II breast cancer patients, 10,000 of whom were Asians, Goel et al.<sup>176</sup> found that

breast conserving surgery for early-stage tumors was lower only among the foreign-born, with 43 percent of foreign-born Asians/Pacific Islanders having had breast-conserving surgery, compared to 56 percent of U.S.-born Asians/Pacific Islanders and 59 percent of whites. These results contribute to the idea that cultural and language factors may underlie some of the disparities in use of breast conserving surgery observed for Asian subgroups. Several qualitative studies are currently underway to address these cultural and language issues that may serve as barriers to receiving standard of care treatment, and their impact on patient-provider communications, treatment decision-making processes, and quality of life. (See additional discussion of this in Section II., Chapter D., Culture.)

Taken together, these studies focusing on factors responsible for the considerably lower receipt of breast conserving surgery among Asian women suggest that the pattern cannot be explained by known demographic or clinical factors. There appears to be some association of breast conserving surgery utilization with immigration and acculturation factors, and with institutional and provider factors, prompting further research into the role of specific cultural factors and patient-provider communication in the treatment decision-making process. This, together with the apparently lower rate of breast conserving surgery utilization in lower-socioeconomic-status black women, suggests that factors associated with available resources may further influence these treatment differences.

## Adjuvant Radiation Therapy

According to the Physician Data Query,<sup>162</sup> adjuvant radiation is recommended following breast conserving surgery to minimize risk of recurrence. The impact on survival is well documented. Adjuvant radiation may be difficult for certain populations because it requires a nearly daily administration for an average of six weeks. Indeed, previous studies report lower breast conserving surgery usage and lower adjuvant radiation therapy among the aged and those living a farther distance from radiation facilities.<sup>177-183</sup> It has been estimated that 20-30 percent of women treated with breast conserving surgery do not receive radiation,<sup>184, 185</sup> and that adjuvant radiation therapy is lower among minority women than non-Hispanic white women.

Similar findings were reported among Latinas in Florida.<sup>173</sup> In a recent analysis of 10 years of SEER data (1988–1998), Joslyn reported that African American women with early-stage breast cancer were less likely to receive follow-up radiation therapy than their white counterparts.<sup>108</sup> This difference was observed in every age group, with the exception of those over the age of 85. Certain Asian subgroups also may be less likely to receive adjuvant radiation therapy following breast-conserving surgery. In a San Francisco Bay Area study, Chinese women were significantly less likely than white women to receive recommended adjuvant radiation or hormone therapy, while Japanese and Filipina women did not differ from whites in their use of adjuvant therapy.<sup>174</sup> In the study based on Hawaiian claims data, Filipinas were slightly, although non-significantly, less likely than white women to have

adjuvant radiation, while Japanese were significantly more likely to have chemotherapy for node-positive disease.<sup>175</sup>

## Adjuvant Systemic Therapy

Systemic adjuvant treatment provides undisputed benefits for women with early-stage breast cancer, but there has been little research on the risks and benefits for minority groups other than African Americans.<sup>186</sup> Studies have suggested that black women are less likely to receive optimal systemic adjuvant therapy than are white women and this may account in part for the disparities in survival outcomes. Several studies have evaluated early discontinuation of therapy and found that African American women were more likely to discontinue adjuvant chemotherapy early,<sup>115</sup> black patients are less likely than other patients to be prescribed tamoxifen,<sup>187</sup> and that they are less likely to be adherent when it is prescribed.<sup>188</sup> The disparity in outcomes became more pronounced in the mid to late 1980s, corresponding to the introduction of adjuvant therapy for this disease. This is particularly important, because if the reasons for disparities in the treatment of breast cancer can be elucidated, they may be modifiable.

One of the factors that may lead to the receipt of suboptimal adjuvant therapy is access to cancer treatment services, which is associated with income, education, and insurance<sup>161, 189, 190</sup> Adjuvant treatment for breast and other cancers is also associated with race.<sup>191</sup> For example, black patients receive less aggressive intravenous chemotherapy,<sup>192</sup> have fewer consultations with medical oncologists, and have a significantly higher risk of recurrence than whites. Only 50 percent of black women appropriate for adjuvant

chemotherapy for breast cancer are estimated to be receiving it.<sup>193</sup> Treatment delays, while uncommon, also may contribute to worse outcomes among black women.<sup>194</sup> Gwyn et al. found a relationship between black race and delays in both initial diagnosis and subsequent surgical treatment.<sup>195</sup>

Less is known about outcomes and treatment disparities in other racial groups. With the exception of blacks, differences in breast cancer incidence rates between most racial/ethnic groups are explained by risk factor distribution. To date, Hispanics and Asians have been underrepresented in the SEER database and, therefore, less is known about health care delivery to these minority subsets. One study looking at delay found that Spanish-speaking Latinas are more likely to experience a delay of three months or more from diagnosis to surgical treatment for breast cancer (36.4 percent vs. 9.1 percent for non-Latina whites, 18.6 percent for blacks, and 12.7 percent for other Latinas,  $p < 0.001$ ).<sup>81, 196</sup> Latinas were recently reported to be less likely to experience appropriate adjuvant therapy than were non-Latino white women. In this study, underuse was defined as omissions of radiation therapy after breast-conserving surgery, adjuvant chemotherapy after resection of hormone-receptor-negative tumors greater than or equal to one centimeter, or hormonal therapy for receptor-positive tumors greater than or equal to one centimeter.<sup>197</sup>

Similarly, for Asians, most research to date has focused on risk. Chinese women were also more likely than were white women not to receive adjuvant therapy, be it radiation after lumpectomy or hormonal therapy for estrogen receptor-positive

disease. One population-based study identified differences in treatment for localized breast carcinoma by race/ethnicity that were not explained by differences in demographic, medical, or socioeconomic characteristics.<sup>174</sup>

As individualized therapy becomes an achievable goal, some researchers are re-examining how race should be incorporated into clinical assessments. The technology is not completely available yet and would require extensive institutional reorganization to disseminate broadly,<sup>198</sup> so the question also becomes what is the best stopgap approach until we reach that goal. Some researchers argue that we should take a race-blind approach to diagnosis, where the genetic profile of the tumor or disease markers should be the sole source of diagnosis and drug development. Others advocate for continuing to diagnose on the basis of both genetic profiling and race/ethnicity.<sup>12, 24, 199, 200</sup> By completely ignoring race/ethnicity, contributory factors to drug efficacy such as underlying genetic factors, cultural practices and institutional barriers could be overlooked. For example EGF-targeted therapies hold some promise for treating basal-like tumors, since they express EGFR, but initial clinical trial results are mixed.<sup>201, 202</sup> Jimeno and Hidalgo hypothesize that one reason for the failures of EGFR-targeted therapies is the variations in EGFR polymorphisms in different ethnicities. Including race/ethnicity in the arsenal as a surrogate for underlying genetics and cultural features is an imperfect, but useful, tool.

## Other treatment issues

Racial/ethnic disparities exist in other domains of breast cancer treatment and treatment-related factors. For black compared to white patients, these include a longer period from diagnosis to treatment initiation, longer follow-up times after an abnormal mammogram, and less frequent minimum expected therapy or follow-up mammogram after diagnosis and treatment of breast cancer.<sup>161</sup> These patterns point to possible lag times in progressing from one aspect of care to another, and reflect poor continuity in cancer care among blacks. In a large multi-center study of disparities in black/white survival, treatment delays were attributed to institutional, rather than individual, factors. However, such delays did not appear to differ between black and white patients.<sup>203, 204</sup>

In a comprehensive analysis of national SEER data, Li et al. examined the differences between racial/ethnic groups who received appropriate and inappropriate treatment for stage I and II breast tumors less than 5.0 centimeters. Inappropriate treatment was defined as not receiving any treatment, adjuvant radiation, or axillary lymph node dissection, or receiving a subcutaneous mastectomy. Blacks, Asians/Pacific Islanders, and certain Hispanic subgroups were more likely than whites to receive “inappropriate” treatment.<sup>147</sup>

It has been theorized that racial/ethnic disparities in cancer treatment may arise in part from a failure of providers to engage patients in the decision-making process. Among blacks, mastectomy was more likely when the decision was perceived to have been made by the surgeon. However, in contrast to this belief, mastectomy over breast

conserving surgery was in fact more likely among patients with greater decision-making involvement, as reported by Katz et al. for a population-based group of 1,844 patients from Detroit and Los Angeles.<sup>205</sup> Black women also visited more surgeons than white women, had more visits before surgery, and were less likely to have made the surgical decision during the first consultation. The authors suggest that these patterns reflect more treatment uncertainty among blacks, but they could again reflect discontinuity in care settings among minorities and the poor. Black women also reported receiving less information about breast conserving surgery. In an accompanying commentary, Nattinger reinforced the idea that decision making regarding early stage breast cancer is complex, and that innovative research on methods to improve the quality of the process is needed. Nattinger also pointed out that social factors may affect not only receipt of information to facilitate decision-making processes, but that the interpretation and synthesis of information may also differ by social factors and context. For example, some patients may have difficulty with the abstract notion that “an irradiated cancer is just as gone as a cancer that has been surgically removed.”<sup>206</sup> It also requires “a high level of faith in medical science and clinical trial results to accept the idea that the possibility of local recurrence or new cancers in a conserved breast does not translate into any survival decrement.”<sup>205</sup>

The observation that Asian women are more likely to receive mastectomy over breast conserving surgery for early-stage cancer has stimulated several qualitative studies aimed at identifying the cultural issues at hand in the breast cancer

treatment decision-making process. In addition to language and financial barriers, these studies identified a number of sociocultural factors unique to Asian women that may influence their treatment.<sup>207-209</sup> These studies are described in more detail in Section II, Chapter D of this Report.

### ***Treatment: Conclusions and future directions***

Apparent racial/ethnic disparities in treatment, particularly for early stage disease, are not necessarily explained by differences in tumor characteristics or clinical attributes of the patient. It is also not clear to what extent women of different racial/ethnic groups are being offered comparable treatment options. Cultural and economic factors appear to play large roles in differing treatment patterns. Black/white differences appear to be better explained by socioeconomic status than by race. Disparities observed for several Asian/Pacific Islander and Latina groups, particularly among recent immigrants, appear to be largely influenced by cultural beliefs, language barriers, and economic resources. Future work in this area will require attentiveness not only to the heterogeneity of breast tumors, but also to the heterogeneity of the patient population, as well as associated inequalities in socioeconomic resources and access to care.

### **Quality of life**

A focus on cancer outcomes and survivorship has become an increasingly important area of research.<sup>210, 211</sup> Quality of life is a major component of survivorship research, particularly with the increasing population of breast cancer

survivors due to improvements in survival and the sheer numbers of women coming into age groups at highest risk of breast cancer. Psychometric research has identified several relevant domains of importance in considering quality of life. For breast cancer, these generally include relationships with family, self-image, relationships with friends, social enjoyment, attractiveness, sexuality,<sup>212</sup> physical function, and symptoms. Determination of quality of life is highly subjective, relying predominantly on patient ratings, and is often subject to errors in reliability and validity. There are also several validated tools for assessing general quality of life, quality of life specific to cancer patients, and quality of life specific to breast cancer patients. Variations in results across studies could in part reflect differences in measurement tools. To date, there has been very little research on the impacts of breast cancer on the quality of life for specific racial/ethnic groups. Existing studies have mostly been qualitative in nature, though there have been a few studies that have applied more quantitative approaches.

Ashing-Giwa et al. conducted a qualitative study with breast cancer survivors of various race groups and reported some important similarities and differences between African American, Asian American and Latina women.<sup>213</sup> They found that all three groups expressed difficulties in adjusting to physical changes from cancer. These negative feelings about body image are of particular interest for Latina and Asian American women, who are more likely to have been diagnosed at a younger age and to undergo mastectomies. Asian American women, like African American and Latina women, cited spirituality and family support as critical factors in their recovery and

copied with their illness. However, unlike African American women, Asian American and Latina survivors identified language barriers and lack of time with their doctor along with lack of insurance (i.e. insurance status) as concerns for their health care and treatment. Such findings may correlate with their “choice” of mastectomy. Similarly, another qualitative study of Asian American women also found that these women expressed negative feelings about their bodies after their cancer surgeries, including feelings of inadequacy, loss of self-confidence and self-worth, unhappiness, and depression.<sup>209</sup> Asian women also expressed concerns related to worry about children and burdening their family. Since Asian American breast cancer survivors tend to seek professional assistance for psychosocial problems at a significantly lower rate than white women,<sup>207</sup> the burden of psychosocial stress may be more pronounced; no research has explored the implications of such psychosocial stress in this group.

Ethnic variations in quality of life exist among Asian/Pacific Islander women. In a population-based multiethnic study in Hawaii, Gotay and colleagues found that Filipina breast cancer survivors reported worse emotional functioning, as well as significantly more nausea, vomiting and overall symptoms, compared to other racial/ ethnic groups.<sup>214</sup> However, the observed difference may be attributable, in part, to Filipinas defining quality of life differently than other groups.<sup>215</sup>

A qualitative study of Chinese breast cancer patients reported important differences between American-born and foreign-born Chinese women in their beliefs about, perceptions of, and

experiences with breast cancer.<sup>216</sup> Cancer carries a stigma for both groups, but is more prominent in the immigrant group. Furthermore, whereas American-born women named independence and freedom to describe quality of life, foreign-born Chinese women viewed wealth as an important dimension of quality of life.<sup>216</sup> These findings suggest that acculturation can influence quality of life and can have varying impacts on different dimensions of quality of life.

The most-studied group for quality of life, besides non-Hispanic whites, has been African American breast cancer survivors, for whom breast cancer diagnosis and treatment has been reported to negatively influence family and marital relationships, employment security, economic well-being, and satisfaction with body image and sexuality.<sup>217</sup> Qualitative research to identify and understand possible means of coping with these quality of life challenges have identified several distinctive factors in the African American breast cancer survivorship experience. For example, as compared to other ethnic groups, African American breast cancer survivors tend to rely more heavily on their spiritual faith as a source of support and on the church community as an important source of social support. The long history of African American resilience and survivorship has also been identified as an important coping resource.<sup>213</sup> A focus group including rural African American breast cancer survivors identified several intriguing areas for further research into breast cancer-related quality of life. This study identified as major concerns finding “safe,” respectful sources of social support in light of the stigma of cancer, finding ways to feel comfortable and optimistic about the future,

and finding help with adjustment to the role of and the pressure of serving as a cancer survivor role model. Focus groups reinforced the important roles that spiritual faith and prayer, ensuring family support, and other social networks have for addressing these concerns.<sup>218</sup>

Studies of quality of life among Latinas after breast cancer suggest that Latina survivors have lower quality of life than do white women. Latinas in northern California reported higher rates of pain and numbers of symptoms after breast cancer treatment than white women.<sup>219</sup> In a study by Carver et al. of long-term breast cancer survivors diagnosed at early stage, Latinas reported more frequent negative feelings, more social avoidance, more distress about their family's future, and more distress about the possibility of recurrence than did other women. These differences did not appear to be rooted in differences in socioeconomic status.<sup>220</sup> Focus groups also found that Latina breast cancer survivors may experience more financial burden than other groups.<sup>213</sup>

Few studies specifically examining quality of life among American Indian/Alaska Native breast cancer survivors have been published. Several cancer survivor support groups exist, including the National Native American Breast Cancer Survivor's Network, a project conducted by the Native American Cancer Initiative of the Denver Indian Center and "A Gathering of Cancer Support." The project is designed to improve survival from breast cancer and quality of life.<sup>221</sup> Bauer also examined social networks and perceived social support among American Indian cancer survivors. The investigator found that

family appears to be the principal source of social support compared to close friends, church, or community.<sup>222</sup> Palliative care has only recently formally been addressed for Indian Health Service and tribal health programs. Kitzes describes the needs for and barriers to palliative care, and several successful programs.<sup>223</sup>

### **Quality of Life: Conclusions and future directions**

In summary, little research has been dedicated to exploring quality of life among specific racial/ethnic groups of breast cancer survivors. The few studies conducted in this area offer some insights into understanding the impact of the illness on these women, but more refined efforts are needed, especially in a population with such cultural diversity. To date, the studies seem to indicate some common themes of negative body image and other forms of emotional burden. Research attention should be given to examining some of the specific sociocultural burdens of psychosocial stress on breast cancer survivors and ways to reduce such stress in each of these groups. In order to evaluate ethnic variations across studies, reliable and valid measurement tools to measure the quality of life construct need to be developed and used.

### **Survival/Mortality**

Breast cancer mortality rates vary widely by broad racial/ethnic group (Table 3, Figure 2). Most notable is the persistently higher death rate among African Americans compared to whites, despite a lower incidence rate.

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**Table 3. Average annual female breast cancer mortality rate (cases per 100,000), U.S. SEER data, 1998-2002<sup>36</sup>**

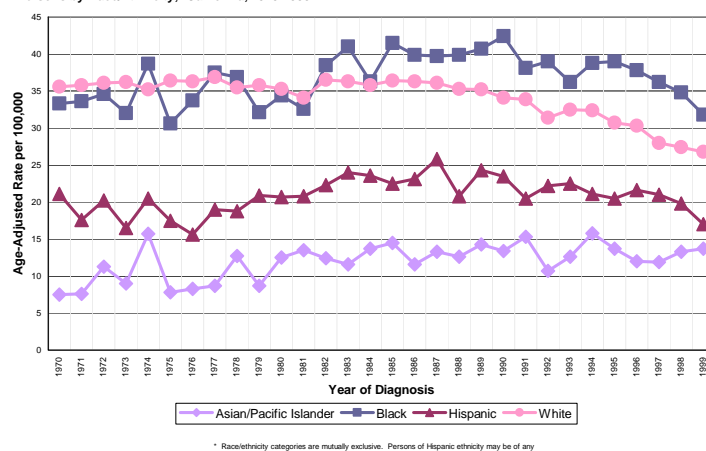
Race/ethnicity	Breast cancer mortality rate (per 100,000)
White	25.9
African American	34.7
Hispanic	16.7
Asian/Pacific Islander	12.7
American Indian/Alaska Native	13.8

While breast cancer mortality has been steadily decreasing since 1990,<sup>19</sup> this decline has not been realized equally among all racial/ethnic groups in the U.S.. In fact, although rates are decreasing over time among both African Americans and whites, the rate among whites is decreasing faster, so the net effect has been a widening disparity in breast cancer mortality.<sup>19</sup> In the 1980s there was no difference in breast cancer mortality rates between African Americans and whites; in 1990, the mortality rate among African Americans was 16 percent higher than among whites; in 2002-03, that difference increased to 36 percent.<sup>19, 36</sup>

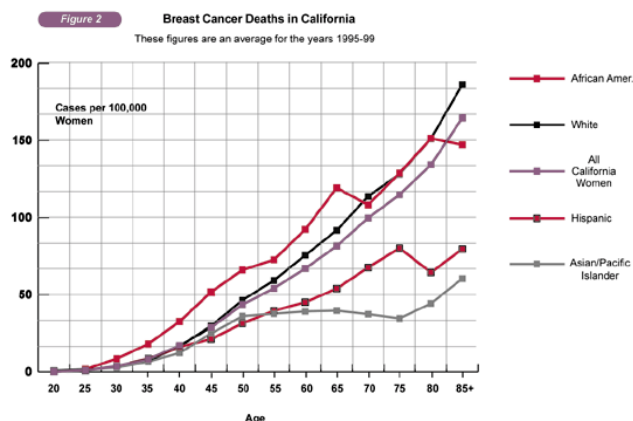
The disproportionately high death rate and worse survival among African American women has been the focus of a large body of research. While

African Americans do tend to be diagnosed at a later stage, it is well established that survival disparities persist even after adjusting for stage.<sup>32, 203, 224</sup> Research on the impact of treatment differences between blacks and whites on survival outcomes has not been entirely consistent. As previously noted, it is well documented that while African Americans are more likely to have breast-conserving surgery than are whites, they are less likely to receive a full course of adjuvant radiation therapy. In a recent examination of these treatment differences on subsequent survival,<sup>108</sup> Joslyn found that adjustment for these treatment differences attenuated, but did not completely eliminate, survival differences between blacks and whites. These results support a previous study that found significantly worse survival among African Americans compared to whites given equivalent treatments,<sup>225</sup> but conflict with the findings of another study which reported no residual mortality disparities after adjusting for treatment among a population with equal access to care.<sup>106</sup>

**Trends in Female Breast Cancer Age-Adjusted (2000 U.S. Population) Mortality Rates per 100,000 Persons by Race/Ethnicity,\* California, 1970-1999**



\* Race/ethnicity categories are mutually exclusive. Persons of Hispanic ethnicity may be of any



It also has been suggested that racial/ethnic disparities in breast cancer survival may be a function of differential responses to treatment (reflecting underlying biological differences). A

recent review of clinical trials evidence where tumor biology was assessed using classical pathological classifications suggests that there are few or no major underlying biological differences between blacks and whites that influence the effectiveness of breast cancer treatment.<sup>161</sup>

However, in 2006 researchers are reporting that young blacks are prone to developing more types of tumors that are more resistant to current therapies than other groups.<sup>58, 226, 227</sup> Data on this issue is fairly limited and not entirely consistent. One study at the University of Kansas Medical Center found higher systemic recurrence rates (but not local recurrence rates) and shorter time to recurrence among blacks compared to whites treated with breast conserving surgery and radiation for stage II cancer.<sup>228</sup>

The degree to which black/white differences in tumor characteristics may impact survival has been an area of intense interest. Because different tumor characteristics may require different treatment protocols, it is important to take these differences into account when evaluating the degree to which treatment differences explain racial/ethnic disparities in survival. It has long been noted that African American women are at higher risk for being diagnosed with more aggressive tumors that are more likely to be non-hormonally responsive and of a higher grade.<sup>224, 229, 230</sup> Recently, evidence has emerged that African American women are also more likely to have tumors with a variety of molecular genetic compositions (e.g. higher mitotic index, over-expression of cyclin E and p53, higher S-phase fractions, basal-like subtypes) that are associated with shorter disease-free survival times.<sup>58, 231</sup> While treatment decisions are complex and

multifactorial, it is important to try to disentangle differences required by clinical profile versus those that are due to modifiable factors such as access to care, cultural beliefs, and potential discrimination.

It is likely that the persistently worse stage-adjusted survival seen among African Americans compared to whites is a function of a myriad of factors discussed throughout this Report, including lower socioeconomic status and poorer access to medical care, receipt of lower-quality cancer treatment, existence of more comorbidities, and more aggressive tumor biology. Studies that have examined these factors in univariate analyses (socioeconomic status, treatment, life expectancy, and comorbidities) have found that these variables appear to attenuate, but not fully explain the differences in breast cancer survival.<sup>116, 224, 232-236</sup> However, to date no studies have controlled for all of these factors concurrently along with prognostic tumor/disease characteristics.

Comorbidity appears to be a strong predictor of overall survival and breast-cancer-specific survival and is likely to explain much of the black/white disparity in all-cause mortality, but it does not fully explain racial disparities in breast-cancer-specific survival.<sup>116</sup> Two studies out of the MD Anderson cancer center have found that equal treatment of tumors with similar characteristics in African American and Caucasian women may not lead to equivalent clinical outcomes.<sup>226, 227</sup> Woodward et al. also compared clinical outcome in Hispanics, who had a similar referral process and socioeconomic status profile to African Americans in their study, and found that Hispanics had similar overall survival rates to Caucasians.

Institutional factors, however, such as health insurance coverage, hospital characteristics, delay in treatment, and continuity in care are increasingly being recognized as perhaps the more important contributors to the disproportionate burden of breast cancer mortality experienced by African American women.<sup>106, 112, 161, 237-241</sup> For example, in a recent study from data in the Metropolitan Detroit Cancer Surveillance System, the risk of death from breast cancer among African American women was not statistically different from white women after adjustment for age, marital status, stage, Medicaid status, census tract poverty, and surgical treatment. In fact, Medicaid status was a larger contributor to mortality than was race.<sup>112</sup> In a large meta-analysis explicitly designed to examine the respective roles of cancer biology and differential access to treatment on survival in black vs. white patients, Bach et al.<sup>232</sup> reported a significantly elevated (20 percent higher) breast cancer mortality rate for black women, even after accounting for treatment differences. However, difficulties inherent to the meta-analysis study design sometimes mitigate its increased power to detect significant differences. Difficulties include inability to control for quality of original studies included in the meta-analysis, varying factors analyzed among the different studies, large numbers in the combined studies that result in statistically significant but clinically insignificant results, and individual studies designed to answer hypotheses different than those examined in the meta-analysis.

Compared to the large body of research focusing on breast cancer mortality and survival disparities between white and African American women,

relatively little has been done to document and explain other racial/ethnic disparities in breast cancer survival. While compared to non-Hispanic whites, mortality rates for other racial/ethnic groups are lower on an absolute scale, important racial/ethnic differences in relative survival exist. In a recent analysis of SEER data for 1975-1999, breast cancer survival rates were significantly better for Asian American women compared to non-Hispanic white women.<sup>242</sup> All other racial/ethnic groups examined—including Native Hawaiians, Hispanics, African Americans, and American Indian/Alaskan Natives--experienced worse survival. This study, however, did not examine more specific subpopulations within the Asian American population.

As was previously noted for other breast cancer outcomes, further examination of more detailed racial/ethnic subgroups may reveal important survival disparities masked by these broad categories.<sup>147, 243, 244</sup> For example, it has been noted that Latina women have worse survival than non-Hispanic white women, while Asians/Pacific Islanders, as a broad group, tend to have better survival, even after adjustment for stage at diagnosis.<sup>19, 234, 242, 245</sup> More detailed analyses of Latina women have shown important survival differences depending on country of origin, with those of Mexican ethnicity having 30 percent higher mortality than whites after diagnosis, while survival among South and Central Americans, Puerto Ricans, and other Hispanics were comparable to whites.<sup>147</sup>

In similar analyses among Asians/Pacific Islanders, mortality among Japanese American women was 40 percent lower compared to whites,

while mortality among Native Hawaiians was 30 percent higher, and mortality rates among the other Asian subgroups were similar to whites.<sup>147, 244</sup> To our knowledge, there have been no studies of cancer treatment effectiveness or biological differences in response to treatment in racial/ethnic groups other than African Americans.

Given that we still cannot completely explain racial/ethnic disparities in breast cancer survival, it is important to look beyond issues of treatment and biology towards other factors that are likely to impact survival. There is a substantial and growing body of work devoted to understanding psychosocial factors such as stress, social support, and coping strategies in relation to breast cancer survival.<sup>246-250</sup> Immune systems are affected negatively by stress and the mitigating effect of some positive psychosocial characteristics on a patient's anxiety level may have an indirect, but potentially significant, effect on cancer survival. Effects on survival have been reported for some of these factors, yet few studies have considered psychosocial factors among racially/ethnically diverse populations. While some notable racial/ethnic differences have been observed for these factors that have included both white and non-white study participants, the degree to which such differences may explain disparities in survival is not known. This avenue of research remains largely unexplored.

#### ***Survival/Mortality: Conclusions and future directions***

The greatest burden of breast cancer mortality is borne by African American women. Compared to non-Hispanic whites, all racial/ethnic groups, other than Japanese American women, have worse

relative survival. These differences persist after adjusting for stage at diagnosis. Clearly issues related to socioeconomic class, such as access to care and treatment, play a role in the worse survival experience among minority women but they are not the whole story. As yet unidentified biological factors may play a role in survival disparities. Identifying the factors that impart better survival among Japanese Americans may provide important clues to improving survival among other groups.

#### **4. Conclusions and future directions**

A number of well-documented racial/ethnic disparities exist across the breast cancer continuum. With the exception of incidence, which is markedly higher among non-Hispanic white women, minority women bear a disproportionate share of the burden of breast cancer. They are more likely to be diagnosed at a later stage, less likely to receive timely, appropriate, and complete treatment, and have worse survival rates than non-Hispanic white women. Most notable of all the disparities identified to date is the persistently higher breast cancer mortality rates suffered by African American women in this country. The fact that this disparity has widened over the last twenty years represents one of the most troubling failures of our efforts to address racial/ethnic disparities in breast cancer.

By far, the bulk of the research conducted to date on racial/ethnic disparities in breast cancer incidence has focused on the degree to which differences in the prevalence of established risk factors between racial/ethnic groups explains the differences in breast cancer incidence rates. This

research suggests that reproductive and behavioral risk factors (especially age at first birth and parity, but also body mass index, alcohol consumption and use of exogenous hormones) explain some, but not all, of the racial/ethnic disparities in incidence. Because most of the established risk factors were primarily identified in populations of white women, and in fact, only explain about half of breast cancers among white women, this approach is particularly limited for evaluating disparities in breast cancer incidence. Addition of risk factor information to the California Cancer Registry database could greatly enhance this avenue of research, by providing population-based data on breast cancer risk factors in a large and ethnically diverse population.

Determining the degree to which individual behaviors explain some of the noted disparities in breast cancer outcomes other than incidence is complex. While the choice to obtain screening or seek treatment, or choose specific treatments, ultimately lies with the individual, such a decision is embedded in complex layers of sociocultural, physical, financial, and institutional factors. The challenge in disparities research is to disentangle these factors in a way that can identify inequities in opportunities for behaviors that can increase screening, improve treatment, and ultimately eliminate disparities in survival. Thus in evaluating rates of breast conserving surgery usage, for example, it is critical to be able to distinguish between the woman who chooses a mastectomy over breast conserving surgery because of a strongly-held cultural belief, versus the woman who makes that choice based on insurance coverage or other economic challenges, versus the woman who is not presented with any

choice at all because her physician believes (based on her race/ethnicity or socioeconomic situation) that she will not be likely to complete adjuvant therapy and therefore mastectomy is the only option offered. Disentangling such complex factors is critical for identifying avenues for reducing disparities, and cannot be achieved through studies solely based on large registry data, but must come from thoughtfully-designed, culturally-sensitive qualitative studies.

A small but growing body of literature aimed at identifying racial/ethnic genetic differences may explain noted disparities in breast cancer. The findings that there are racial disparities in breast cancer incidence and mortality are almost exclusively based on data from studies using the social definition of race, whether it is through self-reporting or observer assessment. Sequencing of the human genome has given scientists new tools to examine how closely genetic constructs correlate with social definitions of race. If the genetic constructs correlate, then it lends support to the argument that there could be a biological component to the observed disparities in socially defined race. If not, then there is an opportunity to redefine populations with high or low susceptibility to disease at the genetic level.

A good deal of research directed toward understanding contributions of biology to disparities in breast cancer has been concentrated on understanding how pathological and genetic risk markers are distributed between races and ethnicities and how to target them for risk assessment, diagnosis, and the development of treatments. Scientists are moving away from the primarily morphological prognosticating protocols

of the past. DNA tissue microarrays, proteomics and other bioinformatics analyses are uncovering new, more predictive systems for classifying breast tumors.<sup>56, 57, 251</sup> This has allowed researchers to categorize cancers in a way that could not only predict which tumors would respond to specific therapies, but provide clues regarding the exposures that caused the tumors.

The significance of race in the context of disease research is that it serves as a proxy for other susceptibility factors, in which genes and physiology interact to some extent with cultural attitudes and behaviors, geography, and environment. Migrant studies have consistently demonstrated that there is a strong cultural/environmental component to breast cancer incidence, although some portion of observed disparities may still be due to differences in genetic make-up. Studies that definitively tease out the biological contributions from the sociocultural ones will not only inform our understanding breast cancer etiology, but also speed the development of therapies that will be effective in diverse populations.

Because race/ethnicity and socioeconomic status are so highly correlated in the U.S., it is impossible to examine racial/ethnic disparities in health without considering socioeconomic status. Although non-whites are over-represented in lower socioeconomic status groups, it is clear that race/ethnicity is not simply a proxy measure for socioeconomic status.<sup>86</sup> Racial disparities in breast cancer outcomes generally remain even after adjusting for socioeconomic status, although much of the research seems to suggest stronger effects of socioeconomic status than of

race/ethnicity. Differences by race that remain after adjustment for socioeconomic status do not necessarily mean that there are underlying biologic differences or mechanisms.<sup>252</sup>

Differences can be due to remaining confounding and incomplete understanding of the influences of the social and physical environments on breast cancer outcomes. It has been well documented that people of color and people living in low-income areas are disproportionately exposed to environmental pollutants.<sup>253-255</sup> Institutional factors such as discrimination, insurance status and usual source of care are also very important to consider when examining socioeconomic status differences. To better understand racial/ethnic disparities in breast cancer outcomes, researchers will need to more comprehensively examine the complex interactions between socioeconomic status, race/ethnicity, physical exposures, occupations, stress, and social environments. A growing number of researchers, community activists, and policy makers have taken a broader, more inclusive view of the environment that incorporates all of these factors in ways that consider the effects of multiple stressors and multiple exposures.<sup>253, 256, 257</sup> For more on this topic, see Section III of this Report.

While there is a small, but growing body of literature suggesting psychosocial factors such as stress and social support are important determinants for breast cancer outcomes such as quality of life and survival, this avenue of research generally has not been pursued in the literature examining racial/ethnic disparities in breast cancer. One study which explicitly examined black/white breast cancer patient differences in social support and coping suggested that while

these are important independent predictors of survival, they do not explain the black/white disparities.<sup>246, 247</sup> Racial discrimination has been implicated as a race-specific stressor and potential predictor of racial inequalities in health (see Section III of this Report). In other health outcomes research, physiological changes such as elevations in blood pressure have been documented in response to discrimination.<sup>258, 259</sup> Additionally, research in other fields has shown that individual coping behaviors, particularly in dealing with discriminatory actions, and social support networks may mediate or buffer negative effects due to stress and are important to consider.<sup>259-264</sup> Beyond the stresses associated with discrimination, the numerous barriers to access to care encountered by minority women suggest there may be racial/ethnic differences in stress and support presented specifically by the process of seeking care for breast cancer. Examining the role of psychosocial stress in explaining racial/ethnic disparities in breast cancer outcomes is a glaring gap in the research conducted to date.

This review highlights a number of examples that underscore the need to disaggregate the data to look at more detailed ethnic and ancestry subgroups whenever possible. This need is particularly acute for American Indian/Alaska Natives for whom reliable data are lacking. Furthermore, the Asian/Pacific Islander population in California is particularly heterogeneous with respect to a number of factors which are likely to

contribute to breast cancer disparities, such as immigration status, acculturation, and socioeconomic status. Thus, aggregate data on this population may be especially problematic.

To date, there has been little consideration of the role of differential physical exposures, in the general environment and in the workplace, in breast cancer disparities research. The large body of literature on breast cancer incidence among migrants underscores the importance of looking at both environmental and behavioral aspects of breast cancer etiology. To determine which specific aspects of race/ethnicity are associated with breast cancer risk and outcomes, a multidisciplinary approach is needed to comprehensively examine the complex interactions between race/ethnicity, socioeconomic status, physical exposures, stress, acculturation, genetics, and social environments. California, with its large, racially and ethnically diverse population of women, is the ideal place to study this important topic. More than merely study this topic, California is also the most appropriate place to address and reduce disparities in breast cancer outcomes.

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## *Identifying Gaps in Breast Cancer Research*

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