Woodrow Wilson International Center for Scholars

Global Health Initiative

AVON FOUNDATION

PUBLIC HEALTH DEMOCRACY:

U.S. and Global Health Disparities in Breast Cancer

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We live in an age disturbed, confused, bewildered, and afraid of its own forces, in search not merely of its road but even of its direction. There are many voices of counsel, but few voices of vision; there is much excitement and feverish activity, but little concert of thoughtful purpose. We are distressed by our own ungoverned, undirected energies and do many things, but nothing long. It is our duty to find ourselves.

— Woodrow Wilson
Baccalaureate address as
President of Princeton University,
June 9, 1907

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PREFACE

The title of this report, "Public Health Democracy: U.S. and Global Health Disparities in Breast Cancer", was selected to highlight democracy (or lack thereof), the primary basis of the United States government system, particularly during an election, as well as its application to the public health of its citizens. A fundamental test of a nation's democracy is the impact of its economy, governance, education, criminal justice, and health systems on its people. Public health is more than a state of general well-being, particularly as it pertains to cancer. It includes how health services are delivered, who benefits, who carries the burden of disease, and how the costs of illnesses affect our society. This document addresses a major public health problem in the United States and worldwide that of cancer.

Recent global statistics indicate a rising incidence of breast cancer. Since the war on cancer was declared in the early 1970s, the focus of the U.S. National Cancer Institute has been eliminating suffering and death due to cancer. We can all be proud of the technological advances in science and the significant progress that has been made in the screening, early detection, and treatment of cancer. Unfortunately this progress has not benefited minorities and the underserved in an equitable fashion, particularly African Americans (AAs). Furthermore, the cancer incidence in developing countries is rapidly rising. The problem is more than access to care, and is multi-faceted and complex.

This report is intended to synthesize health disparities information and increase the level of awareness and understanding of breast cancer-related health disparities, particularly in AAs, minorities, and medically underserved women. Furthermore, it will serve as a point of reference for taking action towards increasing research on the differences in a subtype of breast cancer that affect the young, AAs, and BRCA1 mutation carriers at a disproportionate rate.

This country is primed for participating in the democratic electoral process. Let us take that same enthusiasm to tackle the public health problem of breast cancer health disparities. For more than three decades we have discussed health disparities, yet the gap between discovery and delivery of cancer care has either remained unchanged or increased as health disparities have increased. It is now time to more equitably alter the course of breast cancer in AAs, other minorities, and the underserved through a democratic public health process. Let us not let the past be prologue for the future of breast cancer care.

HISTORICAL OVERVIEW SUMMARY

Despite significant scientific advances in cancer research, not all population groups have benefited equally, and broad-range health disparities persist.

African Americans are 34 percent more likely to die from cancer than non-Hispanic whites, and are twice as likely to die from cancer as other minority groups.

Some scientists diminish the significant role that race has on cancer outcomes, solely addressing race as a social construct. However, it is extremely difficult to disaggregate the impact of race on cancer outcomes.

In 2007, the National Cancer Institute issued a report indicating a decline in suffering and death from breast cancer. However, minority and underserved populations, especially African Americans, showed little or no change.

This paper presents possible solutions to improving the lives of African American and minority women at risk for breast cancer in the United States and globally.

HISTORICAL OVERVIEW

Many acknowledge that the diversity of the American population is one of the nation's greatest assets, yet there are striking health disparities in the United States along racial, ethnic, and socio-economic lines. Cancer mortality began to rise from the eighth-leading cause of death in the 20th century to the second-leading cause in the 21st century; it is now second only to cardiovascular disease as the leading cause of death among Americans. The passage of the National Cancer Act of 1971 increased funding for the National Cancer Institute (NCI), emphasizing training and research directed toward developing a systematic approach to conquering cancer mortality as soon as possible.[1] Despite significant scientific advances in cancer research, not all segments of the U.S. population have benefited from this progress. A closer look at cancer rates for racial and ethnic groups reveals significant differences in incidence, mortality, and survival that constitute health disparities.

In 1927, the federal government allocated its first funding for cancer research, and in 1937, Congress established the National Cancer Institute, which operated with modest funding for several decades. It was not until 1971 that President Nixon declared a national "war on cancer" and the National Cancer Act was passed. At that time, Congress was led to believe that an infusion of funding devoted to cancer research could produce a cure for cancer before the American Bicentennial in 1976. Needless to say, that goal has yet to be achieved. Perhaps the issue is not lack of funding, as Congress has increased the budget for the National Cancer Institute to more than $2 billion for fiscal year 2008. Research has primarily focused on treatment, but there should now be at least an equal focus on environmental factors and preventable causes of cancer. In addition, the focus should be on eliminating cancer health disparities in African Americans (AAs) and other minorities, the underserved, and the poor.

Broad-range health disparities still exist today, even though they were well-documented more than 20 years ago in reports such as the Heckler Report (1985)[2], the Institute of Medicine (IOM) reports on unequal burden of cancer (1999)[3], unequal treatment (2002)[4], health disparities (2006)[5], and others. These reports documented that persistent disparate health status existed in four racial/ethnic groups, defined by the Office of Management and Budget guidelines (OMB Circular 15)[6] and the Department of Health and Human Services *Healthy People (HP) 2000* report (1990)[7],

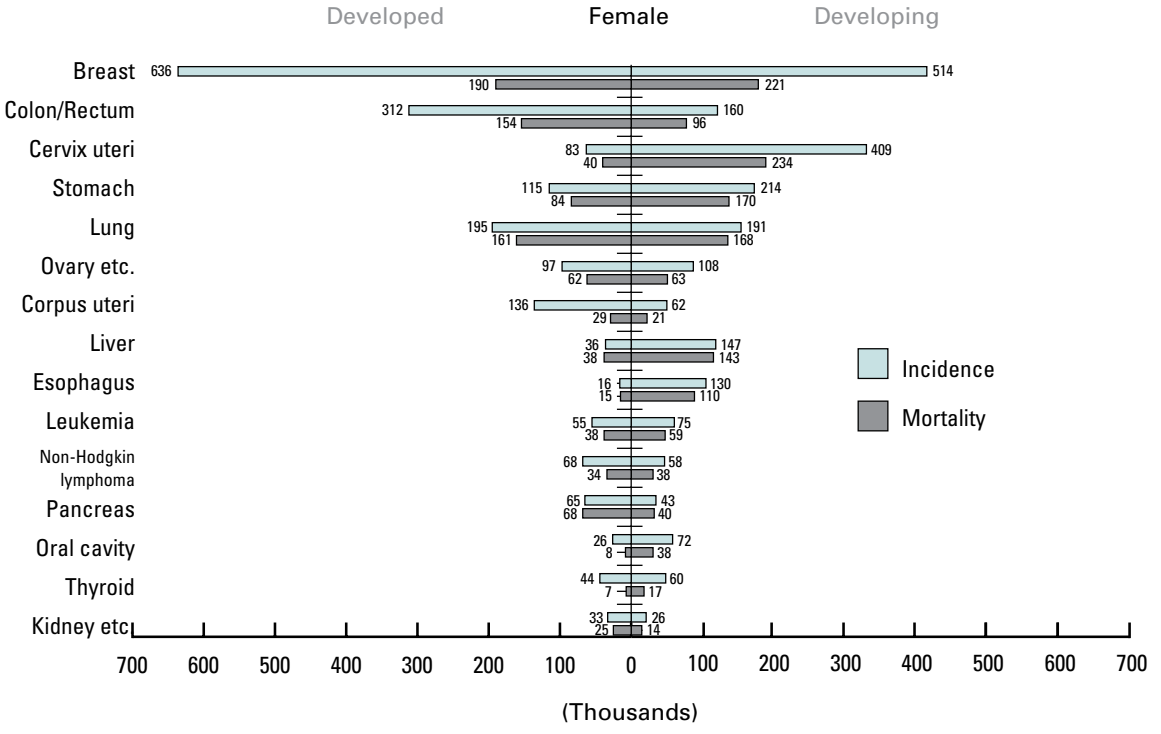
as AAs, Hispanic Americans, Native Americans/Alaskan Natives, and Asians/Pacific Inlanders. These reports also outlined the need to improve the health status of minority populations, as certain racial/ethnic groups experience higher rates of specific cancers than other groups.

HP 2000 indicated that progress was being made in 8 of 17 cancer priority areas. Yet not all population groups showed benefit, especially AAs, who were 34 percent more likely to die from cancer than non-Hispanic whites and twice as likely to die of cancer as other minority groups.[8] The mortality rates for cervical and colorectal cancer in AAs increased, while breast cancer mortality rates were unchanged, when compared to other racial/ethnic groups. The breast cancer mortality rates for AAs exceeded the 2000 target of no more than 25 cases per 100,000 people.[9]

The *HP 2010* report indicated that the *HP 2000* target reduction was met for all cancers, with an overall mortality rate of 27.9 cases per 100,000 for breast cancer. The 2010 report retained most of the objectives from *HP 2000* and added new targets to further challenge the United States to obtain better health. The objective for breast cancer mortality rate was set at less than 27.3 cases per 100,000 for whites and 35.7 cases per 100,000 for AA women (age adjusted to the year 2000 census standard

CHRONOLOGY OF HISTORICAL EVENTS IN CANCER	
1971	National Cancer Act (P.L. 92-218)
1973	Surveillance, Epidemiology, and End Results (SEER) program established
1985	Heckler Report outlined health disparities between racial/ethnic minorities and non-minorities
1988	Cancer Prevention Awareness Program directed at high-risk AAs
1990	Office of Research on Minority Health and Office of Research on Women's Health established at the National Institutes of Health (NIH)
1990	Department of Health and Human Services (DHHS) Healthy People 2000 report
1993	NIH Revitalization Act encouraged expansion and enhanced efforts in breast and other women's cancers
1999	IOM report on unequal burden of cancer
2000	DHHS Healthy People 2010 report
2002	IOM report on unequal treatment
2006	IOM report on health disparities research
2007	NIH Annual Report to the Nation on the Status of Cancer

Figure 1. Estimated numbers of new cancer cases (incidence) and deaths (mortality) in 2002. Data shown in thousands for developing and developed countries by cancer site for females.



Source: Parkin, D.M., Bray, F., Ferlay, J. & Pisani, P. (2005). Global cancer statistics, 2002. *CA: A Cancer Journal for Clinicians,* 110, 2119-2152.

population).[10] Decreasing the number of new cases and deaths from cancer in accordance with the *HP 2010* objectives remains an important goal.

In the 2007 National Institutes of Health (NIH) *Annual Report to the Nation on the Status of Cancer*, the overall trend in cancer mortality was very positive, continuing a trend started in the early 1990s of an overall decline in cancer deaths in both men and women of all races.[11] The report also indicated an unprecedented improvement in survival, widespread advances in cancer technologies, and a narrowing gap between discovery, dissemination, and delivery of care demonstrating progress in the fight against cancer. Unfortunately, this very positive trend did not reflect the lack or unevenness of progress that has consistently plagued a large segment

of the U.S. population: racial/ethnic minorities, the poor, the uninsured, and the underserved.

Today, health disparities persist among minority and underserved populations. They are manifested as increased mortality, shorter life expectancy, and higher incidence rates for cancers, infant mortality, asthma, diabetes, strokes, and cardiovascular diseases. Many of the differences in cancer mortality rates stem from several factors, some related to socioeconomic status, ethnicity, and comprehensive therapeutic options, including lack of or limited access to health care, increased risk of disease due to occupational and environmental exposure, low socio-economic status, and co-morbid conditions. Some experts believe the decline in breast cancer deaths in non-Hispanic whites is attributable to the increased use of screening mammograms, which has led to detection of the disease in an earlier, more treatable stage. AA women generally have a later stage of the disease at diagnosis, resulting in a greater disparity.

The three IOM reports clearly expressed the need to ensure that the cancer research requirements of racial/ethnic minorities and the medically underserved are addressed. The findings from these reports suggest that more effective programs targeting resources at identifying the root causes of health disparities were required to reduce the suffering and death of minorities with cancer. Such a comprehensive solution must be multi-faceted and involve providers, consumers, and health systems managers. The National Cancer Institute's plan to preempt cancer and to eliminate its ill effects is considerably aggressive; however, such an aggressive pursuit is needed if we are going to make significant progress in erasing health disparities between all racial/ethnic groups.

This document is intended to synthesize health disparity information and increase understanding of cancer-related health disparities in AA and African women, highlighting specific global problem areas in breast cancer. The objective is to stimulate breast cancer research through the identification and validation of biomarkers for basal-like breast cancer; to reduce health disparities in AAs at high risk for breast cancer; to present achievable solutions that can be of use in policy decision making; and to improve the quality of breast health care leading to healthy outcomes for African and AA women. This document will ultimately present possible solutions to the breast cancer challenges that would improve the lives of AA and other minority women at risk for breast cancer in the United States and globally. The idea is to recommend achievable solutions to these challenges as we strive to end cancer for *all* American citizens.

EPIDEMIOLOGY SUMMARY

Cancer is a leading cause of death throughout the world and is a major public health burden.

Among women, breast cancer is the most common cancer, and is the second-leading cause of death in the United States behind lung cancer.

Breast cancer is also the second-most common cancer among black South African and Nigerian women.

African American women have a higher breast cancer mortality rate than non-Hispanic white women, despite having lower incidence rates.

Breast cancer disparities between African American and non-Hispanic white women may be due, in part, to an early-onset type of breast cancer that is over-expressed among African Americans. Early-onset cancers are aggressive, while late-onset ones are more indolent in behavior.

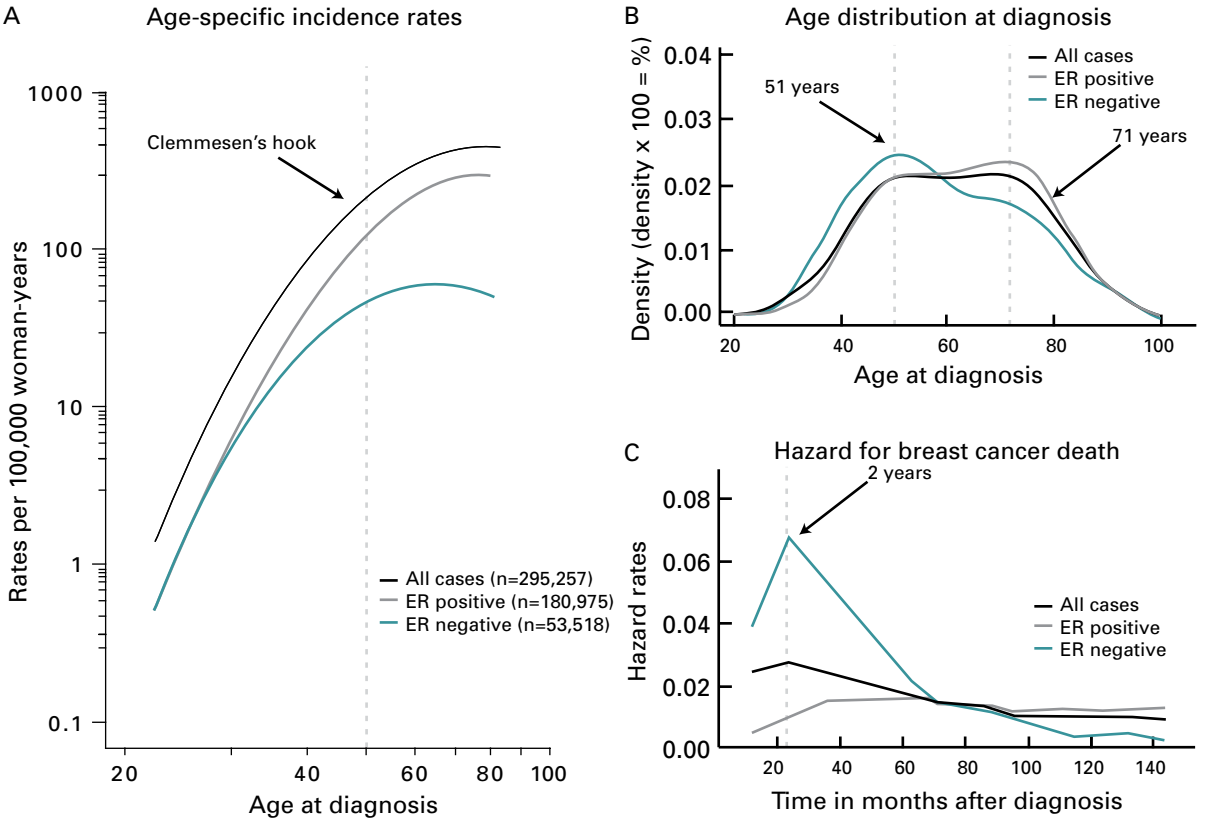
EPIDEMIOLOGY

Cancer is a leading cause of death throughout the world and is a major public health burden. The incidence and mortality rates vary among countries and regions of the world, with the highest rates occurring in developing countries. Recent global cancer statistics indicate a rising global incidence of breast cancer. This increase is occurring at a faster rate in populations in developing countries that previously experienced a low incidence of the disease. Among women, breast cancer is the most common cancer and is the second-leading cause of U.S. cancer death behind lung cancer. The annual global incidence rate of breast cancer cases exceeds 1.1 million each year, representing more than 10 percent of all new cancer cases worldwide and more than 400,000 breast cancer deaths.[12]

In the United States, 2008 statistics projected 1,437,180 new cancer cases and 565,650 cancer deaths, including 184,450 new breast cancer cases and 40,930 breast cancer deaths.[13] Cervical cancer accounts for the highest number of cancer deaths in developing countries, followed by breast cancer (Figure 2). As in the United States, breast cancer is the second most common cancer in black South African and Nigerian women. In Nigeria, the breast cancer incidence rate increased from 33.6/100,000 in 1992 to 116/100,000 in 2001.[14] In South Africa, the incidence rate (age adjusted) was 25/100,000 in 1993.[15] These figures were based on diagnoses made through pathology laboratory reports, so they probably underestimate the incidence rates.

As globalization, lifestyles, and longevity change in developing countries, incidence rates for non-infection-related cancers, such as lung, breast, and colorectal cancers, are increasing. Historically, breast cancer was thought to remain local for a long period of time. However, breast cancer is a heterogeneous disease and the etiology and prognosis are complicated by many factors. According to the linear model of breast cancer, there is a rapid rise in incidence rates until the age of 50, then a plateau in incidence rates, followed by a slower ascension (Figure 3).[16] This midlife pause is known as the Clemmesen's hook, which is attributable to hormonal changes during menopause and may reflect a mixture of two different incidence curves—one based on age of onset and the other on hormonal-dependent breast cancer. This theory is juxtaposed against the early-onset estrogen receptor negative and late-onset estrogen receptor positive breast cancer. Breast cancer has two peak incidences, one around age 50 and the second around age 70. These incidence patterns may be linked to prognostic indicators that are unique for early-onset and late-onset breast cancers.

Figure 2. Age at diagnosis of breast cancer by estrogen receptor status: rate per 100,000; percentage age distribution; and hazard ratio for mortality rate after diagnosis.



Source: Anderson, W.F. & Matsuno, R. (2006). Breast cancer heterogeneity: A mixture of at least two main types. *Journal of the National Cancer Institute,* 98, 948-951

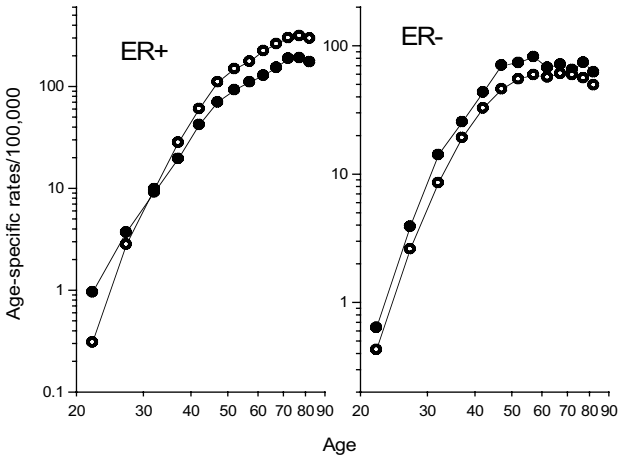


Figure 3. The five year age-specific breast cancer incidence rates for white women (open circle) and black women (closed circle) from 25 through 84 years of age by estrogen receptor status for breast cancer.

Source: National Cancer Institute. (2007). Surveillance, epidemiology and end results homepage. Retrieved November, 2007, from http:www.seer.cancer.gov.

Early-onset cancers are aggressive, while late-onset are more indolent in behavior and tend to parallel the ER-negative (basal-like) and ER-positive (luminal) patterns, respectively.

It is well-documented that AA women have a lower incidence of breast cancer, but a higher breast cancer mortality rate when compared with non-Hispanic white (NHW) Americans. This is especially true for postmenopausal women in both racial groups. Yet there is evidence that young AA women (≤45 years of age) have both a higher incidence rate and a higher mortality rate than NHWs. While high mortality might be explained by the later stage at diagnosis in AA women, other factors also play a significant role.

AA women experience higher ER-negative breast cancer incidence rates at every age level. According to the Surveillance, Epidemiology and End Results (SEER) database, the patterns are similar for both AA and NHW women (Figure 4).[17] However, racial disparity between AA and NHW women may be due, in part, to an early-onset type of breast cancer that is over-expressed among AAs. The mortality rates for breast cancer in the United States highlight the differences in clinical outcome based on race and ethnicity. AA women with breast cancer have a worse outcome (34.4 deaths per 100,000) than NHW women (25.4 deaths per 100,000).[18]

From a historical perspective, recent improvements in human health have been significant, and many unprecedented challenges have been conquered in cancer with sophisticated technological advances, unprecedented gains in treating certain cancers, increases in cancer education, and convergence with the health status of Americans. Unfortunately, these advances tend to mask widening disparities, as a large segment of the population remains at a health disadvantage in the United States and around the world. These pervasive inequities encompass everything from access to health care to health services delivery and include treatment, follow-up, rehabilitative, palliative, and end-of-life care. These disparities require a prioritized health strategy that does not overlook them. According to the Disease Control Priorities Project (DCPP), "in far too many countries health conditions remain unacceptably and unnecessarily poor," which serves as a source of misery and grief and results in the stagnation of economic growth and the persistence of poverty.[19]

ETHNO-ONCOLOGY

Following the initiation of the "war on cancer," a schism developed in the cancer movement between those who believed there was a need for a national plan of action and those who opposed such a plan. Independent, uncoordinated cancer research programs have not equally decreased mortality rates for all, especially minority and underserved populations. Therefore, more emphasis should be placed on the significance and implication of thorough cancer research planning that includes all racial and ethnic groups. One such planning mechanism was elucidated by M. Alfred Haynes, Professor of Public Health Emeritus, at the 1999 National Action Plan on Breast Cancer Multicultural Aspects of Breast Cancer workshop, where he coined the term "ethno-oncology."[20] It is based on the existence of ethnic groups in the United States with differences in lifestyle, culture, diet, and environmental exposures. He referred to ethnic group as a social construct characterized by distinctive social, cultural, and belief traditions maintained within the group from generation to generation; a common history of origin; and a sense of identification within the group. Members of the group maintain distinctive ways of life, shared experiences, and common heritage; these features may also be manifested in their health and disease experiences.

The field of ethno-oncology seeks to learn as much as possible about the causes of cancer by exploring different manifestations of cancer across ethnic groups. The genetic boundaries that were once thought to separate minorities from the majority do not really exist, and racial classification does not provide a very firm basis for cancer research. There is, however, much to be learned by focusing on the cultural and genetic heritage of racial and ethnic groups. This also requires an accurate data set of statistical information from which to draw viable conclusions. Although some theorists contend that cancer is due to genetic changes 100 percent of the time, genetics is not always the cause of cancer. The role of the environment remains unclear.

It is critically important to have accurate statistics to draw reasonable conclusions on cancer etiology. However, existing data is limited and does not allow for standardized racial admixtures. There is much to be learned from focusing on cultural and genetic heritage of racial/ethnic groups. Currently, health data collection is based on self-identified racial and ethnic groups. Several studies have advanced the identification of race and ethnicity by using molecular marker analysis to show a

lineage relationship between genetic short tandem repeats and single nucleotide polymorphism (SNP). This results in the identification of population groupings worldwide that is consistent with the primary racial and ethnic groups in the United States, such as African American, Caucasian or NHW (European and Middle Eastern), Asian, Pacific Islander, and Native American. Racial admixtures also provide another avenue for examining molecular and genetic markers in different population groups.

MIGRATION

Cancer is a worldwide problem, but it manifests differently in different parts of the world. Breast cancer is very common on the continent of Africa, second only to cervical cancer in African women. While breast cancer cases seem to have stabilized in many developed countries, they continue to rise in developing countries. Reasons for this continuing rise in developing countries have been ascribed to changes in demography, socio-economic status (SES), and different epidemiological risk factors. The incidence rates and frequency of breast cancer in African women tend to peak earlier than in NHWs by at least a decade. This is potentially confounded by a lower life expectancy of 45-55 years in Africa, as compared to 75 years for NHW in the United States. Young women presenting with advanced-stage breast cancer is more the rule than the exception in Nigeria and other African countries; generally, the breast lump is accidentally discovered, as there are very limited mammography programs and a lack of screening and awareness campaigns. Therefore, the stage of the disease at presentation is reflective of breast cancer awareness in the general population.

Young women who are still menstruating have been found to have the highest breast cancer incidence rates in Nigeria and in AAs in the United States. In a Nigerian study, 75 percent of the cases had only gender and age as risk factors.[21] Another Nigerian study found that 19 percent of women were pregnant or lactating at presentation and that 80 percent of women in the study had advanced stage cancer.[22] Risk factors and reproductive behavior, such as early age at first birth, which play a role in U.S. incidence, may not apply in African communities. African women are characterized by high fertility rates and multiparity. Studies have found associations between breastfeeding, multiparity, and breast cancer in African women.[23] [24] Differences have also been shown in the incidence rates in urban versus rural populations.

The effect of migration and migration patterns have been studied as possible contributors to the higher mortality rates, including migrations from Africa to the United States and southern—northern migration within the United States. One study postulated that there might be a "migration gradient" that interacts with the length of stay in an urban environment. The role of genetics, lifestyles, and childhood exposure to environmental hazards play a significant role in breast cancer risk, but is modified when migration occurs.[25] Several studies have looked at the migration of people from several African countries to the

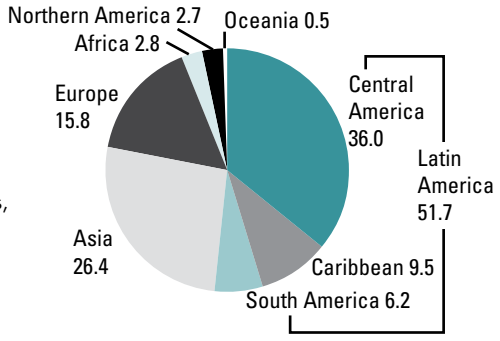


Figure 4. Percent distribution of foreign-born population by world region of birth: 2000

(Data based on sample. For information on confidentiality protection, sampling error, nonsampling error, and definitions, see www.census.gov/prod/cen2000/doc/sf3.pdf.)

Note: Adds to 99.9 percent due to rounding.
Source: U.S. Census Bureau, Census 2000, Summary File 3.

United States and the differences in their cancer risk. African women tend to present with late stage disease, and the cancer is an aggressive type similar to that observed in young AA women. The late stage at presentation links directly to lack of screening programs, poor cancer education and knowledge of self examination, inadequate medical facilities, and failure to seek medical attention after traditional and local methods have failed.

Studies have also addressed migration from the southern United States to the northern United States, as well as migration from rural to urban areas.[26] The data on south-to-north migration indicated that native northern AAs had higher cancer incidence rates than southern natives. However, rural-urban differences also existed for breast cancer, where the ratios were slighter higher for southern urban natives. A study by Greenberg and Schneider in 1995 indicated that southern-born AAs who moved north had greater cancer mortality rates, in contrast to the low rates seen in foreign-born blacks.[27] Another study reviewed the differences in cancer risk among childhood and adult migrants and compared them to native-born AAs; the conclusions affirmed that there is a regional difference in breast cancer proportional to the incidence rates seen in these racial groups.[28] However, other factors, such as occupation, SES, environment, lifestyle, and access to medical care also play a role in breast cancer outcomes.

Mobility of immigrants once they have arrived in the United States is also an issue worth exploring. According to 2000 census data, foreign-born persons accounted for 24 percent of two or more races of those responding to the census survey; 6.1 percent of AAs, 3.5 percent of NHWs, and 40 percent of Hispanics were foreign-born.[29] U.S. foreign-born populations increased by more than 50 percent between 1990 and 2000. The number reporting Latin American, African, and European ancestries more than quadrupled during the same decade—for instance, the African population grew from 246,000 to 1.2 million. AA and Mexican ancestry were the most commonly reported in the ten largest cities. Of this number, 16 million were from Latin America, representing 52 percent of the total foreign-born population. Only about three percent were from Africa (Figure 6). The mobility rate (changing of usual residence) for Africans once in the United States is 68 percent. Understanding migration patterns of the foreign-born U.S. population is becoming increasingly important as the patterns of migration may hold some significance, not only for population growth issues, but also on health care requirements and consequent economic impact.

SOCIO-ECONOMIC AND ENVIRONMENTAL FACTORS

Cancer is influenced by both environment and genetic factors; nevertheless, the direct influence of various environmental triggers on genetic factors has not been well-delineated. Because of the mutational spectra within breast cancers of women from different racial and ethnic backgrounds, p53 mutations are present in a significantly higher proportion of transitional-type mutations among tumors in AA women when compared with NHW women.[30] Although AA women are more likely to have low SES, based on education, family income, and occupation, many have better health coverage because of public insurance programs. Despite this, AA women are significantly more likely to be diagnosed with later-stage cancer, with 54 percent of AA women diagnosed with ER-negative tumors as compared to 39 percent of NHW women.[31]

There are many reasons proposed for the differences in breast cancer seen between AA and NHW women. High mortality rates in conjunction with low incidence rates and low survival rates were previously believed to be the result of late-stage diagnosis and lack of access to health services. Today, we recognize that while access and SES factors are important, there are many other factors that must be considered. One study researched cultural reasons—including customs, norms, values, beliefs, language, and health systems—driving the high mortality rates and low survival of AA women with breast cancer.[32] The study found that fear, hopelessness, fatalism, and disease perception all influenced the ability and willingness of AA women to seek screening, diagnostic, treatment, and preventive services in an appropriate and timely manner.

A significant percentage of AA women are influenced by popular myths about breast cancer. For instance, many believe that breast cancer is a white women's disease; that trauma—including surgery—provokes the outgrowth of the cancer, causing the primary tumor to grow and metastasize; and that if a woman does not know she has breast cancer, it will disappear. These are some of the myths that influence 61 percent of AAs and 29 percent of NHWs in the United States.[33] These perceptions lead to a delay in seeking medical care and follow-up. Peer education has been effective in correcting some of these false perceptions and minimizing the fear of cancer. Education has resulted in a sense of empowerment for AA women, providing them with a more proactive role in their health status.

RISK ASSESSMENT AND GENETIC SUSCEPTIBILITY

Known risk factors for breast cancer include increased age, personal and family history of breast cancer, atypical hyperplasia, early onset of menarche (≤ age 12), late age of menopause (≥ age 50), and first live birth after age 30. Other risk factors, such as hormone replacement (estrogen/progestin) therapy, ionizing radiation, alcohol consumption, and obesity have also been correlated with increased breast cancer risk. Increased breast density, high fat diet, little or no exercise, and (possibly) electromagnetic fields may also play a role.

One theory regarding the origin of breast cancer is that it arises from a series of genetic events linked to morphologic changes in cell progression. Another theory postulates that breast cancer evolves in normal ductal tissue through a series of changes that result in cancer. Estrogen has been associated with molecular changes in breast tissue and plays a significant role in breast carcinogenesis. Estrogen is important because it acts as a highly potent mitogen to normal breast epithelial cells. Many believe that the length of exposure of the breast epithelium to estrogen determines its role in the development of breast cancer. Therefore, the duration and level of estrogen exposure are very significant risk factors for breast cancer. The age of onset of menses and menopause, the age of first live birth, and the number of pregnancies are all reproductive risk factors that are directly related to estrogen exposure. Hyperplastic changes commonly occur in the breast; however, the progression to cancer occurs in only a small percentage of the breast. Breast cells' progression from normal to premalignant hyperplasia and then to *in situ* carcinoma is thought to be the result of estrogen's effect on the cell and the resulting mutation effect on the receptor cells.

Between five and 10 percent of breast cancers are caused by mutation in the breast cancer genes, BRCA1 or BRCA2. The BRCA gene mutation is more likely to occur at a young age, in ER-negative tumors, and in an environment where other gene interactions play a role. The BRCA1 gene mutation corresponds with the high incidence of cancer seen in AA women between the ages of 30-49. BRCA1 mutation cancers are poorly differentiated, have high S phase fraction, medullary or atypical histology, high p53 mutations, and are ER-negative/PR-negative. A similar pattern is seen in young AA women who exhibit polymorphisms and other variants.[34]

Childbearing seems to have a dual effect: Early age (younger than 30 years) at first live childbirth is protective. Multiple births at a young age (prior to age 45 years) may increase breast cancer risk; however, it is protective against breast cancer after age 45. A study by Pathak indicated that the increased risk for breast cancer in AA women may be due to the higher prevalence of early childbearing in AA women compared to NHW women.[35] The typical profile of Nigerian women with breast cancer is consistent with that of other developing countries, in that they are generally multiparous, premenopausal, and have prolonged breastfeeding. In a 10-year review of Nigerian women, the mean parity was 5.35, the age at first full term pregnancy was 20 in 57 percent of cases, and breastfeeding continued for a mean of 8-12 months.[36]

The ability to determine if a women is at high risk for acquiring breast cancer is based on the presence of several known risk factors. Mitchell Gail of the National Cancer Institute developed a risk assessment tool, known as the Gail model, which is designed to determine the eligibility of a woman to participate in cancer clinical trials.[37] Data for this model were based primarily on NHW women, and the usefulness and applicability of this model for AA women has been challenged by several groups. The Claus model was developed using some of the criteria from the Gail model, with additional modifications in an attempt to have greater applicability for AA and other minorities.[38] The number of AA women in clinical trials remains small, as the eligibility criteria (based on number of first-degree relatives with breast cancer, age at menarche, age at first live birth, and number of breast biopsies) exclude many women who are interested in participating in such trials. The Study of Tamoxifen and Raloxifene (STAR) trial is an excellent example of the increased interest of AA women in participating in a cancer prevention trial. In this study, 20,278 AA women were screened and completed the risk assessment tool. However, only 2.5 percent (488) were deemed eligible to participate in the study of 19,747 women.[39]

In 2007, Gail and his team of researchers developed a new risk assessment tool to more accurately predict the breast cancer risk of AA women, using data from the SEER program and the Women's Contraceptive and Reproductive Experiences (CARE) study.[40] The CARE study involved a comparison of 1607 AA women with invasive breast cancer and 1637 AA women of similar age without breast cancer. Factors used to create this new model were age at first menarche, number of first degree relatives with breast cancer, and number of previous benign breast biopsies. Age at first live birth was not identified as a predictive factor of significance in AA women. Risk was calculated by combining the above factors with the rates of invasive breast cancer and mortality rates in SEER. The outcome of the CARE model was validated using two risk profiles. One group consisted of AA women in the Women's Health Initiative study with no history of breast cancer. The comparison group was AA women who were screened for the STAR trial, but were deemed to be ineligible.

The results revealed that the risk for invasive breast cancer in AA women was 30.3 percent based on CARE, compared to 14.5 percent based on the Breast Cancer Risk

Assessment Tool that determined previous eligibility for the STAR trial and other cancer studies. This is a major step forward in determining breast cancer risk in AA women. Nevertheless, it is important to recognize that this tool may be inappropriate for all minority women and certainly has no benefit for women with a prior history of breast cancer. Moreover, it may not provide an accurate prediction for women with the breast cancer gene mutation or who have been exposed to radiation treatment. While the CARE model is effective in AA and other minority women, it still needs further validation.

Genetically engineered animal models can provide important venues for analyzing prevention and treatment mechanisms. Such models could serve as useful preclinical testing grounds for potential interventional agents, as well as predictive models for human response. Recently, research has compared the gene expression profiles of mouse mammary tumors and human breast cancers. For instance, a UK research group performed an engineered mouse model for basal-like carcinoma expressing the triple-negative phenotype using BLG-Cre, BRCA1, and p53. The BRCA1 gene was inactivated in luminal epithelial cells of mouse mammary gland, and all cells had one wild-type allele of p53. The analysis of tumors arising in these mice was consistent with human tumors that were ER-negative/HER2-negative, expressed basal markers 78 percent of the time, and had 88 percent homologous metaplastic elements. This model may provide the necessary link between basal-like phenotypes and BRCA1 pathways, as well as prove useful for testing novel therapy for human basal-like cancers.[41] This work is similar to work performed in the United States by Green at the National Cancer Institute (NCI), who performed a genomic analysis of the T antigen mouse model and identified a gene expression signature containing many genes involved in proliferation, DNA repair, metabolism, cell cycle, and apoptosis.[42] The T antigen signature is similar to what is seen in human basal-like tumors and is predictive of survival in breast cancer patients. The applicability in AA women has yet to be validated.

TUMOR BIOLOGY SUMMARY

Statistically significant characteristics of breast tumors in African American women include later stage at diagnosis, larger size, positive lymph nodes, higher histologic and nuclear grade, and aggressive growth. These result in poorer overall survival rates.

African American women are diagnosed twice as often as non-Hispanic whites with advanced stage breast cancer with poorly differentiated nuclear grade.

Mutations in p53 and c-met both result in negative prognoses for women, and African American women are significantly more likely to have tumors with these mutations.

TUMOR BIOLOGY

Generally, AA women have a lower incidence rate of breast cancer than their NHW counterparts. However, young AA women (≤ age 45) have higher incidence rates. The disease in AAs is more aggressive and usually presents earlier as high grade histology with estrogen receptor negativity, resulting in a poorer overall survival rate. Many studies confirm that AA women tend to have breast tumors with high-grade nuclear atypia, high mitotic activity, higher S phase fraction, poor differentiation, ER-negativity, and progesterone receptor (PR) negativity. Mutations in p53 and c-met both result in negative prognoses for women, and AA women are significantly more likely to have tumors with p53 mutations and c-met positive tumors, even when adjusted for age and other confounding factors. However, confounders such as ER- and PR-negative hormone status and obesity may skew the potential association between c-met expression and mortality rates in AA women. A study by Poola et al revealed that a beta isoform expression in the estrogen receptor, which may be protective against proliferative changes in mammary epithelial tissue, may be disproportionately low in AA women.[43] Other biomedical studies have found that hormone-receptor negative, aneuploidy, and node positive breast cancer appear to be specific to AA breast cancer, even after controlling for stage at diagnosis and age.

Demographics of Africans and AAs, such as younger age at presentation and dietary, genetic, and environmental factors, may independently or simultaneously influence the biological and clinical patterns of breast cancer observed in these groups and contribute to the aggressiveness of the disease and poorer outcomes. One African study found that after adjusting for these factors, the results were similar to U.S. studies where AA patients had higher mitotic activity and nuclear grade atypia.[44] The higher proliferative activity may be partially explained by several factors, such as the prevalence of obesity, which is associated with high plasma estrogen levels. Obviously, the concept of tumor biology should be used to aid in predicting the outcome of breast disease.

Several studies[45] [46] [47] [48] have shown that younger women tend to have breast carcinomas that are endocrine negative, have poorer outcomes, and have higher local failure rates following surgery. While these tumors may be smaller, they are biologically more aggressive, with high vascular potential and a greater probability of regional nodal metastases. Statistically significant characteristics in the breast tumors of AA

women include later stage at diagnosis, larger size, positive lymph nodes, higher histologic and nuclear grade, and aggressiveness of growth. These same characteristics have also been seen in studies of young African women. Factors influencing late presentation include religious beliefs, denial, SES, herbal treatments, fear, unfriendly hospital atmosphere, preference for indigenous or non-allopathic healers, general lack of breast cancer awareness, and, in some cases, a lack of knowledge among primary health care providers about breast cancer.

Increased breast cancer awareness has led to greater use of mammograms and may be partially responsible for the increase in the presentation of ductal carcinoma *in situ* (DCIS) cases. One study of premenopausal women (ages 19–35 years) found a DCIS correlation in most of the invasive cancers, which may indicate that a pathogenic mechanism in the pathway to invasive breast cancer progressed through an *in situ* phase in these young women.[49] These findings suggest that biological changes progressing toward the development of breast cancer start very soon after puberty. The presence of intermediate to high nuclear-grade DCIS elements was used to explain the rapid invasion into the stroma observed in this study.

The pathologic predictive indicators for HER2/neu gene amplification and/or over-expression also seem to differ for AA women and NHW women, but are not likely to explain the survival differences between the two groups. AA women are diagnosed twice as often as NHW women with advanced-stage breast cancer that has poorly differentiated nuclear grade.

MOLECULAR PROFILING

Molecular profiling is a tool used for better classification of cancer origins; it ultimately aids in providing a more accurate prognostic and therapeutic selection. The mechanism identifies sets of genes whose expression classifies breast cancer into distinct intrinsic subtypes and allows for an association with survival. Molecular profiling allows the comparison of different tissue types on a molecular level to a global scale through the use of two primary techniques, one supervised and the other unsupervised. The supervised technique uses sample groups that have known clinical outcomes in order to generate gene expression data that is useful in determining differences in gene expression within the known outcomes group. The unsupervised method characterizes samples into sub-classes through differing gene expressions from a cohesive set of samples. The goal of molecular profiling is to identify a distinct subset of breast cancer that will be helpful in determining the variability of response to treatment and clinical outcome. Because of the heterogeneous nature of breast cancer, molecular profiling has lead to subsequent identification of five intrinsic subtypes: Luminal A, Luminal B, normal, HER-2 over-expressing, and basal-like. Differentiation into these sub-types is based on a comparison of gene expression data from the unknown sample with known expression controls.

Of the five subtypes, two are estrogen receptor-(ER) negative tumors: the basal-like and HER2-positive/ER-negative. The HER2-positive/ER-negative subtype is characterized by an over-expression of a HER2-related cluster of genes. The basal-like subtype is characterized by low expression of HER2-related genes, but a high expression of a group of genes having characteristic of normal basal epithelial breast tissue. These basal cells stain with antibodies to cytokeratin 5/6, 14, and 17; BRCA-1 gene mutations; and have higher proliferation rates, aggressive histology, and unfavorable clinical outcomes. Evidence suggests that the basal-like type is a distinct subtype of invasive carcinoma. They are also characterized by ER negativity, PR negativity, HER-2 negativity, BRCA-1 mutations, high-grade nuclei, mitotic index and aggressive histology, shorter survival, p53 over-expression, unsupervised gene expression profiling, and a lack of response to endocrine therapy. This histologic subtype is most often consistent with the ductal, but medullary or non-specific cell types have also frequently been seen. Because of the earlier age at diagnosis (more prevalent in

premenopausal women), higher tumor grade, and greater proportion of basal-like (ER-, PR-, HER2-) tumors, researchers suggest that this type of breast cancer is more commonly seen in AA women and is biologically different.

Studies show that 80-90 percent of triple-negative carcinomas are basal-like and are characteristic of mouse stem cells. There are also findings that subtypes are affiliated with mammary cells of origin, indicating that changes in gene expression patterns may be associated with carcinogenesis occurring early in the cell progression process.[50] One study identified 10-17 percent triple-negative carcinomas, which is comparable to the reported incidence of basal-like cancer. Using triple-negative as a surrogate marker for basal-like breast cancer reveals that pre-menopausal AA women are a high-risk group and that there is a biologically distinct negative survival correlated with having the triple-negative phenotype.[51]

In order to characterize triple-negative (ER-, PR-, HER2-) phenotypes with regard to age, ethnicity, SES, and survival, a population-based study observed all new invasive breast cancer cases in 92,358 women in the California Cancer Registry between 1999 and 2003.[52] Using micro-array profiling, 13 percent (6370 cases) were identified as triple-negative phenotypes, with 63 percent being diagnosed before the age of 60. The percent of AA women with triple-negative phenotypes was twice that of other racial and ethnic groups. Approximately 85 percent of triple-negative breast cancers were basal-like, although all basal-like tumors are generally triple-negative. Reports indicate that women with higher SES tend to have higher breast cancer incidence and smaller tumors.[53] The median tumor size is generally larger in women with the triple-negative phenotypes and the primary histology is classified as poorly differentiated or undifferentiated. Women under age 40 are 1.53 times more likely to develop triple-negative cancer than those women age 60 or older. Survival rates are also lower for women with triple-negative, with only 77 percent of women surviving beyond five years in comparison to 93 percent survival rates for other subtypes.

A population-based study involving 196 AA women and 300 NHW women concluded that despite the presence of all the subtypes in both populations, there was an interaction between race, age, and subtype.[54] Basal-like tumors were present in 39 percent of the AA population and probably impacted the poor outcome for the AA cohort. Genetic and biologic variation in cancer gene expression is evidenced in the higher mortality rates coupled with low incidence rates generally seen in AA women.

SCREENING AND EARLY DETECTION

Population-based, single-institutional, multi-center, and meta-analysis studies have shown that AA women of all ages tend to present with advanced stage disease compared with NHW women. Failure to present with early stage disease is consistent with the absence of optimal screening practices by AA women. Screening recommendations from the NCI, American Cancer Society (ACS), and the National Comprehensive Cancer Network (NCCN) in the United States include an annual clinical examination and mammogram and monthly breast self-examinations, with 40 as the baseline starting age. Mammography may be started earlier in high-risk individuals, as decided by the patient and the health care provider. However, data from ACS reveal a statistically insignificant difference in mammography screening utilization between NHW (70 percent) and AA (67 percent) women. Obviously, other factors impact the late stage at diagnosis prevalent in AA women.

Screening and early detection are paramount to improved outcomes and increased survival rates in AA women. National Health Interview Survey (NHIS) data shows an increase in screening mammograms among both AA and NHW women, indicating a usage rate of 68 and 71 percent, respectively, for those over age 50. For women age 40–49 years, usage is 61 and 67 percent, respectively.[55] However, studies focusing on SES found that "outcome disparities will not be eliminated entirely by intensive screening efforts alone".[56] One report showed that even after adjusting for SES, stage, and age at diagnosis, AA women had a 22 percent higher mortality risk.

In African countries like Nigeria, where mammography is a scarce resource and there are no recommended guidelines, most subjects present with large tumors involving extensive skin pathology of the whole breast (26 percent) and axillary nodes (84 percent).[57] Experts propose that using the count of mitotic figures as a prognostic tool is a less expensive and more cost-effective diagnostic method for Nigeria.

PREVENTION

There is a critical need to develop innovative strategies for preventing and treating breast cancer in order to identify a more comprehensive approach to reducing the disproportionate number of breast cancers in AA women in particular, but also to eliminate breast cancer health disparities more broadly. Cancer chemoprevention uses either naturally occurring or synthetic chemical agents to prevent, reverse, or arrest the progression of preneoplastic lesions to invasive breast cancers. The progression from normal, preneoplastic, dysplasia, hyperplasia, *in situ* to invasive cancer may also be blocked from progressing by inhibiting epithelial mutagens and mitogens. This can occur when modification or prevention of carcinogenesis steps takes place by preventing DNA damage from free radicals, decreasing epithelial cell proliferation, and/or increasing differentiation.

An investment in cancer prevention research that began in 1998 with the initiation of the first breast cancer prevention trial (BCPT) demonstrated an effective agent for the reduction of breast cancer incidence among high-risk women. The study results showed that tamoxifen, a selective estrogen receptor modulator (SERM), caused a 49 percent reduction in invasive breast cancer in high-risk postmenopausal women and an overall reduction of 50 percent in the incidence of breast cancer in pre- and postmenopausal women.[58] This offers proof of principle for targeting the estrogen receptor in ER-positive breast cancer. The STAR (Study of Tamoxifen and Raloxifene) Trial in 2006 yielded consistent results in further advancing ER-positive breast cancer prevention by showing a second SERM, raloxifene, to be equivalent to tamoxifen in preventing breast cancer, but with less serious toxicity.[59] It demonstrated a preventive effect for invasive breast cancer in high-risk postmenopausal women, and in 2007, this agent became the second breast cancer prevention agent approved by the U.S. Food and Drug Administration for human use. In fact, the overall reduction reflects a 70 percent reduction in ER-positive disease, but no reduction in ER-negative breast cancer—leaving a major gap in breast cancer prevention. Definitive Phase III cancer prevention trials based on cancer incidence are intensive in their requirement for clinical resources and will become more difficult to fund in the future.

However, an attractive way to study potentially useful chemopreventive agents is to perform short term (pilot or Phase 0) studies examining the effect of interventional

agents on molecular, imaging, and histologic surrogate endpoints of disease status in populations at high risk for developing invasive cancer. A clinical opportunity for prevention of ER-negative (basal-like) breast cancer presents itself in using this pre-surgical model in women with an initial diagnosis of ER-negative cancer on biopsy specimens that require a definitive excision procedure. Investigators might consider smaller studies that measure biomarkers of interest (for example, HER2/neu). Prior to definitive surgery, the effect of a single or multiple dose oral agent with prospects for prevention could be given. Following excision, a measurement of targeted tissue or biomarkers would be obtained and compared with placebo to determine pharmacokinetic measures and changes in concentration of the molecular targets of interest (for example, progenitor cell characteristics) in the definitive excision material. This is the model used previously in preclinical or animal studies to determine the efficacy of chemoprevention agents.

Due to advances in molecular biology, promising agents for chemoprevention studies in ER-negative breast cancer may be discovered, such as kinase inhibitors (e.g. Epidermal Growth Factor Receptor (EGFR) or Kit) and rexinoid (RXR) agonists, which may interact with multiple nuclear receptors, anti-inflammatory and anti-angiogenesis agents, Vitamin D analogs, Poly ADP-ribose polymerase (PARP) inhibitors, or a combination of these agents. One such example may be kinase inhibitors activity targeted at EGFR1 and HER2/*neu*, which might reduce the risk of developing ER-negative breast cancer. For BRCA1 mutation carriers who are diagnosed with ER- negative breast cancer, biomarker studies need to be organized with a focus on drug modulatable targets.

TREATMENT AND SURVIVAL SUMMARY

Some reasons for the racial/ethnic disparities in survival are differences in treatment utilization, co-morbid conditions, insurance coverage, and/or provider biases.

African American women tend to obtain appropriate primary treatment (surgery), but not adequate adjuvant chemotherapy.

While the United States is starting to address the impact of breast cancer as the leading cause of death in younger women, African countries have not, and the ravages of this disease continue, due to poor health conditions and inadequate health care facilities.

In Nigeria and other African countries, breast conserving options are not readily feasible, due to late-stage presentation, lack of adequate radiotherapy facilities, few diagnostic oncology specialists, inability to characterize prognostic factors, young age of patients, and poor follow-up.

TREATMENT AND SURVIVAL

Large prospective randomized, controlled trials have shown that adjuvant therapy is an integral component of breast cancer early stage management, even for ER-negative disease. Such treatment has led to an increased rate of survival. Even in areas where there are multi-disciplinary teams of breast cancer providers, large disparities exist in the provision of appropriate adjuvant treatment (i.e., under-use of efficacious adjuvant treatment was 16 percent for NHWs versus 34 percent for AAs in a New York study).[60] Poor survival continues to occur in AA and other minority women. The reason for this poor survival is not well-defined. In part, it may be due to the severity of the disease, larger tumors, and late stage at diagnosis. Some reasons for the racial differences in survival are disparate treatment utilization, co-morbid conditions, insurance coverage, and/or provider biases. While AA women seem to receive appropriate primary treatment (surgery), they do not receive adequate adjuvant chemotherapy, and when the accompanying co-morbid conditions are controlled for, the disparity in treatment continues to persist. One study found that AA women do not receive recommended oncology consultation, which leads to missed opportunities for optimal treatment and may partially explain the poorer survival. Enhanced communication between patients and providers may help in reducing racial disparities in cancer care. Improving the overall quality of breast cancer care and ensuring that AA women receive the required intensive treatment is a cost-effective way to decrease the mortality differential. [61]

Despite the poor prognosis of basal-like and HER2+/ER-negative subtypes, they demonstrate high rates of pathologic complete response (pCR) when treated with neoadjuvant chemotherapy and may benefit more from chemotherapy than Luminal A tumors, according to results from a study by Morris and Carey.[62] Negative associations of triple-negative phenotype with survival disappeared in the group receiving chemotherapy, which indicates better response to this form of therapy. Analyses of survival found that nodal status, tumor size, and negative androgen receptor status correlated with reduced disease-free intervals and overall survival. However, nodal status and size were the only markers with independent prognosis significance. Less than 10 percent of ER-negative, PR-negative tumors respond well to chemotherapy. There are limited options for treatment of triple-negative tumors, which require additional biomarkers

to be more clearly characterized as a subgroup. There are no known specific targets identified in triple-negative breast cancer, thus limiting treatment strategies. Attention has been given to conducting exploratory investigational new drug studies or the so-called Phase 0 studies.

Successful cancer management varies substantially between developing and developed countries, and one primary challenge is to decrease the significant gap between survival rates in developed and developing countries. Early breast cancer detection and treatment are not readily available in most sub-Saharan African countries, for instance, so women tend to present with late-stage disease and have poor survival rates. If the care regimen requires multimodality therapeutic or a complex preventive regime, it is very challenging to provide in a country that lacks appropriate infrastructure and/or specialized medical staff. Additionally, in the case of breast cancer in young women, the effect of tumor biology and its aggressiveness must be considered. While the United States is starting to address the impact of breast cancer as the leading cause of death in younger women, African countries have not, and the ravages of this disease continue, due to poor health conditions and inadequate health care facilities.

In Nigeria, most tumors are diffuse, large, and multi-focal, and radiation therapy is not readily available. Poor compliance and poor outpatient clinic attendance limit the ability to assess the efficacy of using hormonal therapy in women whose ER status is either positive or unknown. While chemotherapy is readily available and used, high cost limits widespread use. Advanced-stage breast cancer is difficult to manage and results in a less than 10–15 percent five-year survival rate. Adjuvant chemotherapy is the primary treatment method in many developing countries due to the limited availability of radiation therapy.

Treatment modalities in Africa also vary. Data from one study in Nigeria evaluated 185 subjects who had undergone surgeries spanning mastectomy to modified radical mastectomy. Neoadjuvant chemotherapy was used in 64 cases, and adjuvant chemotherapy was used in 178 cases. Only 70 (33 percent) of the surgery patients returned for radiotherapy, although all patients were referred back for radiation by their surgeons. All 70 were deemed to have good treatment compliance. Follow-up care varied from a mean of 8.4 months; 91 percent died within the first year of diagnosis, while 89 percent of those lost to follow-up also died within the first year after diagnosis.[63] However, in Nigeria and other African countries, breast conserving surgical options are not readily feasible due to late stage presentation, lack of adequate radiotherapy facilities, few diagnostic oncology specialists, inability to characterize prognostic factors, young age of patients, and poor follow-up.

Breast cancer surgery is generally aimed at making a diagnosis, reducing the tumor burden, controlling disease at a loco-regional level, and obtaining prognostic information. However, in Africa, surgery may soon become an adjuvant form of therapy. Adjuvant chemotherapy helps to reduce local recurrence and to increase overall survival in women regardless of menopausal or nodal status. Preoperative

(neoadjuvant) chemotherapy is being used to down stage the tumor and allows for selection of women with poor prognosis. Neoadjuvant chemotherapy has also been considered for managing operable cancer and as a prognostic factor; subjects who do not respond to neoadjuvant therapy will not be given similar drugs post-operatively. Doxorubicin and Taxane are mainstay combinations that have shown better pathologic complete response than other drug regimens. Cisplatin-based regimes seem to be more effective in ER-negative tumors. The direct treatment cost for early stage breast cancer in Nigeria is at a minimum is US$800.00 and the cost for advanced stage disease is much more, neither of which includes the full economic potential of the patient or associated cost for care. The gross national product in Nigeria is only about US$250.00 per person. The rising cost of cancer management makes emphasizing prevention a very important management option.

Cancer treatment spending in the United States continues to rise, along with total health care spending. Unexplained cancer-related health disparities remain among population subgroups, especially AAs and Hispanics. AAs and people with low SES have the highest rates of both new cancers and cancer deaths. In addition, AAs and other minorities, poor, and underserved populations are likely to have poorly controlled co-morbid conditions that impact their response to cancer therapy. Co-morbid conditions, such as hypertension and diabetes, have accounted for the resulting poor survival of up to nearly 50 percent of AAs with breast cancer, as reported in several studies.[64 65 66 67 68]

HEALTH SYSTEMS DISPARITIES SUMMARY

The U.S. health system is marred by many cases of neglect and/or failure to enact and implement health policy mandates that have the potential to minimize suffering and death from cancer experienced by African Americans and other minorities.

If the United States is to eliminate health disparities, we must acknowledge that poverty and race/ethnicity do affect health.

Efforts to eliminate breast cancer health disparities must address the roles of the health care provider, insurer, and industry, as well as those of government and academia.

Health disparities can be eliminated by the identification and implementation of evidence-based, cost-effective, and culturally appropriate interventions.

HEALTH SYSTEMS DISPARITIES

If the United States is to eliminate health disparities, we must acknowledge that poverty and race/ethnicity do affect health. In certain situations, poverty should probably be considered a carcinogen, although in certain cancer epidemiological studies, it is difficult to distinguish the impact of poverty from that of race. Efforts to eliminate breast cancer health disparities must address the role of providers, insurers, industry, government, and academia. Obviously, if we are to close the gap in breast cancer health disparities, the research agenda must use multidisciplinary approaches to care and address mechanisms for removing all barriers leading to the provision of high quality effective care to the poor, minorities, and the underserved. Unfortunately, the health system is marred by far too many cases of neglect and/or failure to enact and implement health policy mandates that have the potential to minimize suffering and death from cancer experienced by AAs and other minorities.

Data from the Disease Control Priorities Project-2 (DCPP2) indicated that a number of inequities remain as a result of disparities in health care services.[69] For example, one-third of the world's population has no effective access to essential modern medicines or vaccines. Nearly 47 percent of those in sub-Saharan Africa cannot obtain essential drugs when needed. Many barriers prevent people from obtaining appropriate breast health care. These barriers can be categorized as the following:

a) ***Services***—transportation costs; distances to service facilities; hours of operation; poor quality of care; inappropriate care; cultural and linguistic differences; and negative staff attitudes
b) ***Customers***—social and cultural constraints; lower income for women; burden of assigned family roles; limited educational awareness; to a degree, rights and availability of services; and poor understanding of health information provided
c) ***Providers/Institutions***—stigma and discrimination in health settings; lack of involvement in decision-making process; perception of illness; cultural incompetency; bias in provision of recommended screening and treatment guidelines; health costs; and perceptions
d) ***Insurers***—coverage of effective interventions to improve survival; greater cost containment concern; and health budgets

The question is how these inequities can best be addressed while maintaining and advancing previous technological and historic gains in health status. Our challenge is to identify specific evidence-based and cost-effective interventions that apply culturally appropriate, intelligent policy changes that will help us progress toward equitable health care for all. The application of health policies to support quality health care, reduce barriers to access, and generate knowledge in specific prioritized areas of cancer, specifically breast cancer, is critical to eliminating health disparities. Such a program will likely require additional human and financial resources.

The DCPP2 report gives special attention to strengthening the health systems. It indicates that it will be almost impossible to improve health outcomes in a cost-effective manner unless the health system is better equipped to provide efficient, effective, and equitable services. Changes to the system would require all components (providers, insurers, and government) to critically analyze business practices and make drastic changes that will benefit all people. A major step in that direction is to make health a priority and to focus intensely on prevention. Additionally, recommendations from the 2007 ER-negative Think Tank, sponsored by the NCI, further supported the need to recognize that ER-negative breast tumors are aggressive. Therefore, it is important to design studies that will elucidate effective strategies not only for screening, early detection, prevention, and treatment, but also to assess the biology of these tumors. Insight into health disparities and the biology of ER-negative breast cancer can be gained through collaborative studies. Investment priorities should include:

a) Developing evidence-based criteria for identifying breast cancer subtypes;
b) Evaluating research interventions to improve prevention and treatment outcomes;
c) Identifying biomarkers for young women at high risk for developing aggressive breast cancer;
d) Determining whether differences in tumor microenvironment and/or normal tissue contribute to differences in ER-negative cancer between AA and NHW women;
e) Ensuring equal access to care;
f) Conducting collaborative studies that collectively analyze available data to optimize return on past investments;
g) Examining the relationship between SES and ER-negative/basal-like breast cancer;
h) Developing the infrastructure to support and integrate high-throughput clinical studies on ER-negative and/or triple-negative breast cancers.

POLICY IMPLICATIONS SUMMARY

The most effective approach to solving cancer health disparities must focus on patients/consumers, health care providers, and the health delivery system.

In order to begin to minimize health disparities between developed and developing countries, each high-technology approach developed to address early detection, screening, prevention, and treatment must have a feasible low technological counterpart available.

The top priority in ending cancer health disparities is creating incentivized prevention measures.

Policies should include legislative requirements to cover screening, prevention, early detection, and payment coverage by Medicaid, Medicare and other insurers.

Creating a more equal health field also requires changes outside the health sector, within economic, employment, and social policies.

POLICY IMPLICATIONS—CLOSING THE GAP

Unless we begin to seriously and effectively address cancer prevention and early screening, cancer incidence will increase from 10 million to approximately 20 million by the year 2020. Estimates suggest that more than 70 percent of all new cancers cases will occur in people in the developing world and with these new cases, the mortality rate will increase from 6 million to more than 12 million each year. Greater efforts must be made to address and eliminate health disparities in cancer. Such disparities have persisted and in some cases worsened during the 23 years since the Heckler report.[70] Race as a social construct must be removed from consideration in the decisions affecting our public health whether deliberate or subconscious. All aspects of public health—including behavioral and social science, politics, economics, and medicine—must be embraced in the effort to eliminate health disparities.

If we truly value and desire an increase in cancer survival—not simply longevity, but high-quality survival—then we need to adopt a new health system management approach. Such a program will include education and training for the public and providers, and will develop a health service delivery system that is accessible to all, with a special emphasis on those incapable of paying. Perhaps most importantly, it will create incentivized prevention measures. The most effective approach to solving cancer health disparities will focus on patients/consumers, health care providers, and the larger health delivery system. In order to begin to minimize health disparities between developed and developing countries, each high-technology approach developed to address early detection, screening, prevention, and treatment must have a feasible low technological counterpart available.

Policy implications include legislative requirements to cover screening, prevention, early detection, and payment coverage by Medicaid, Medicare, and other insurers. Independent eligibility criteria for Medicare should be instituted to reach those with conditions that could become economically catastrophic. In Africa, insurance and additional resources (financial and human) are needed to improve the provision of high-quality, multidisciplinary, evidence-based breast health services.

Cost remains a major constraint for many nations, including the United States, so early detection is an important factor in obtaining effective treatment for all—and will continue to play a major role in the future. Strategies must be tailored and take into

account the potential for cooperation and synergy between different health programs. Priorities for global cancer prevention need to strike a balance between research, development, and implementation.

Another possible approach to initiating the reduction in health disparities and to creating a more equal health field would be to make changes outside the health sector, such as within the economic, employment, and social policies listed below:

BARRIERS TO REDUCING HEALTH DISPARITIES	SOLUTIONS TO HEALTH DISPARITIES
1. Poverty and lack of employment	1. Increase employment options
2. Lack of insurance and underinsured	2. Universal insurance coverage
3. Modified clinical trials criteria	3. Increase research opportunities
4. Impact of race construct as variable	4. Understand & overcome racial biases
5. Unequal health service delivery	5. Monitor quality of health systems
6. Co-morbid conditions	6. Evaluate relevance of co-morbidities
7. Detrimental lifestyles	7. Educate and incentivize healthy choices
8. Impact of genes and environment	8. Evaluate gene/environment interaction
9. Differences in tumor biology	9. Measure and validate biological differences
10. Lack of effective targeted therapies	10. Research targeted therapy for minorities
11. Inability to manipulate the system	11. Provide patient navigators

ECONOMIC IMPACT SUMMARY

In 2001, cancer accounted for more than 7 million deaths worldwide (translating into more than 100 million DALYs), with the majority occurring in developing countries.

Although breast cancer represents 85 percent of the global cancer disease burden, breast cancer research receives less than four percent of all available cancer research funding.

Return on research investment can be quite lucrative, but greater emphasis must be placed on prevention and early detection, as well as on altering the trend in outcomes for all groups.

ECONOMIC IMPACT

In 2001, cancer accounted for more than 7 million deaths worldwide, with the majority occurring in developing countries. That translates to more than 100 million disability adjusted life years (DALYs), of which two-thirds occurred in developing countries.[71]

The economic impact of cancer and other chronic diseases in the U.S. is currently more than $1 trillion per year.[72] Unless we initiate dramatic changes in health care soon, the cost is anticipated to rise to $6 trillion by the year 2050. A 2007 Milken Institute report, "Unhealthy America: The Economic Burden of Chronic Disease", indicated that this economic impact includes not only the cost of treating the disease, but also decreased job performance, increases in sick days, and losses associated with caregiver requirements.[73] Former U.S. Surgeon General Richard Carmona stated that "the disease burden is rapidly mounting along with the economic burden and this current trajectory is unsustainable".[74]

Chronic disease management, which includes cancer, costs roughly $277 billion annually, based on 2003 data. With the concomitant loss of productivity, this cost increases to more than $1.3 trillion for the nation's businesses and government. Cancer leads the chronic diseases in avoidable cost of care and output losses with $37 billion in direct costs and $373 billion in indirect costs. While the National Cancer Institute issued the 2007 cancer report indicating a decline in suffering and death from cancer, especially in breast cancer mortality, this was not indicative of the mortality rates for all segments of the population.[75] Minority and underserved cancer rates, especially breast cancer mortality rates for AAs, experienced little to no change. Even with the reported decline in mortality rates from cancer, the economic impact of cancer care remains greater than other chronic diseases because cancer treatment is very expensive, patients are more debilitated, time lost from work is greater, and caregiver support is greater than costs associated with other chronic diseases. If the current trend continues, it is projected that by 2023, the incidence of seven leading chronic diseases in the United States will increase by 43 percent, for a cost of $230.7 million and $4.2 trillion in treatment and lost economic output, respectively.[76]

Shifting the primary focus to early detection and prevention could drastically reduce health expenses. Improvements in prevention and treatment could potentially

Figure 5. National cancer treatment expenditures in billions of dollars (1963-2004)

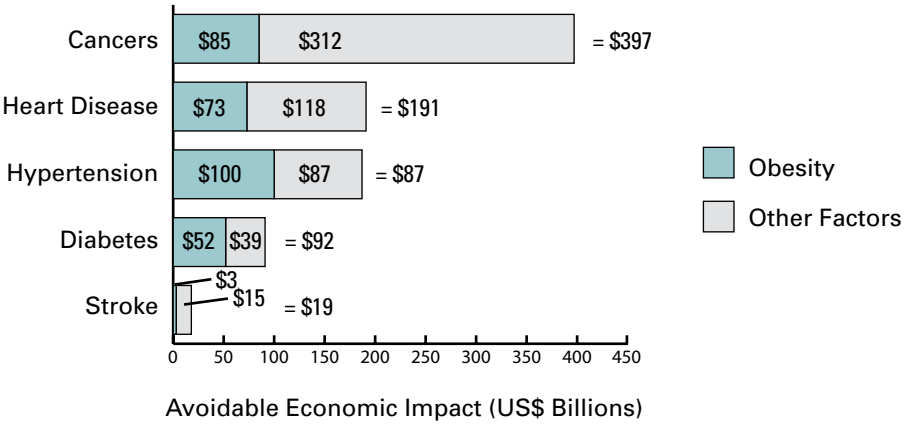
Year	Cancer treatment spending (billions)	Total personal health care spending (billions)	Percent of cancer treatment spending to total
1963	$1.3	$29.4	4.4%
1972	$3.9	$78.0	5.0%
1980	$13.1	$217.0	6.0%
1985	$18.1	$376.4	4.8%
1990	$27.5	$609.4	4.5%
1995	$41.2	$879.3	4.7%
2004	$72.1	$1540.7	4.7%

Source: 1963-1995: Brown M.L., Lipscomb J. & Snyder C. (2001) The burden of illness of cancer: Economic cost and quality of life. *Annual Review of Public Health,* 22, 91-113. 2004: National Institutes of Health (2005). Cost of Illness Report to the U.S. Congress.

eliminate 40 million cases of chronic diseases and reduce the economic impact by 27 percent (representing $1.1 trillion, an increase in the gross domestic product (GDP) by $905 billion in productivity gains and a decrease in treatment cost by $218 billion per year) by 2023. One very simple step is to institute lifestyle changes that have been shown to have a major impact on chronic disease outcomes. For example, obesity increases the risk of breast cancer as well as several other chronic diseases. Decreasing obesity by 15 million cases by 2023 would result in a $60 billion savings in treatment costs and would increase productivity by $254 billion. Currently, avoidable costs associated with breast cancer are escalating, but reducing obesity is an achievable goal. Such programs would ensure that we not only reach, but surpass, the 2010 Healthy People goal for all racial and ethnic groups.

The return on research investment can be quite lucrative, but we must change the order of our research priorities, placing greater emphasis on prevention and early detection in an effort to alter the trend in outcomes for all groups. This requires redirecting funds from treatment toward prevention and early detection. Private insurers and Medicare spend more dollars on treatment interventions than for preventive health, education, screening, and counseling efforts. The Milken report states that a reorientation towards prevention could avert 40 million cases of the seven chronic diseases (cancers, diabetes, heart disease, hypertension, stroke, mental disorders and pulmonary

Figure 6. Avoidable economic cost attributable to decline in obesity, 2023

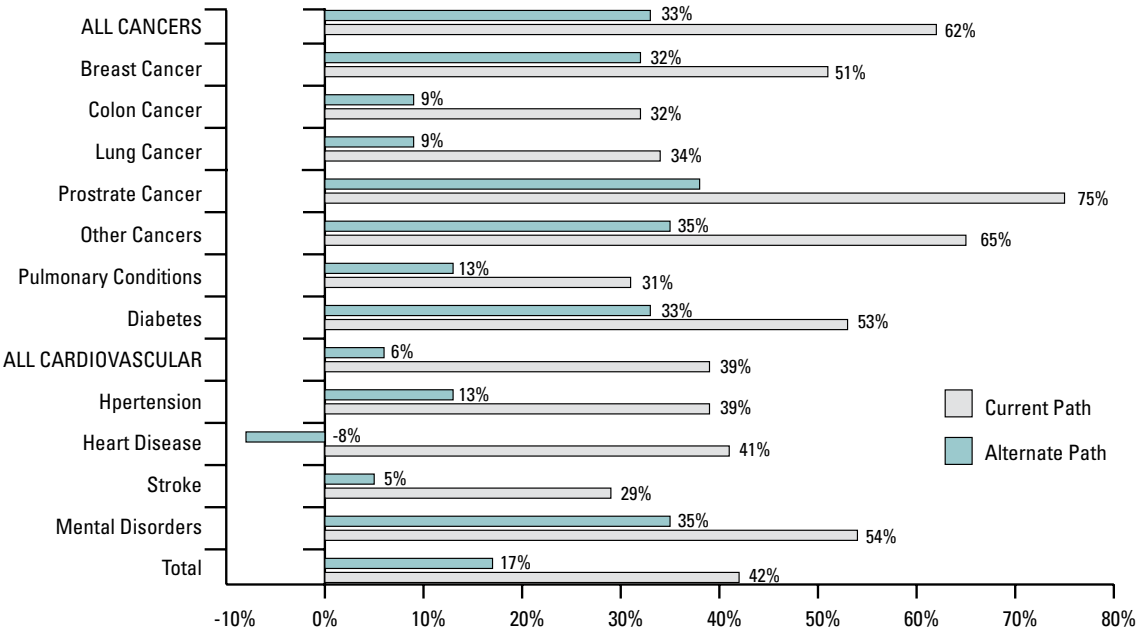


Source: Milken Institute. (2007 October). *An unhealthy America: The economic burden of chronic disease—charting a new course to save lives and increase productivity and economic growth.* Santa Monica, CA: DeVol, R. & Bedroussian, A.

conditions) by the year 2023 with economic gains and reduced treatment costs that would more than cover the payment for such efforts.[77]

Worldwide, there is a persistent imbalance in health service delivery based on the under-utilization of services by women, minorities, uninsured, and underinsured and the lack of research funding in areas where it is needed most. Although breast cancer represents 85 percent of the global cancer disease burden, breast cancer research receives less than four percent of all available cancer research funding. Attention and action must hone in on the disconnect in service delivery, according to the findings of the DCPP2 report.[78] Since minorities and other medically underserved populations typically have a higher burden of disease, delivering prevention services to these groups is another area that should be emphasized.

Figure 7. Percent growth in number of people reporting chronic diseases, 2003-2023: current path versus alternative path



Source: Milken Institute. (2007 October). *An unhealthy America: The economic burden of chronic disease—charting a new course to save lives and increase productivity and economic growth*. Santa Monica, CA: DeVol, R & Bedroussian, A.

CONCLUSIONS AND RECOMMENDATIONS SUMMARY

Environment and lifestyle are key risk factors for cancer and should be studied in a comparative fashion between African American women and other racial and ethnic groups.

Current clinical studies should include significant numbers of participants from racial and ethnic minorities in order to improve the acceptability and applicability of the study results.

It is also important to develop useful techniques and education tools that will work within the cultural norms of various racial and ethnic groups.

Future research efforts should focus on better understanding risk factors and the underlying biology of tumors in young AA women in order to refine therapy to reflect the fact that not all breast cancers are the same.

CONCLUSIONS AND RECOMMENDATIONS

Some scientists diminish the significant role race has on cancer outcomes, solely addressing race as a social construct. However, it is extremely difficult to disaggregate the impact of race on cancer outcomes. Numerous breast cancer studies have shown that the provision of adequate breast health care is the major factor in breast cancer health disparities when comparing AA and NHW. Several reasons have been evaluated for these differences, including lack of convenient, accessible care and unequal and inappropriate treatment.

Thus, it is critically important to understand the beliefs and perceptions within racial and ethnic subcultures in order to determine ways to maximize the health benefit to the group. Current clinical studies should include significant numbers of participants from racial and ethnic minorities in order to improve the acceptability and applicability of the study results. It is also important to develop useful techniques and educational tools that will work within the cultural norms of various racial/ethnic groups. Research efforts aimed at identifying successful screening, treatment, and prevention models targeted for AA women should be culturally sensitive and appropriately address differences in age, SES, language, culture, and also biology of the disease. Environment and lifestyle are also key risk factors for cancer and should be studied in a comparative fashion between AA women and other racial and ethnic groups.

In the approach to preventing and treating breast cancer in AAs, it is important to research the differences in tumor biology, the interaction of tumor biology with non-biological factors as well as defining specific drug targets. Drug metabolism may differ in racial and ethnic groups, in order to better define effective therapeutic and preventive agents drug evaluation studies should address the following issues:

a) Drug selection in AA women based on pharmacogenomic studies;
b) Appropriate drug dosing for overweight AA women in epidemiological studies; and
c) Incidence of under-dosing in overweight AA and NHW women.

Greater collaboration between population scientists and cancer researchers is critical in efforts to identify unique germ line alleles and allelic combinations that may

alter cancer risk and molecular profiles of breast tumors. Future efforts should focus on supporting women who seek care, providing affordable screening tests, providing culturally acceptable awareness campaigns, and encouraging an increase in breast self-examinations and annual clinical breast examinations. In countries where mammograms are not readily available, easily accessible alternative screening methods should exist. Additionally, future research efforts should focus on better understanding risk factors and the underlying biology of tumors in young AA women in order to refine therapy to reflect the fact that not all breast cancers are the same. Given today's tools and resources, health conditions should be reasonable everywhere, but far too many populations do not enjoy 'reasonable' health conditions. Let us effectively chart the course toward eliminating breast cancer health disparities and take the necessary action to achieve positive results in a realistic time frame, perhaps by 2020.

GLOSSARY

AA African American

BCPT Breast Cancer Prevention Trial

BRCA1 A gene on chromosome 17 that normally helps to suppress cell growth. A person who inherits a mutated BRCA1 gene has a higher risk of getting breast, ovarian, or prostate cancer.

BRCA2 A gene on chromosome 13 that normally helps to suppress cell growth. A person who inherits a mutated BRCA2 gene has a higher risk of getting breast, ovarian, or prostate cancer.

CARE Contraceptive and Reproductive Experiences study

DALY Disability Adjusted Life Years, a composite measure that combines years lived with disability and years lost to premature death in a single metric

DCIS Ductal carcinoma in situ. A non-invasive condition in which abnormal cells are found in the lining of a breast duct. The abnormal cells have not spread outside the duct to other tissues in the breast. In some cases, DCIS may become invasive cancer and spread to other tissues, although it is not known at this time how to predict which lesions will become invasive. Also called ductal carcinoma in situ and intraductal carcinoma.

DCPP Disease Control Priorities Project. The DCPP is a collaborative project of the National Institutes of Health's (NIH) Fogarty International Center, the World Health Organization, the World Bank, and the Population Reference Bureau, with funding support from the Bill and Melinda Gates Foundation.

DHHS	Department of Health and Human Services
ER	Estrogen Receptor. A protein found inside the cells of the female reproductive tissue, some other types of tissue, and some cancer cells. The hormone estrogen will bind to the receptors inside the cells and may cause the cells to grow.
ERN	Estrogen Receptor Negative. Describes cells that do not have a protein to which the hormone estrogen will bind. Cancer cells that are estrogen receptor negative do not need estrogen to grow, and usually do not stop growing when treated with hormones that block estrogen from binding. Also called ER-.
EGFR	Epidermal Growth Factor Receptor. The protein found on the surface of some cells and to which epidermal growth factor binds, causing the cells to divide. It is found at abnormally high levels on the surface of many types of cancer cells, so these cells may divide excessively in the presence of epidermal growth factor. Also called EGFR, ErbB1, and HER1.
GDP	Gross Domestic Product
HER2	Human Epidermal Growth Factor Receptor 2 gene. A protein involved in normal cell growth. It is found in high levels on some breast cancer cells. Also called human epidermal growth factor receptor 2 and c-erbB-2.
IOM	Institute of Medicine
NHW	Non-Hispanic Whites
PARP	Poly-ADP-Ribose Polymerase. A protein involved in a number of cellular processes with mainly DNA repair and programmed cell death.
PR	Progesterone Receptor. A protein found inside the cells of the female reproductive tissue, some other types of tissue, and some cancer cells. The hormone progesterone will bind to the receptors inside the cells and may cause the cells to grow.

PRN	Progesterone Receptor negative. Describes cells that do not have a protein to which the hormone progesterone will bind. Cancer cells that are progesterone receptor negative do not need progesterone to grow and usually do not stop growing when treated with hormones that block progesterone from binding. Also called PR-.
RXR	Rexinoid. A novel synthetic specific ligand of the nuclear hormone receptor family used in regulating critical cellular pathways essential for mammalian physiology and development.
SEER	Surveillance, Epidemiology, and End Results. The NCI cancer statistical database from a number of population-based cancer registries.
SERM	Selective Estrogen Receptor Modulator. A drug that acts like estrogen on some tissues, but blocks the effect of estrogen on other tissues. Tamoxifen and raloxifene are selective estrogen receptor modulators. Also called SERM.
STAR	Study of Tamoxifen and Raloxifene
WHO	World Health Organization

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