

# CANCER DISPARITIES

CAUSES AND EVIDENCE-BASED SOLUTIONS



RONIT ELK  
HOPE LANDRINE  
EDITORS





**Cancer Disparities**  
**Causes and Evidence-Based Solutions**

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# Cancer Disparities

## Causes and Evidence-Based Solutions

Ronit Elk, PhD  
Hope Landrine, PhD  
Editors

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*We owe a debt of gratitude to the many people—  
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community advocates, and others—who have committed their  
lives' work to reducing health disparities:  
The leaders who paved the way;  
Those who are currently engaged in the work, and  
Future generations who will continue their commitment until  
health equity is achieved.*



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# Preface

## American Cancer Society Strategies for Reducing Cancer Disparities

*Linda G. Blount*

Significant progress has been made in the reduction of cancer incidence and mortality rates. Delay-adjusted incidence rates for all low-income, racial, and ethnic groups combined decreased by 0.7% per year from 1999 to 2007, after stabilizing from 1989 to 1999 and increasing by 1.2% per year from 1975 to 1989. The decline in overall mortality rates accelerated from 1.1% per year from 1993 to 2001 to 1.6% per year from 2001 to 2007 (Jemal et al., 2008). This is real progress. However, very real and widening gaps are masked by these statistics. In fact, cancer mortality rates are falling much faster for some populations than for others. And, in the case of breast cancer and colorectal cancer, the difference in mortality rates between African Americans and Caucasians, rich and poor, is greater now than 25 years ago.

There are many reasons why cancer disparities exist. These reasons have been analyzed and described in many books and peer-reviewed publications over the past 25 years. The role that social determinants of health, access to quality care, and culturally relevant health communications materials and delivery methods can play in cancer prevention and optimal cancer health outcomes is understood to a great degree. But where do researchers and practitioners turn for evidence-based interventions that have narrowed the disparities gap in cancer incidence and mortality? Unfortunately, very few scientific articles, and no book to date, explain these disparities in a language suitable for medical, public health, and social-behavioral scientists, and even fewer publications present concrete interventions that can be used to reduce or eliminate cancer disparities.

*Cancer Disparities: Causes and Evidence-Based Solutions* is the first book on cancer disparities that provides *evidence-based interventions proven to reduce cancer disparities*. This book constitutes a novel, long-overdue, comprehensive

approach to cancer disparities and their reduction. While cancer researchers, faculty, and graduate students in medical schools, cancer centers, and schools of public health will find this book an important addition to the academic syllabus, public health and cancer-control leaders in community organizations will find this book a valuable resource for understanding cancer disparities and interventions efforts to end them. Eminently readable for nonresearchers, this book will act as a guide to community-based studies that have been evaluated and provide real-life examples of how barriers to cancer care, prevention, and information can be reduced or even eliminated.

The research presented in this book reflects the commitment of the American Cancer Society (ACS), the largest nongovernmental funder of cancer research, to reducing and eliminating cancer disparities. The Society has a long history of funding research, programs, and services to help those facing a disproportionate cancer burden and inequities in cancer care. A decade before Dr. David Satcher, Surgeon General of the United States, coined the phrase "Elimination of Health Disparities," then ACS National President, Dr. Harold Freeman, convened a Board-led Oversight Committee to study cancer control in underserved communities. The 1989 report, *Cancer Control and the Socioeconomically Disadvantaged*, was the first strategic plan by the ACS to address cancer disparities, and was developed in response to ACS-sponsored regional hearings on cancer in the poor. The report concluded that reaching out to socioeconomically disadvantaged populations was "a top priority" and that "all components of the Society should be involved" (Freeman, 1989). The Committee's action strategies for the Society centered around three areas: public policy (including calls for health reform); patient advocacy and empowerment (working with community partners, adapting the ACS direct response system to address the information needs of the poor, and training staff and volunteers to address the cancer control needs of the disadvantaged); and education and early detection (increasing behavioral research on effective ways to reach culturally diverse subgroups, messaging and advertising campaigns to counteract the work of tobacco companies, and funding community-level demonstration projects on cancer prevention, detection, and education).

In 2002, a team of volunteers and staff reviewed progress toward Dr. Freeman's plan and determined if new strategies were required. Their recommendations largely supported those of the earlier initiative, including implementing community outreach and partnerships with community-level organizations, offering evidence-based interventions, providing education, disseminating information, focusing on government regulation and legislative advocacy, and building more infrastructure and capacity at the community level. Two years later, the Society adopted a strategic framework of information, prevention, detection, quality of life, and research that

represents the Society's optimal role in the fight against cancer. Because of its importance, strategies for reducing health care disparities were included in every aspect of that framework.

The formation of the Office of Health Disparities in 2007, working in collaboration with national and division departments, ensured the continuity of the strategic focus on health equity and the elimination of disparities, encompassing a broad spectrum of work, including: front-line advocacy for increased access to high-quality, affordable cancer care and work with state and local lawmakers to ensure that the needs of the underserved are met, particularly through adequate funding of the National Breast and Cervical Cancer Early Detection Program (NBCCEDP); linguistically and culturally appropriate awareness, prevention, and screening information; hip-hop artists targeting anti-tobacco messaging to youth and young adults; patient navigation programs in disproportionate share hospitals and *promotoras* serving low-income Hispanic patients; partnerships with minority media outlets, professional, and civic organizations; and scores of community-based programs that have provided patient support and increased understanding of cancer, prevention, and early detection among thousands of low-income and minority individuals.

The Society has both an intramural and an extramural research focus. Intramural research conducted by ACS scientists centers primarily on surveillance and analytic epidemiology and health services research. The Surveillance and Health Policy Research department plays a key role in promoting cancer control in the underserved population by compiling and disseminating information on disparities in cancer incidence, survival, mortality, and risk factors to cancer control advocates, the media, educators, and the general public. It does so through its annual *Facts and Figures* publications, the most widely cited cancer publications, and through its annual *Cancer Statistics* article in *CA: A Cancer Journal for Clinicians*, which reaches a wide clinical audience. The department's *Annual Report to the Nation* monitors the nation's progress in reducing cancer incidence and mortality overall, as well as by specific racial and ethnic populations. The Department of Analytic Epidemiology is responsible for the Society's largest intramural research study, Cancer Prevention Study 3 (CPS-3), which will eventually accrue up to 500,000 participants, 25% of whom will be racial and ethnic minorities ([www.cancer.org](http://www.cancer.org)). The research in this department also has, as a primary focus, studies on the impact of nutrition and physical activity on cancer risk, treatment, and outcomes. The findings of CPS-3 should make a significant contribution to the understanding of cancer, its etiology, and the risk factors among racial and ethnic minorities. This department has conducted all of the Society's large cohort studies to provide insights about causes of cancer and prevention. The three main cohorts, Hammond-Horn and the CPS-I and

CPS-II, feature prominently in many Surgeon General Reports on tobacco (Thun, Calle, Rodriguez, & Wingo, 2000).

Over the past 60 years, the Society's Extramural Research Grants (EG) Department has funded more than \$3 billion in cancer research, primarily basic science, to help understand the etiology of cancer and to develop interventions to prevent and treat the disease. In 1999, in response to the Society's 2015 goals of eliminating disparities in cancer burdens, the ERG department designated poor and medically underserved populations as a high-priority area of focus, with set aside dollars. The goals of this focus area, called the Targeted Program, were to explore innovative research that would lead to the discovery of effective cancer treatments, prevention practices, and early detection measures for high-risk populations, and to increase the evidence base on which programmatic and public policy decisions were made. In recognition of the importance of this area of research, up to 10% of the total ERG budget, approximately \$10 million per year, was set aside for this program. In the 10 years from 1999 to 2009, \$99 million has been awarded to targeted research, constituting 10.9% of the \$908 million awarded to nontargeted research over the same period.

In an effort to meet the goals of making ACS-funded research relevant to the policies and programs of the Society, and to enhance the implementation of evidence-based programs in the Divisions, the results of funded studies are shared through the Targeted Grants Program and the Office of Health Disparities on an ongoing basis with the National Department of Health Promotion and ACSCAN, and through partnerships formed with ACS-funded researchers and Divisions.

The Targeted Program of the Extramural Grants Research Department has been reviewed by several Advisory Boards over the years. In prior years, there were recommendations that the EG Research Program continue with this special Targeted Program, due to its strong relevance to Society goals and its high potential to benefit the populations it is targeting. The 2009 evaluation recommended both expanding and broadening the scope of the program. On these recommendations, it has been made a high-priority area of funding in the Cancer Control and Prevention Research Program of the Extramural Grants Program.

Attracting new researchers into this field was another stated goal of the Targeted Program. This program has attracted researchers from racial and ethnic groups that are traditionally underrepresented in science (including researchers of African American, Hispanic, and Native American descent). While the majority of the applicants in both "Targeted" and "non-Targeted" extramural grants programs are Caucasian, significantly more applicants from populations underrepresented in science applied for research grants in the Targeted Program.

The Targeted Program has funded studies across the cancer continuum. By far the majority (86%) are those that focus on cancer control and prevention, quality of life, and health policy/health services research, with just a few in the clinical research or basic sciences. The majority of the funded studies focus on ethnic-minority populations in which health care disparities exist, with African Americans being the largest group studied. Ninety-three percent of funded studies examine an aspect of prevention, early detection, and screening. Prevention studies look at specific behaviors, with the largest number targeting diet and exercise modification, followed by smoking cessation. Screening and early detection primarily address breast, colorectal, and cervical cancer, with many examining the use of Lay Health Advisors to change screening behaviors.

A significant number of the studies used Community-Based Participatory Research (CBPR) methods, in which a partnership between the community of focus and the research team is formed in order to identify the questions of concern and the culturally appropriate methods for jointly finding solutions. Chapter 12 is an outstanding example of a true community-research partnership, in which Dr. Christopher and at least 20 women leaders from the Apsáalooke tribe worked hand in hand, at every step of the way, in designing and testing a program titled “Messengers for Health” that would enhance cervical cancer screening for women of the community.

Studies focusing on treatment include those describing treatment differences between various ethnic or other underserved groups, provider–patient interactions, and the effect of health care systems and policies on differential outcomes. In chapter 16, Dr. Sheppard and colleagues describe a unique culturally based intervention, “Sisters Informing Sisters™,” that is designed to help African American women understand and embrace the need to complete adjuvant treatment for breast cancer.

Health policy research is an important area of interest, particularly as health care reform implementation moves forward. In chapter 11, Dr. Adams examines the effect of legislative change (extending Medicaid coverage to any uninsured woman under 65 in need of cancer treatment, with breast or cervical cancer or pre-cancerous cervical conditions) on outcome. Women got into the program more quickly, received the right treatment, and in the case of cervical cancer, extended treatment in some groups, in a timely manner.

This unique and highly competitive Targeted Program funds esteemed researchers across the nation to develop interventions to reduce cancer disparities and promote health equity. Fifteen of their studies, which highlight effective interventions across a broad range of underserved populations, were chosen for this book. They serve as evidence that, with the right culturally appropriate interventions, *change is possible*.



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# Introduction

## Cancer Disparities: The Scope of the Problem and Possible Solutions

*Otis W. Brawley*

### THE BIRTH OF A DISCIPLINE

In 1973, a landmark paper was published documenting the increasing disparities in cancer mortality between Black and White Americans (Henschke et al., 1973). In many ways, this paper was inspired by the U.S. Civil Rights Movement. It was the signal that the struggle for racial equality was broadening beyond social and economic equality to include equality in health care. The Henschke paper and similar papers related to other diseases would eventually be the start of the academic discipline known as “minority health.” Over time, the field became known as “special populations” and later—in the mid-1990s, with the wisdom of then Surgeon General Dr. David Satcher—it became known as “health disparities” (Nkwa-Mullan et al., 2010). The name “health disparities” was descriptive of the field. The phrase was less open to criticism from politicians who did not support programs and research in minority health or special populations. It became difficult for a politician to stand up and speak up against programs intended to reduce disparities in health. Today, there is a movement toward calling the field “health equity.” The documentation of disparities in race and the expansion of the discipline became a significant influence on the current health care debate.

The basic principle behind health disparities is the reality that there are populations that do not do as well as others in terms of health outcomes. Initially, those focusing on minority health were physicians who recognized racial differences in presentation of disease and mortality. As the academic field grew, it attracted the talents of professionals in diverse medical

disciplines, epidemiologists, and social scientists. Anthropologists helped define populations, and nursing scientists and the palliative care movement helped expand the field further by better defining disparities and expanding the measures of disparities. Patient advocacy was equally important in the birthing of the field. In the 1980s, Congress legislated establishment of the NIH Office for Research on Minority Health and the Department of Health Education and Welfare (later the Department of Health and Human Services) Office of Minority Health. Eventually, almost every federal health agency opened an office for special populations and, later, an office for health disparities. Provisions within the National Institutes of Health Revitalization Act of 1993 strengthened research into the field (Freedman et al., 1995) and in 2010, the Affordable Care Act transformed the NIH Office for Research on Minority Health into an institute, with the ability to fund grants and programs across the country. Cancer was one area where the disparities in screening and treatment were clearly documented (Greenberg, Weeks, & Stain, 2008). In an effort to address this, Congress passed legislation creating the CDC Breast and Cervical Cancer Treatment Program, to give poor women access to breast and cervical cancer screening. (Later, this program was modified to pay for treatment for those diagnosed with those cancers, an evaluation of which appears in chapter 11.)

### **HEALTH DISPARITIES BECOMES MORE THAN BLACK AND WHITE**

At one time, the only disparate outcomes discussed were differences in incidence and mortality among Blacks and Whites. Today, our concern for health disparities and achieving health equity has expanded beyond concern for the health of African-Americans. During his tenure as volunteer president of the American Cancer Society in 1989, Harold Freeman brought tremendous focus on the fact that America's poor, be they Black, White, Hispanic, Asian, or Native American, have disparate cancer outcomes. In the early 1990s, NCI director Sam Broder made a now famous statement that "poverty is a carcinogen." This led to studies of the effects of poverty and social deprivation on the cause and course of malignant disease. Health disparities research dramatically increased in the field of oncology (Freeman, 1998). Significant advances have been made in defining the scientific and political issues that cause disparities in health, and the interventions (public health, medical, and sociopolitical) that can alleviate such disparities and lead to health equity. Much can be learned through comparing and contrasting well-defined populations. Efforts to determine why one cohort has a low rate of a cancer can help us find interventions to lower that rate in other populations.

## **DATABASES ENHANCE THE MEASUREMENT OF DISPARITIES**

The development of cancer databases and registries has increased the availability of data and helped to define disparities through assessment of other outcomes and in other populations. The CDC National Center for Health Statistics (NCHS), established in the early 1960s, began providing state-by-state mortality data. Eventually, NCHS began the National Health Interview Survey (NHIS) and the Behavioral Risk Factor Surveillance System (BRFSS) to provide additional data (Cyrus-David, King, Bevers, & Robinson, 2009). The NCI Surveillance Epidemiology and End Results (SEER) Program was launched in 1972 as part of the implementation of the National Cancer Act. It provided incidence and 5-year survival data. As its data matured, additional outcomes measures became available. Researchers began looking at practice patterns data and even geographic differences. In the early 1990s, the NCI SEER program went beyond publishing Black–White data and began publishing data for the five racial and ethnic categories as defined by the U.S. Office of Management and Budget. The National Cancer Data Base (NCDB) was launched in the late 1980s. It is run by the American College of Surgeons Commission on Cancer and supported by the American Cancer Society. The NCDB registry has grown to include hospitals that treat more than 70% of Americans with cancer. It gathers such demographic data as insurance status and time to treatment received, thereby allowing additional analysis of differences in quality of treatment. Questions addressed include the proportion with a specific disease not receiving standard care and differences in quality of treatment (Fry, Menck, & Winchester, 1996). Recently, quality of life for cancer patients and cancer survivors (pediatric and adult) has become a concern in the health disparities community. Focus areas include the availability of adequate pain control, as well as access to programs for physical and emotional rehabilitation (Lafleur, Said, McAdam-Marx, Jackson, & Mortazavi, 2007).

## **KEY ASPECTS TO CONSIDER IN CATEGORIZING POPULATIONS**

If we are to truly attack disparities in health outcomes, we must be open minded, question the standard prejudices and paradigms, and carefully define the scientific and medical questions that need to be addressed. Key to defining the problem has been adequately categorizing populations, identifying the outcomes that are disparate, defining how to measure those outcomes, and defining the causes of disparities. Only then can we identify the interventions necessary to overcome the disparities (Brawley and Berger, 2008). Today, we recognize that there are numerous ways to define

populations. Categories frequently used include race, ethnicity, and area of geographic origin or socioeconomic status. There are significant cautions that need to be taken when defining populations using these categories. These are words whose meaning and history are not well understood by the lay and medical public, and they are frequently used with differing meanings. Our race-based labels crudely predict for groups of people that are less likely to do well with cancer and other diseases, but we must realize the sociopolitical nature of these categories (Witzig, 1996). Race is not a biologic categorization. In the assessment of risk of cancer, a form of “benevolent racial profiling” is sometimes appropriate; however, overcommitment to this view without deep, careful thought can obscure the truth and actually impede science from benefiting disparate populations.

The concept of *race* originated in the eighteenth century. It has to do with superficial facial features and presumed geographic area of origin. It does not even deal with skin color, as dark-skinned people from the Indian subcontinent are considered Caucasian. There are no distinct races, and racial groups are overlapping populations (Brown, 2007). The one “drop rule” in which a person with just one known African ancestor is considered Black is still practiced in this country and is the ultimate example of how unscientific the concept of race is. Many who describe themselves as Black or African American are actually a mixture of European and African ancestries (Witzig, 1996). *Ethnicity* involves culture, habit, lifestyle, and behavioral patterns and other environmental influences that can cause disease or even lower the risk of disease (Faulkner and Merritt, 1998). Ethnicity defines foods consumed and how foods are prepared. Different ethnic groups often have different attitudes toward health and medical care. They interact differently with medical professionals. Appreciation of this is important to health care professionals who want to provide appropriate care. Ethnicity is appreciated as distinctly different from race. Both are important in cancer causation. Hispanic is an ethnicity. An individual can be categorized as Black race and Hispanic ethnicity or White race and Hispanic ethnicity. Ethnicity might be a bit more scientific than race, even though it is not necessarily static. Some people identify themselves as belonging to a particular ethnic group in one context, and to another in a different context (Corral & Landrine, 2008). The racial and ethnic categories used in most U.S. health care data are defined by the U.S. Office of Management and Budget (OMB). These definitions are used in the U.S. Census. The census data is then used to determine the size of the population in calculating rates of disease. In their directive defining race and ethnicity, OMB notes that the categories are sociopolitical in nature and not based in science.

*Area of geographic origin* is another way of categorizing populations. It can loosely correlate with ethnicity and race, but tends to be more specific

than race. When asked about area of origin, Americans of Korean and African ancestry are more likely to identify as Korean and African, whereas racially they might consider themselves Black or African American.

*Socioeconomic status* (SES) is a category that often correlates with health status. Its definition has also evolved over time; SES was once defined by household income or education and occupation (Albano et al., 2007). Today, we recognize that insurance status and even degree of medical sophistication are important factors in outcomes. European social scientists have taken SES to a higher level, with deprivation indices that in some cases even take into account whether one has indoor plumbing or household help (Byers et al., 2008). SES can be highly correlated with differences in outcome and related to unknown environmental influences that cause cancer, cause a delay in diagnosis of cancer, or cause less than optimal treatment of cancer. Access to care and lack of convenient care are SES-based variables that play a tremendous role in disparities in the United States (Faggiano, Partanen, Kogevinas, & Boffetta, 1997). SES is also related to the quality and types of foods consumed, the neighborhood and environment one lives in, and the work one does (Faggiano et al., 1997). Numerous surveys suggest that poor Americans are more likely to have harmful health behaviors and less likely to practice healthy behaviors. The poor are more likely to consume higher-calorie diets and have diets higher in carbohydrates and fats. Poor Americans are also more likely to be overweight or obese, and less likely to consume diets high in fruits and vegetables, compared to middle- and upper-middle-class Americans (Satia-Abouta, Patterson, Neuhauser, & Elder, 2002).

*Area of residence*, too, can be a factor in cancer risk. In the United States, area of residence can be viewed as rural versus urban, with differing access to health care. It can include living in polluted areas with greater exposure to disease-causing chemicals, such as a landfill or an industrial area (Law & Morris, 1998). It can also include living in crime-ridden inner-city neighborhoods, where opportunities for healthful habits such as exercise are limited (Bennett et al., 2007; Gaskin, Price, Brandon, & Laveist, 2009).

These categories can overlap and make attribution of cause of disease difficult. For example, as discussed in chapter 5, in the United States low SES can be associated with the Black race and living in an inner-city area. An outcome caused by low SES in a group of Blacks might be mistaken as being due to race or to area of residence. It could also be truly related to all three (Kaufman, Cooper, & McGee, 1997). A higher proportion of Americans of African heritage are poor compared to Whites. It is appropriate to ask what the effect of poverty is on our race-based health statistics. Indeed, socioeconomic status and its incumbent environmental influences may be the cause of many health disparities. It is possible that socioeconomic factors that act

largely through and are associated with race are responsible for much of the disparity between Black and White (Ward et al., 2004).

## **RACE MEDICINE: DISPARITIES IN CANCER RISK AND INCIDENCE**

Cancer is caused by an aberration of genetics. The aberration can be due to an inherent genetic mutation that can be passed on through generations. It can also be due to environmental influences on a gene or series of genes. Some cohorts have a higher prevalence of a specific genetic mutation or a series of genes that increase risk. Some cohorts have increased or decreased risk due to environmental exposures. An understanding of both cancer genetics *and* population genetics is critical for those who wish to approach disparities in health in a rational scientific way, in which pertinent questions are identified and clearly stated.

Over the years, American medicine has placed much interest on genetic differences among the races. The concept that phenotypic differences translate into biologic differences was the basis of "Race Medicine." This concept was commonly accepted in the America of the 19th and early 20th centuries. It was one of the reasons that the study commonly known as the "The Tuskegee Syphilis Study," which began in 1932, was thought reasonable and ethical. Syphilis was thought to be a very different disease in Blacks versus Whites. Many actually believed that syphilis rarely killed infected Blacks, but frequently killed infected Whites (Brawley, 1998). Race Medicine is still with us today. This belief in biologic differences among the races has crept into the discipline of health disparities (Goldson, Henschke, Leffall, & Schneider, 1981). It is unfortunate we do sometimes read that "breast cancer is a different disease in Blacks versus Whites" or that "prostate cancer is a different disease in Blacks versus Whites." Truth be told, as explained in chapter 1, there are highly aggressive, bad-prognosis cancers and there are less aggressive, good-prognosis cancers. No race has a monopoly on the good cancers or on the bad cancers. It is also true that a higher proportion of Black American women with breast cancer have the more aggressive types (Brawley, 2010; Lund et al., 2009).

A good scientific question is, "Why do a higher proportion of Black women with breast cancer have the poorer-prognosis disease compared to White women?" A second good question rarely discussed is, "Why do a higher proportion of White women have the good-prognosis breast cancers?" It is known that there are racial differences in a number of environmental factors that are correlated with breast cancer risk. Indeed, in the United States there are racial differences in the proportion beginning menstruation at an early age, birthing patterns, the proportion that is obese, and the use of

postmenopausal hormones (Lund et al., 2008). Could race be a surrogate for SES status? Some data suggests that SES and social deprivation not only correlate with the risk of cancer, but also with pathologic factors (Gordon, 1995; Gordon, 2003). Several studies suggest that poor White women with breast cancer are more likely to be diagnosed with estrogen receptor negative tumors (Gordon, 1995; Thomson, Hole, Twelves, Brewster, & Black, 2001). It is unknown how poverty influences pathology of disease. It may be through life-long diet, and birthing habits. Diets high in calories during childhood can affect age at menarche. Earlier age at menarche is known to be associated with increased breast cancer risk later in life. A higher proportion of the poor are overweight or obese. Increased body mass index has been correlated with increased risk of postmenopausal breast cancer. Similarly, increased body mass index, which is more common in African-American males compared to White males, has been correlated with increased risk for more aggressive prostate cancer (Amling et al., 2004; Spangler et al., 2007).

While it is important to study race, it is also important not to overemphasize race. Even when a specific genetic difference is highly associated with a race or ethnicity, it might more appropriately be considered familial rather than racial or ethnic. A specific gene or series of genes can be conserved among families, and a closed society will conserve genetic traits within that society. Segregation on the basis of race, ethnicity, economics, or other factors can lead to increased prevalence of a specific gene or series of genes in the segregated population. This has been demonstrated in several diseases with a well-defined genetic basis, such as Tay Sachs disease, cystic fibrosis, and sickle cell disease. Each of these diseases has a higher prevalence in, but is not exclusive to, a specific racial/ethnic group. Even the mutation of BRCA common among Ashkenazi Jews has been linked to a small number of individuals having it about 1,000 years ago, and it is now preserved through ethnic segregation. As populations in Europe and America mix, these genetic differences will lessen (Offit et al., 1996).

There are genetic variations between human populations. A gene, or even a single nucleotide polymorphism (SNP) allele, that is common in one geographic, racial, or ethnic group may be rare in another. Some of these genetically based differences translate into a difference in disease risk among populations. Some of these differences have been associated with an environmental influence and can offer a survival advantage. Sickle cell disease, for example, is associated with area of geographic origin. People from Spain, Italy, Greece, and the Middle East, as well as northern and sub-Saharan Africa, have sickle cell trait and sickle cell anemia. While the prevalence of sickle cell trait and sickle cell anemia is higher in sub-Saharan Africa, there is also a prevalence in people originating from southern Europe and considered to be of White race. Sickle cell is not found among Black Africans originating



from southern Africa. This genetic mutation is thought to be an example of genetic selection. Those who had sickle cell trait had some advantage during a massive malaria epidemic several thousand years ago. That advantage extends to those with sickle cell trait to this day (Brawley et al., 2008). Sickle cell disease is an excellent example of environmental influences on genetics. The fact that it parallels a geographic area where people are considered of White race and Black race is also a good lesson, as most Americans think of sickle cell disease solely as an affliction of Blacks.

There are other genetic markers that correspond with areas of geographic origin far better than with skin color or race (Fijumara & Rajagoplan, 2011). Glucose 6 phosphate dehydrogenase deficiency is common in, but not monopolized by, people originating in the Middle East and Mediterranean regions (Beutler, Lisker, & Kuhl, 1990). Alcohol dehydrogenase deficiency is common in persons from certain areas of Asia. There are differences in metabolism of some drugs by genetic markers that tend to parallel area of geographic origin. The drug irinotecan, or CPT 11, is used in the treatment of colon cancer. It is metabolized by the UDP-glucuronosyltransferase 1-1 gene (*UGT1A1*) gene in the liver. Certain polymorphisms of the gene metabolize the drug slower than others. The U.S. Food and Drug Administration recommends that patients with certain polymorphisms of *UGT1A1* receive reduced doses of the drug. It is one of the first cancer drugs dosed according to genotype. Asian populations tend to have a slower *UGT1A1* compared to populations originating in Europe (Beutler, Gelbart, & Demina, 1998). The word “tend” is important. It is best to do the laboratory tests necessary to assess *UGT1A1* in the specific patient than to do racial medical profiling and assume that all Asians should be dose reduced. Racial medical profiling can deprive a patient of a therapeutic dose of this drug. The movement toward personalized medicine, with its emphasis on the genetics of the individual, may be one way that we stop racial medical profiling.

### **RACE MEDICINE: SCREENING, DIAGNOSIS, AND TREATMENT OF CANCER**

Much cancer research shows that equal treatment yields equal outcomes, among equal patients (Bach, Cramer, Warren, & Begg, 1999). Race in and of itself need not be a factor in the outcomes of cancer treatment. Unfortunately, as is clearly documented in chapter 6, numerous patterns of care studies show that there is not equal treatment; race *is* a factor in treatment (Shavers and Brown, 2002). There are Black–White disparities in both the availability and use of care and in the quality of care received. In the field of oncology, these studies overwhelmingly show that the proportion of Blacks getting

adequate screening, diagnostics, and treatment is less than the proportion of Whites. Some studies show that Blacks in the southern United States are more likely to get less than optimal cancer care compared to Blacks in the northeast, who are less likely to get optimal care compared to Blacks in the west (Harlan, Brawley, Pommerenke, Wali, & Kramer, 1995).

As suggested earlier, while race is a correlative factor in these disparities, the driver of the disparities may be due to socioeconomic differences, and not racial. Studies suggest that some disparities in treatment are due to racism and some are due to SES discrimination. Other important factors are lack of access to good therapy or lack of convenient access to needed therapy. Comorbid diseases (including obesity) can also make aggressive cancer therapy inappropriate. Some disparities in cancer treatment may be due to comorbid diseases and may be appropriate (Griggs et al., 2007). Unfortunately, very few studies have looked at disparities by socioeconomic status, and even fewer have looked at practice pattern disparities in other racial/ethnic groups such as Hispanics, Asians, or Native Americans. Little effort has been put into assessing outcomes in other disenfranchised communities, such as refugee communities, or the lesbian, gay, bisexual, and transgender communities (Mayer et al., 2008). Chapter 21 discusses one of the few studies focusing on sexual-minority women with breast cancer.

Cultural differences in acceptance of therapy and lack of education about the disease are huge drivers in the disparate receipt of health care. Some cultures have fatalistic views toward cancer and a cancer diagnosis. This causes them to run away from good care when it is available. Culturally sensitive interventions to educate and create understanding about disease can help bring about health equity. Experience tells us that a successful intervention is created by someone who understands and cares about the population with the disparity. All interventions should be carefully and rigorously assessed for effectiveness before full implementation. These interventions must be implemented with sensitivity and by a trusted source. For example, as described in chapter 9, research has found that in some situations a beautician can be a highly trusted source and a very effective teacher. At the same time, a highly degreed health care expert may be unsuccessful. The concept of community-based participatory research is based on this finding (Ford et al., 2009).

## **CONCLUSION**

Health equity can only be achieved through open-mindedness and a committed interest on the part of health care providers, social scientists, health consumers, and health advocates. In some instances, the medical and

medical–social professions have to change their preconceived notions. In order to achieve health equity, it is imperative that we:

- Realize the meaning of race, ethnicity, area of geographic origin, and socioeconomic status, and appreciate the limitations of those categories.
- Understand the role of cancer genetics, population genetics, and the role of environmental interactions with genes.
- Value the scientific method as we rigorously assess culturally sensitive interventions to reduce health disparities and bring about health equity.
- Care about the fact that there are disparities, and care about and respect the uniqueness of the patients we serve.

Each of the researchers whose works are presented in this book has taken steps along this journey. If we all follow these principles, think of the major impact we can have on the lives of future generations.

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# I

UNDERSTANDING CANCER DISPARITIES





# 1

## The Biology of Cancer and Its Relationship to Disparities in Cancer Occurrence and Outcomes

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and Margaret K. Offermann*

### **DNA DAMAGE AND THE DEVELOPMENT OF CANCER**

Cancer is a group of diseases in which cells have developed the ability to invade into surrounding tissues and potentially metastasize to distant sites (Kessenbrock, Plaks, & Werb, 2010; Talmadge & Fidler, 2010). There are many different types of cancer, but they all occur as a consequence of acquired mistakes in the DNA, including epigenetic changes (Hoeijmakers, 2009). The DNA provides the master plan for all organisms in which four nucleotide bases (guanine, cytosine, adenine, and thymine) occur in specific arrangements and spell out the exact instructions required to create a particular organism with its own unique traits. The coding contained in the DNA is responsible for the formation and function of the complete spectrum of different cells and organs, as well as the biologic changes that occur as we age. The changes in the DNA that lead to cancer alter critical cellular processes that govern cell behavior, leading to cells that can invade and move to places where they do not belong (Markowitz & Bertagnolli, 2009; Michor, Iwasa, Vogelstein, Lengauer, & Nowak, 2005; Vogelstein & Kinzler, 2004). The different types of cancer reflect the different types of cells that undergo changes in their programming as a consequence of the alterations in the DNA (Aranda, Nolan, & Muthuswamy, 2008; Asselin-Labat et al., 2008; Lindvall, Bu, Williams, & Li, 2007; Lukacs et al., 2008; Mishra, Glod, & Banerjee, 2009). For example, kidney cancer occurs when the DNA in kidney cells changes to allow cells to invade and metastasize (Valladares Ayerbes et al., 2008), whereas breast cancer occurs when breast cells develop critical changes in their DNA (Lindvall et al., 2007; Turner & Grose, 2010). The types of mistakes that lead to cancer create additional subtypes of cancer. For example, breast cancer with amplification of the *HER-2/neu* gene is different from breast cancer that

over expresses the estrogen receptor (Charafe-Jauffret et al., 2005; Livasy et al., 2006). Thus, cancer is hundreds of different diseases, and knowledge of the shared and unique features of the different types of cancer is leading to more effective strategies for prevention, early detection, and treatment.

To understand why some people get cancer and others do not, it is important to understand that people are protected against cancer by many biologic processes designed to ensure that the more than 3 billion nucleotides in the DNA are properly copied each time a cell divides (Bartek & Lukas, 2007; de Bruin & Wittenberg, 2009; Talos & Moll, 2010). Both genetic and environmental factors affect the likelihood that mistakes will occur, and both contribute to disparities in cancer occurrence and outcome in various populations.

There are many different types of errors that can occur when DNA is replicated, and when they are not corrected, the changes are usually detrimental to the cell, but occasionally they give a growth advantage. While nearly all cells have the same DNA, different types of cells use distinct portions of the DNA for defining cellular characteristics and behavior, and making proteins that address each cell's specific needs. Access to distinct portions of the DNA code are regulated through a process called epigenetics, in which the ability to read the DNA code is changed without changing the DNA sequence, and epigenetic changes can also contribute to cancer (Clark, 2007; Omura & Goggins, 2009; Weidman, Dolinoy, Murphy, & Jirtle, 2007). Most cancers also contain alterations in the DNA sequence. Simple substitutions of nucleotides can lead to mutations that alter proteins or change regulatory regions in the DNA (Lee et al., 2010; Salk, Fox, & Loeb, 2010). Sometimes changes involve large portions of DNA, including duplications, deletions, inversions, or movement of DNA to distant regions (called translocations); these changes often affect hundreds of genes simultaneously (Argos et al., 2008; Dreyling et al., 1995; Grushko et al., 2002; Murnane, 2010; Nussenzweig & Nussenzweig, 2010; Turner & Grose, 2010). Changes in DNA that are detrimental to the cells usually are eliminated, whereas changes that give cells a growth and survival advantage can rapidly be propagated and set the stage for the development of cancer.

The development of cancer generally requires multiple changes in the DNA, and cells that undergo many divisions are at increased risk for cancer, especially if they are exposed to carcinogenic agents that induce DNA damage (Rajaraman, Guernsey, Rajaraman, & Rajaraman, 2006). The likelihood of multiple mistakes happening within a single cell increases over time and with multiple cell divisions. Thus, the overall risk of cancer increases with age and is more likely to occur in cells that are programmed to undergo frequent replacement, such as skin cells or cells lining the colon (Hoeijmakers, 2009). There can be more than 1,000 mutations and other

genetic mistakes within some cancers (Kwei, Kung, Salari, Holcomb, & Pollack, 2010; Lee et al., 2010), indicating that many biologic processes are likely to be altered and making simple fixes difficult. Cancer cells continue to evolve and acquire additional changes in their DNA (Kwei et al., 2010; Negrini, Gorgoulis, & Halazonetis, 2010; Talos & Moll, 2010). As new variants arise, those that offer survival advantage become more prevalent in the population. The ongoing evolution of tumors can lead to resistance to treatment and clinical relapses, even when the original cancer shows a complete clinical response.

Despite the huge number of changes in DNA that have been identified in some cancers, critical changes converge on a limited number of biologic processes. Pathways that are commonly involved include those that allow replication of damaged DNA, those that promote cellular replication, those that inhibit programmed cell death, those that immortalize cells, and those that stimulate environments favorable for tumor cell growth (Kessenbrock et al., 2010; Tammela & Alitalo, 2010; Turner & Grose, 2010).

### **DISPARITIES IN CANCER INCIDENCE AND OUTCOME**

The incidence and outcome of cancer differ in various segments of the U.S. population, with socioeconomic status, race/ethnicity, residence, gender, and sexual orientation all having an impact (American Cancer Society, 2010). Data from the Surveillance Epidemiology and End Results (SEER) program show that African Americans have the highest incidence and mortality rates of cancer compared to other racial and ethnic groups within the United States. The mortality rate for African American males is 34% higher than among Caucasian males; African American females display a 17% higher mortality rate when compared to Caucasian females. The causes of the increased mortality depend on the type of cancer and involve differences in tumor biology, timeliness of diagnosis, approach to cancer management, and presence of coexisting diseases. Hispanics, Asians/Pacific Islanders, and American Indians/Alaska Natives in the United States have lower incidence rates when compared to Caucasians and African Americans for the most common cancer types. In contrast, Asians/Pacific Islanders display the highest incidence and mortality rates for liver and stomach cancers, cancers that are initiated by infectious agents that are more prevalent in Asia than in the United States, suggesting that immigrants from these areas might be contributing to the higher incidence (Kimura, 2000; Tsai & Chung, 2010). To understand and correct the disparities that exist, it is important to incorporate our evolving knowledge of the complex biologic processes that are affected by various forms of cancer into the analysis of the disparities that exist.

## **INHERITED SUSCEPTIBILITY TO CANCER**

While cancer is due to acquired mistakes in the DNA, the likelihood of acquiring these changes can be affected by inherited factors in the DNA. It is currently estimated that more than 90% of cancers are sporadic and are not due to an inherited susceptibility, whereas 5%–10% of cancers are linked to an inherited susceptibility. The prevalence of some of the inherited factors differs in various populations, thereby contributing to some cancer disparities (Markowitz & Bertagnolli, 2009; Petrucelli, Daly, & Feldman, 2010; Rebbeck, Halbert, & Sankar, 2006). For those who have inherited a defective copy of a gene that increases cancer risk, the development of cancer is still dependent on acquiring additional changes in the DNA, with various environmental factors affecting the likelihood that cancer-causing changes will occur.

Some inherited cancer-susceptibility genes confer risk for many forms of cancer, whereas others confer risk for only a specific type of cancer (Markowitz & Bertagnolli, 2009; Petrucelli et al., 2010; Rebbeck et al., 2006). Inherited defects in the *BRCA1* and *BRCA2* genes increase risk for both breast and ovarian cancers (about 80% lifetime risk in some carriers), whereas they confer a much smaller risk of developing other cancers, including pancreatic cancer (Petrucelli et al., 2010). The *BRCA1* and *BRCA2* proteins play a role in DNA repair, and when the proteins are defective, damaged DNA is more likely to persist and accumulate multiple changes that can culminate in cancer (Kwei et al., 2010; Olopade, Grushko, Nanda, & Huo, 2008; Powell & Kachnic, 2008; Zhang & Powell, 2005). Inherited mutations in the *BRCA* genes are found most often in people of Ashkenazi Jewish descent, but they may also contribute to breast cancer in young African American women, as will be discussed later in the chapter.

Some people inherit defective forms of one of the enzymes in the DNA mismatch repair system, and this predisposes to hereditary nonpolyposis colorectal cancer (Lynch syndrome), with endometrial cancer and ovarian cancer also occurring at increased frequency (Hampel et al., 2005). Many other genes that predispose to cancer have been identified, but most of the inherited cancer syndromes are relatively rare, and thus do not play a large role in overall disparities in the occurrence and outcome of cancer in various populations.

## **ENVIRONMENTAL FACTORS CONTRIBUTING TO CANCER**

Tumorigenesis is a multistage process that usually happens over many years, making it difficult to pinpoint the specific environmental agents responsible for the multiple changes that lead to cancer. Broadly defined, environmental factors include all external forces that act upon an organism,

including dietary factors, infectious agents, sunlight, occupational exposures, pollutants, and all other agents encountered throughout a lifetime, some of which might increase risk for cancer (Chameides, 2010; Clavel, 2007; Monforton, 2006; Robinson, 2002; Tominaga, 1999; Weidman et al., 2007; Zhao, Shi, Castranova, & Ding, 2009). Exposure to carcinogens at a young age is generally more problematic than for older individuals, due to the higher rate of cell division in younger people who are growing and due to the many years over which additional mistakes can accumulate (Barton et al., 2005). Some environmental factors increase the risk of cancer by directly inducing DNA damage, whereas others increase the likelihood that a cell with damaged DNA will survive, proliferate, and go on to develop more damage that leads to cancer.

Cancer clusters that are associated with specific occupations, specific geographic sites, and/or use of specific products have played an important role in identifying carcinogenic agents. For example, boys who served as chimney sweeps in the 18th century were observed to develop scrotal cancer, an otherwise rare form of cancer that was triggered by some of the chemicals in the soot that came in contact with their tissues (Cherniack, 1992; Hall, 1998). In the late 19th century, epidemiologic studies identified an excessive occurrence of bladder cancer among workers in the aniline dye industry. Since that time, multiple studies have firmly established that the risk of bladder cancer increases with exposure to a variety of industrial chemicals known to have carcinogenic effects, including naphthylamine, methylene dianiline, and toluidine (Golka, Wiese, Assennato, & Bolt, 2004). Ship workers and others exposed to asbestos fibers are at increased risk of mesothelioma and of lung cancer, with the inflammation triggered by the fibers playing a large role in tumor development many years after the exposure (Gibbs & Berry, 2008; Maeda et al., 2010). The Environmental Protection Agency, the Consumer Product Safety Commission, the Occupational Safety and Health Administration, and other federal and state groups have enacted regulations to limit exposure to many carcinogenic substances. These regulations reduce risk, but exposures to carcinogens continue to occur, with some occupations and geographic areas posing greater risk than others, and with lower socioeconomic groups proportionally having greater exposures (Steenland, Burnett, Lulich, Ward, & Hurrell, 2003).

## **Tobacco**

Some chemicals that are present in tobacco are carcinogenic, and the risk that they pose increases with exposure (Secretan et al., 2009). Some people also inherit an increased risk to becoming addicted to nicotine and hence are at increased risk of heavy smoking, which thereby increases their cancer

risk (Stevens et al., 2008). There are multiple genes that affect the likelihood that someone will become addicted, and the role of these in racial differences in tobacco use and dependence is only starting to be explored (Sherva et al., 2010). In addition, some people inherit genes that modulate their risk of cancer through differences in their ability to metabolize and clear carcinogens, through differences in their ability to recognize and repair damaged DNA, and through other mechanisms (Weisberg, Tran, Christensen, Sibani, & Rozen, 1998; Wu et al., 2002). The tissues that are most at risk for damage from the carcinogens in cigarettes are those within the respiratory track, mouth, and upper digestive tract, which are exposed to the chemicals in smoke. Some chemicals in smoke get absorbed and are excreted through the kidneys and bladder, which contributes to an increased risk of kidney and bladder cancer in smokers (Green et al., 2000; Lodovici & Bigagli, 2009). Most smokers start as teenagers; the incidence of lung cancer, however, peaks after age 60, which indicates that it often takes a long time for carcinogenic agents to cause damage to the DNA that is sufficient to cause cancer. Quitting smoking reduces but does not eliminate risk, because some of the damage that has occurred is permanent, and these cells remain at increased risk for acquiring additional changes in the DNA (Ebbert et al., 2003). Some agents enhance the carcinogenic nature of tobacco. For example, the combination of heavy tobacco and alcohol poses a greater risk of developing cancers of the oral cavity and esophagus than either agent alone (Scully & Bedi, 2000; Secretan et al., 2009). The mechanisms responsible for these combined effects are not known and are being investigated. The combination of asbestos and tobacco leads to a much higher risk of lung cancer than either agent alone (O'Reilly, McLaughlin, Beckett, & Sime, 2007). Some of the cancers that are induced by tobacco can also occur in nonsmokers. Sometimes, these tumors are linked to secondhand smoke, but some of them have molecular features that indicate that distinct mechanisms are involved in their initiation. For example, while most head and neck cancer in the United States is due to heavy use of tobacco and alcohol, an increasing number are due to infection with human papillomavirus (HPV) (Settle et al., 2009). Many cases of lung cancer in nonsmokers have molecular features that differ dramatically from lung cancer in smokers, pointing to distinct mechanisms involved in their development.

### **Dietary Factors**

Dietary factors can either increase or decrease the risk of cancer through a variety of different mechanisms (Ahn et al., 2007; Carpenter, Yu, & London, 2009; Huxley et al., 2009). People with diets that are low in fruits and vegetables are at increased risk for cancer, yet people who consume high

amounts of fruits and vegetables do not appear to be at less risk for cancer than those who consume moderate amounts. Very low consumption of fruits and vegetables can lead to vitamin deficiencies, including folate, vitamin B6, vitamin B12, and vitamin A, and these can increase mutation rates (Ames, 1999). Several randomized studies indicate that supplementation with micronutrients is often not sufficient to reduce risk, and may increase risk in some situations (Goodman, Alberts, & Meyskens, 2008). For example, deficiencies in beta-carotene (a precursor to vitamin A) have been associated with an increased risk of cancer in people exposed to the carcinogens in tobacco, but randomized trials in high-risk populations have shown that supplementation with beta-carotene increased rather than decreased cancer incidence and cancer mortality among smokers (Bardia et al., 2008). The form in which a micronutrient is delivered can also make a difference. Vitamin C from dietary sources, but not from supplements, is associated with a reduced risk of oral premalignant lesions (Maserejian, Giovannucci, Rosner, & Joshipura, 2007). Consumers are often led to believe that such supplements are safe and effective, but many do not help, and some may be causing harm.

Some studies show that the manner in which the food is prepared plays an important role in the increased risk that is linked to consumption of some foods. For example, grilling of red meats at high temperatures can generate heterocyclic amine carcinogens that would be absent or at lower levels with meat prepared in different manners (Alaejos, Gonzalez, & Afonso, 2008; Cross & Sinha, 2004). This is thought to contribute to some of the increased risk of cancer in people who consume large quantities of red meat. Smoking and salt preservation are thought to contribute to the high rate of stomach cancer in Japan, especially when the bacteria *Helicobacter pylori* (HP) is present (Kimura, 2000). A diet high in fresh fruits and vegetables reduces the risk of stomach cancer in people with HP who consume high quantities of salted and pickled foods, illustrating the complexity of how diet affects cancer risk.

While some methods of food preservation are associated with increased risk of cancer, foods that are free of preservatives are not always better than those that have preservatives, especially if the food is at risk for contamination with microorganisms. Several fungi that grow on grains produce potent carcinogens, with fumonisin and aflatoxin increasing the risk of liver cancer (Larsen, 2010; Moore, 2009; Murphy et al., 1996; Preston & Williams, 2005). Levels of these toxins are carefully monitored and regulated in the United States, but are often found in the food supplies of developing nations, especially those with poor storage facilities. Susceptibility to carcinogens found in food can be modified by many dietary factors. For example, the chlorophyll found in green plants reduces absorption



of aflatoxin, thereby offering some protection from this potent carcinogen (Preston & Williams, 2005).

Some advocacy groups have raised concern that milk products, especially those from cows that receive bovine growth factor, increase the risk of breast cancer. Bovine growth hormone is biologically inactive in humans, and data from multiple epidemiologic studies as well as laboratory studies do not show that dairy products increase risk of breast cancer (Parodi, 2005).

## **Obesity**

There is an increased rate of some forms of cancer in individuals who are obese (Ahn et al., 2007; Brown & Simpson, 2010; Calle, Rodriguez, Walker-Thurmond, & Thun, 2003; van Kruijsdijk, van der Wall, & Visseren, 2009). There are multiple biologic changes that can occur during obesity, including insulin resistance, elevated levels of circulating cellular growth factors, elevated levels of estrogen, and increased inflammation (van Kruijsdijk et al., 2009). These may be working with carcinogens, viruses, and other factors to increase the risk of DNA damage, thereby enhancing the risk of tumor development. Fat also serves as a reservoir for certain types of chemicals, some of which are carcinogenic.

The multiple changes in DNA that lead to cancer generally occur over many years, and thus it is likely that the age at which someone becomes obese and the duration of the obesity both have an impact on cancer risk. Some ethnic and racial groups are at increased risk of obesity, with genetic, cultural, and environmental factors all contributing to variations in its prevalence. Dieting reverses obesity in only a small fraction of people who attempt it, and studies that have looked at the consequences of weight loss in large populations did not show a reduction in mortality, most likely because some of the weight loss was triggered by disease processes rather than by individual choice (Bamia et al., 2010; Dixon, 2010; Eckel, 2008; Nanri et al., 2010). Nonsurgical methods for planned weight loss have been disappointing, with a low percentage of subjects achieving and sustaining the desired weight, but subjects often show improvement in cholesterol and markers of inflammation, providing evidence of probable clinical benefit (Dansinger, Gleason, Griffith, Selker, & Schaefer, 2005; Eckel, 2008; Franco et al., 2007; Rapp et al., 2008; Sacks et al., 2009). One 10-year prospective interventional study showed that bariatric surgery on morbidly obese patients in Sweden led to major sustained weight loss, with a modest reduction in cancer rates in women but not men (Sjostrom et al., 2009). Thus, while obesity may increase the risk of cancer, weight loss in adults is disappointing in its ability to reduce risk. Ideally, efforts should be focused on preventing obesity to reduce short- and long-term health effects, including cancer.

## Inflammation

The immune system is designed to respond to infection or injury, and in most cases it protects the host, but it can sometimes contribute to tumor formation and propagation (Grivennikov, Greten, & Karin, 2010; Sgambato & Cittadini, 2010; Wang & DuBois, 2008). This occurs in part because cells of the immune system are designed to attach and kill foreign organisms, but they can also damage normal cells when inflammation is prolonged. The duration of inflammation is linked to the risk of cancer, with the site of the inflammation being linked to where cancer occurs. The inflammation can be in response to inflammatory diseases, such as ulcerative colitis, which increases the risk of colon cancer (Markowitz & Bertagnolli, 2009). Prolonged stomach acid reflux can lead to chronic irritation of the esophagus that causes cellular changes recognized as Barrett's esophagus, a premalignant condition in which inflammation plays an important role in the subsequent development of esophageal cancer (Edelstein, Farrow, Bronner, Rosen, & Vaughan, 2007; Sharma, 2009a, 2009b). Particle irritation, as occurs with asbestos, triggers an inflammatory response that plays an important role in the development of mesothelioma and lung cancer (Antonescu-Turcu & Schapira, 2010; Heintz, Janssen-Heininger, & Mossman, 2010; Maeda et al., 2010). Prolonged infection, as occurs with some viral, bacterial, or parasitic infections, also plays an important role in the development of some forms of cancer (Heintz et al., 2010; Maeda et al., 2010).

## Infectious Agents

Some reports estimate that 20%–30% of human cancers are initiated by an infectious agent, with specific viruses, bacteria, and parasites serving as carcinogens (Morris, Young, & Dawson, 2008). Some viruses directly contribute to human cancers by bringing genetic materials into cells that permanently alter cellular programming, thereby increasing the likelihood that cells will acquire additional changes that sometimes result in cancer (Morris et al., 2008). Tumorigenic viruses that directly alter cellular programming as an early event in tumor development include HPV, Epstein-Barr virus (EBV), the Kaposi's sarcoma herpesvirus (KSHV), hepatitis B, human T cell leukemia virus, and Merkel cell carcinoma polyoma virus (Carbone, Cesarman, Spina, Gloghini, & Schulz, 2009; Chang et al., 1994; Feng, Shuda, Chang, & Moore, 2008; Kalland, Ke, & Oyan, 2009; Klass & Offermann, 2005; Morris et al., 2008; Ruprecht, Mayer, Sauter, Roemer, & Mueller-Lantzsch, 2008). The inflammatory response that accompanies chronic infection can also lead to some forms of cancer, as occurs with HP and schistosomiasis (Kimura, 2000; Mostafa, Sheweita, & O'Connor, 1999). HP is a bacterium that contributes to the development of most cases of stomach cancer (Perrin, Ruskin, & Niwa,

2010), and the parasite schistosomiasis causes bladder cancer in parts of the world where infection is common (Mostafa et al., 1999). Infections that suppress immune function, including the human immunodeficiency virus (HIV), also contribute to tumorigenesis by reducing the ability of the immune system to suppress or kill tumorigenic viruses and developing tumors (Carbone et al., 2009; Crum-Cianflone et al., 2009). The importance of recognizing the role of infectious agents in tumorigenesis relates to the potential for preventing or clearing the infectious agent, thereby reducing cancer risk.

The likelihood that someone will develop a cancer as a consequence of an infectious agent is affected by place of birth, racial or ethnic background, sexual orientation, socioeconomic status, access to state-of-the-art health care and other factors. For example, hepatitis B is a vaccine-preventable disease that is endemic to certain parts of Asia and Africa (Lee & Lee, 2007; Tsai & Chung, 2010). Women who are carriers can transmit the virus to their newborn offspring, and the virus is also transmitted sexually or through contact with infected blood. People who develop chronic active hepatitis as a consequence of hepatitis B infection are at increased risk for hepatocellular cancer, with most tumors arising after 30 years or more of infection, since tumor development remains dependent on the acquisition of additional changes in the DNA. The risk of hepatitis B infection can be reduced through vaccination, screening of blood products to ensure that the products are free of the virus, using sterile needles for injections and infusions, and educating the public on how to reduce the risk of sexually transmitted diseases. When someone is found to be a chronic carrier and has chronic active hepatitis, treatments are available that clear infection in a high percentage of carriers. These measures are disparately used to prevent and control infection within various populations within the United States, and many of them are not available in poor countries.

In addition to differences in prevalence of infection with tumorigenic agents in different populations, there are differences in exposure to agents that serve as co-carcinogens. For example, nearly 100% of cervical cancers and anal cancers are initiated by HPV, but only a subset of people who are infected with tumorigenic strains of HPV go on to develop cancer (Longworth & Laimins, 2004; Settle et al., 2009; Stanley, Pett, & Coleman, 2007; Woodman, Collins, & Young, 2007). Both smoking and obesity increase the likelihood that someone with HPV infection will go on to develop cervical cancer (Rieck & Fiander, 2006). Screening through the use of Pap smears detects HPV-induced premalignant and malignant changes that can be treated before they become advanced, but the use of these methods and the use of vaccination against HPV is not consistent across various populations.

Infection with HIV increases the risk for cancer, with the greatest risk from cancers linked to tumorigenic viruses such as HPV, EBV, and KSHV

(Carbone et al., 2009; Crum-Cianflone et al., 2009). HIV infection increases the risk for the development of Kaposi's sarcoma 20,000–80,000-fold, with people who acquired HIV through homosexual activity at greater risk than those who acquired HIV through intravenous drug use. Not all people infected with HIV are at equal risk for the development of cancer, in part because lifestyle factors affect the risk of co-infection with HPV and KSHV, and they also affect exposure to co-carcinogens.

## Radiation

Ionizing radiation can induce DNA damage, thereby increasing risk for cancer development (Bolus, 2008; Wall et al., 2006; Williams, 2008). Higher risks are associated with younger age at exposure, and females have somewhat higher risks of cancer from radiation exposure than males do. Some occupations and geographic sites are associated with increased levels of exposure, but the role of ionizing radiation in cancer disparities has not been well studied. Several recent studies report greater occupational exposure among African American than Caucasian workers in the Savannah River Site nuclear power plant, with African Americans more likely to have detectable radiation exposure on their monitors (Angelon-Gaetz, Richardson, & Wing, 2010). Ionizing radiation is used in a variety of screening and diagnostic tests at doses designed to minimize patient risk, but the cumulative effects are not negligible, especially in individuals who have frequent and/or numerous tests at a young age (Wall et al., 2006). The radiation exposure that occurs with CAT scans, angiograms, and nuclear medicine studies is much higher than with mammograms or simple X-rays, and their long-term risk is not fully known, in part because cumulative exposure is not generally tracked in the United States, but exposures from imaging tests can be substantial (Goodman et al., 2008). Ionizing radiation is used at high doses to treat some forms of cancer. It increases the risk of secondary cancers, and thus its use is generally restricted to life-threatening diseases in which the benefit of radiation far outweighs the risks (Doi, Mieno, Shimada, & Yoshinaga, 2009; Li et al., 2010; Shuryak, Hahnfeldt, Hlatky, Sachs, & Brenner, 2009). Improvements in the methods used to deliver therapeutic radiation have reduced its carcinogenicity by more effectively focusing its delivery to the cancers being targeted, with less damage to normal cells. Ultraviolet (UV) radiation in sunlight can also cause DNA damage, thereby increasing the risk of several forms of skin cancer (McPhail, 1997). Skin pigment reduces the ability of UV radiation to penetrate skin and cause damage; thus, light-skinned individuals are more at risk for damage through sunburn and excessive tanning, and this can lead to premalignant conditions such as actinic keratosis, as well as skin cancers.

## **Chemotherapy**

Therapies that damage DNA remain a primary modality for treating many types of cancer, with the hope that cancer cells, due to their higher growth rates, will be more affected than normal cells. These therapies increase the risk of secondary cancers, with some combinations being more carcinogenic than others (Gururangan, 2009). People with inherited defects in DNA repair are at increased risk for secondary cancers induced by chemotherapy and/or radiation. The treatment for many forms of cancer includes the use of radiation and/or cytotoxic chemotherapy, recognizing that the greatest chances of cure are dependent on eradication of all cancer cells. The numbers of long-term cancer survivors have increased steadily, but this trend comes at a price. The cumulative incidence of subsequent cancers approaches 15% at 20 years after diagnosis of primary cancer, representing a three- to tenfold increased risk compared with the general population. Some treatment programs have a much higher risk of subsequent cancers, and when possible, less carcinogenic treatment options have replaced some that have especially high rates of secondary malignancies.

## **BIOLOGY OF BREAST CANCER DISPARITIES**

### **Disparate Incidence and Mortality Rates**

Breast cancer is the most commonly reported cancer of women in the United States, with an estimated 207,090 new cases of invasive cancer expected to affect women in 2010 (American Cancer Society, 2010). Overall mortality rates for breast cancer began a steady decline in the 1990s, due to a combination of increased screening and the utilization of therapies that were developed in response to improved understanding of breast tumor biology and the molecular mechanisms driving disease progression (Newman & Martin, 2007). Caucasian women have the highest age-adjusted incidence rates of breast cancer in comparison with all racial/ethnic groups over the age of 45 years. However, African American women have the highest incidence rates among women under the age of 45 years (Amend, Hicks, & Ambrosone, 2006; Newman & Martin, 2007; Polite, Dignam, & Olopade, 2005). Furthermore, African American women have the highest mortality rates from breast cancer and a lower 5-year survival than Caucasian women (American Cancer Society, 2010; Field et al., 2005). By contrast, Hispanic, Asian/Pacific Islander, and American Indian/Alaska Native women have lower incidence and mortality rates of breast cancer than both Caucasian and African American women (American Cancer Society, 2010).

## Disparities in Breast Cancer Stage and Tumor Characteristics

Early studies undertaken to examine the impact of race and ethnicity on breast cancer were carried out when characterization of breast cancer primarily involved staging and microscopic appearance of the tumors. These studies demonstrated that African American and Hispanic patients were more likely to present with advanced tumors that had more aggressive histologic features than Caucasian patients, but they were unable to determine whether this was due to delays in seeking medical intervention or whether there were biologic differences in the forms of breast cancer that developed. For example, the National Cancer Institute's Black/White Cancer Survival Study, which was a cohort of 1,130 women (518 Caucasian and 612 African American) aged 20–79 diagnosed with primary breast cancer between January 1, 1985 and December 31, 1986 (Eley et al., 1994), reported that African American women were almost twice as likely as Caucasian women to be diagnosed at advanced stages: 30% of African Americans presented with stage III or IV cancers compared to 18% of Caucasians. The microscopic appearance of breast cancer reports the degree to which breast cancers resemble normal breast structures (differentiation), how rapidly the cells are replicating (mitotic index), and how much the normal architecture of cells is altered (atypia). The Black/White Cancer Survival Study reported that African Americans more commonly had poorly differentiated tumors (20% vs. 14%) and tumors with high-grade nuclear atypia (15% vs. 10%) in comparison to Caucasians, and 18% of African Americans had high-grade mitotic activity in comparison to 10% of Caucasians, following adjustment for age and stage (Chen et al., 1994; Eley et al., 1994).

Recent studies continue to show that African American women are significantly more likely to present with later-stage tumors than Caucasian women, and are also more likely to display tumor characteristics associated with a poor prognosis, irrespective of age and stage of disease (Curtis, Quale, Haggstrom, & Smith-Bindman, 2008; Porter et al., 2004). African American women are also more likely to be diagnosed with breast cancer at a younger age than Caucasian women, with 35% of African Americans diagnosed under the age of 50 years compared to 21% of Caucasians (Fiel et al., 2005). This raises the possibility that hereditary syndromes and/or distinct environmental exposures might be contributing to earlier development of breast cancer and the worse outcome in African Americans compared to Caucasians. In addition, African Americans are 40% more likely to be diagnosed with inflammatory breast cancer when compared to Caucasians. Inflammatory breast cancer is a very aggressive form of breast cancer in which tumor cells grow and spread to remote sites very rapidly. Prolonged inflammation is well known to increase the risk of developing certain forms of cancer, but

the inflammation in this condition is not known to precede the development of cancer. Inflammatory breast cancer makes up approximately 2% of total breast cancer cases and thus plays only a minor role in the disparities in outcome that occur (Hance, Anderson, Devesa, Young, & Levine, 2005).

Older African Americans often have a worse outcome when diagnosed with breast cancer compared to their Caucasian counterparts (Curtis et al., 2008). African Americans on Medicare had a 30% increased risk of death from breast cancer when compared to Caucasian patients, after adjustment for hormone receptor status, tumor size, nodal status, and menopausal status.

There is considerable variability in how patients with breast cancer are managed throughout the United States, but this variability is eliminated for patients on clinical trials, who are closely monitored while following strict protocols. When African American patients on clinical trials were compared to Caucasian patients on the same trials, they experienced worse disease-free survival [HR = 1.56; 95% CI (1.15–2.11)] and overall survival [HR = 1.95; 95% CI (1.36–2.78)] after adjusting for hormone receptor status, tumor size, menopausal status, nodal status, and baseline absolute neutrophil count (Hershman et al., 2009). Collectively, these and other studies suggest that there may be differences in breast cancer biology and progression that contribute to the disparities in disease outcome.

While Hispanic women have a lower incidence of and mortality rate for breast cancer than Caucasians, those who develop breast cancer tend to have a more aggressive breast cancer phenotype. When the tumors of 4,885 Caucasian women, 1,016 African American women, and 777 Hispanic women were collected from 31 hospitals nationwide, both African American (49%) and Hispanic (48%) women were more likely than Caucasian women (39%) to have high levels of cell replication and less cellular differentiation seen within their tumors (Elledge, Clark, Chamness, & Osborne, 1994).

### **The Role of Inherited Genes in Disparities**

BRCA1 and BRCA2 are proteins that play an important role in DNA repair (Kwei et al., 2010; Olopade et al., 2008; Powell & Kachnic, 2008; Zhang & Powell, 2005). People who inherit mutant forms of either *BRCA1* or *BRCA2* have a 40–80% lifetime risk of developing breast cancer. *BRCA1* and *BRCA2* mutation frequencies vary by geographic region and ethnicity (Fackenthal & Olopade, 2007). Within the United States, the Ashkenazi Jewish population has the highest reported frequencies of *BRCA1* and *BRCA2* mutations, mainly due to three founder mutations (*BRCA1* 187delAG and 5385insC, *BRCA2* 6174delT) that have a combined carrier frequency of 1 in 40 for this population. By comparison, the overall prevalence of *BRCA1* and *BRCA2* mutations is estimated to be between 1 in 400 and 1 in 800 (Petrucci et al., 2010).

Patients taken from the Northern California Breast Cancer Family Registry were used to assess the *BRCA1* mutation carrier frequency within various racial and ethnic groups who developed breast cancer within the United States. These patients were under the age of 65 and were diagnosed with invasive breast cancer between January 1, 1995 and December 31, 2003. Five racial/ethnic groups, including 549 Caucasians (encompassing both Ashkenazi Jewish Caucasians and non-Ashkenazi Jewish Caucasians), 444 Asians, 393 Hispanics, and 341 African Americans, were tested for *BRCA1* mutations. After the Ashkenazi Jewish patient population (8.3%), Hispanics (3.5%) had the highest frequency of inherited *BRCA1* mutations, followed by non-Ashkenazi Caucasians (2.2%), African Americans (1.3%), and then Asians (0.5%). Interestingly, this study also reported that African American patients (17%) diagnosed under the age of 35 had a significantly higher *BRCA1* mutation frequency when compared to the other non-Ashkenazi Jewish populations (Hispanics [8.9%], Asians [2.4%], Caucasians [7.2%]) in the same age range. Additionally, this study found that the types of *BRCA1* mutations varied among the different racial/ethnic groups. The most frequent *BRCA1* alterations in Hispanics and Caucasians (including both the Ashkenazi Jewish and non-Ashkenazi Jewish populations) were frame-shift mutations, whereas in African Americans, the most prevalent *BRCA1* alterations were missense mutations (John et al., 2007). Other studies have also reported unique and distinct *BRCA1* and *BRCA2* mutations within the African American population (Ademuyiwa & Olopade, 2003; Olopade et al., 2003). Awareness of different types of mutations helps in screening patients for inherited defects that predispose to breast and other cancers. African Americans also appear to have a higher incidence of unclassified variants of *BRCA1* and *BRCA2* in comparison to other racial/ethnic populations. These variants are sequences within the gene that differ from sequences found in most people, yet they are not known to adversely affect the structure of the protein and hence are not currently considered mutations. Due to the undetermined significance of these variants, it is unknown whether they modify breast cancer risk and survival.

With the advent of high-throughput sequencing and whole-genome technologies, studies show that the major genetic component contributing to breast cancer predisposition is likely caused by multiple and common low-penetrance genes that act in conjunction to modify breast cancer risk (Olopade et al., 2008). Genome-wide association studies have led to the identification of single nucleotide polymorphisms (SNPs) within a small number of genes, primarily within Caucasian populations with estrogen receptor positive breast cancers. A primary example of this phenomenon was the identification of four SNPs in the *FGFR2* gene that were highly associated with breast cancer risk in a study of 1,145 postmenopausal women of European ancestry with invasive breast cancer and 1,142 controls (Hunter



et al., 2007). Additional SNPs that are significantly associated with breast cancer risk have been identified in four genes (*CASP8*, *TNRC9*, *MAP3K1*, and *LSP1*) and three genomic regions (*2q35*, *8q24*, and *5p12*). These findings were validated in additional cohorts of Caucasian women; however, in studies of other racial/ethnic populations, the SNPs had a modest effect in an Asian cohort and discordant results in cohorts of African ancestry (Olopade et al., 2008). These studies indicate that associations between genomic variants and cancer risk vary among racial/ethnic populations and, further, they demonstrate the need to assess the relationships between SNPs and disease risk within diverse patient cohorts. The identification of these modifiers of cancer risk may further elucidate why differences exist in genetic susceptibilities to cancer among individuals and populations.

### **Differences in Proteins That Regulate Cellular Proliferation, Apoptosis, and DNA Repair**

The changes in DNA that occur in cells that become cancerous lead to changes in the expression of many proteins, some of which play critical roles in the malignant behavior of the cells. These include cyclins, proteins that serve as co-factors to enzymes that regulate progression through the cell cycle (Malumbres & Barbacid, 2009). Alterations that occur in cancer can lead to high levels of several cyclin proteins independent of the usual signals for their production. In general, women with breast cancer who exhibit low levels of cyclin E expression and high levels of cyclin D1 expression are significantly less likely to die from their breast cancer than women with high levels of cyclin E and low levels of cyclin D1 (Porter et al., 2004). African American women had higher levels of cyclin E (OR [odds ratio] = 4.3) and lower levels of cyclin D1 expression (OR = 0.5) than Caucasian women in their breast cancer cells, potentially contributing to the worse outcome for African American women.

One of the most common events in the development of cancer involves the tumor suppressor protein p53 that is mutated or eliminated in over 50% of human cancers (Green & Kroemer, 2009). Protein p53 is a transcription factor that is induced when abnormal DNA is present or under cellular stress, and it leads to expression of multiple proteins, including proteins that inhibit DNA replication, help repair damaged DNA, and induce programmed cell death—all functions that are designed to protect the integrity of the DNA. When the function of p53 is disrupted, cells with damaged DNA are more likely to be propagated and acquire more mistakes. The mutations in the p53 gene (*TP53*) that most commonly occur in tumors lead to a stabilization of the protein and a loss of its ability to function as a transcription factor, so that high levels of p53 protein reflect loss of p53 function. Patients with stage I and II breast cancers displayed no difference in the frequency of *TP53* gene

alterations between African Americans (20%) and Caucasians (19%), but there were differences in the types of *TP53* alterations that were encountered (Blaszyk et al., 1994; Shiao, Chen, Scheer, Wu, & Correa, 1995). When more advanced stages were included in the analysis, tumors of African Americans (OR = 1.7) more frequently displayed high levels of mutant p53 protein expression when compared to the tumors of Caucasians (Porter et al., 2004). In general, tumors that display high levels of mutant p53 have a more aggressive phenotype, are less likely to respond to adjuvant therapy, and thus might contribute to the worse outcome of African American patients.

### **Differences in Hormonal Factors That Contribute to Breast Cancer Disparities**

Estrogen is known to play an important role in the development and progression of many cases of breast cancer, especially those that express high levels of estrogen receptor (ER) and progesterone receptor (PR). Both genetic and environmental factors affect the levels and types of estrogen that are present. Estrogens are synthesized from cholesterol, with estradiol being the predominant form (Taioli et al., 1999, 2010). The ovaries make most of the estradiol until menopause, but estradiol is also made by fat cells and may play a role in the increased rate of ER positive breast cancer in obese postmenopausal women (Brown & Simpson, 2010).

Two mutually exclusive pathways are involved in metabolizing estradiol. One pathway utilizes the enzyme CYP1A1 to generate an inactive metabolite (2-hydroxyestrone), and the other pathway uses CYP3A4 to generate a metabolite that continues to have estrogenic activity (16 $\alpha$ -hydroxyestrone) (Masi & Olopade, 2005). There is an inherited variant of CYP3A4 that is more active and leads to higher levels of the 16 $\alpha$ -hydroxyestrone metabolite, and it was more common in African American girls (62%), when compared to Hispanic (52%) and Caucasian girls (17%) in a study of 137 healthy 9-year-old girls (Kadlubar et al., 2003). This high-activity variant was associated with earlier onset of puberty. These data suggest that higher physiological levels of active estrogen, along with earlier onset of puberty, may contribute to the higher prevalence of both early onset breast cancer and breast cancer-specific mortality in African American women (Masi & Olopade, 2005).

### **Differences in Molecular Characteristics of Breast Cancers**

The alterations in DNA that lead to breast cancer lead to changes in gene expression, which can be assessed using complementary DNA (cDNA) microarrays, a method that allows evaluation of hundreds of genes simultaneously.

Comparison of breast cancer specimens to normal breast cells has revealed that some breast cancers are derived from cells that line the breast ducts (luminal cells), whereas others arise from cells that are beneath the luminal cells (basal or myoepithelial cells). Six distinct subtypes of breast cancer have been identified that have distinct patterns of gene expression: luminal A, luminal B, HER2-enriched, basal-like, normal breast-like, and claudin-low (Perou et al., 2000; Prat et al., 2010). Luminal A tumors have relatively high expression of genes, such as the *ER* gene, that are normally expressed by cells that line the breast ducts (luminal cells) (Carey et al., 2006; Oh et al., 2006; Prat et al., 2010; Sorlie et al., 2001). Luminal B tumors show low to moderate expression of *ER*, whereas they express high levels of genes that induce cell proliferation and block programmed cell death (apoptosis), reflecting a more aggressive form of breast cancer compared to luminal A cancers. The HER2-enriched subtype demonstrates overexpression of *ERBB2/HER-2/neu* and low levels of *ER* and *ER*-associated genes. The basal-like subtype generally does not express *ER*, *PR*, or *ERBB2/HER-2/neu*, whereas it has high levels of expression of other proteins, such as keratin 5, keratin 17, and laminin. The normal breast-like subtype is distinguished by high expression of genes characteristic of basal epithelial and adipose cells, along with low expression of genes characteristic of luminal epithelial cells.

Of all the subtypes, luminal A tumors have the best prognosis, demonstrating the highest overall survival and relapse-free survival (Prat et al., 2010; Sorlie et al., 2001). The tumors are slower to metastasize than some of the other forms, and treatments that attack the ability of hormones to drive these tumors have been available for many years. Basal-like, claudin-low, and HER2 classified tumors are more aggressive tumors that metastasize more readily, leading to a worse outcome both in terms of overall survival and relapse-free survival (Di Cosimo & Baselga, 2010). The use of herceptin has dramatically improved the prognosis of patients with HER2-classified tumors, indicating that knowledge of factors that drive tumor growth and survival can be exploited for developing new treatments (Mukai, 2010). Basal-type tumors metastasize early and have been especially difficult to treat, but new insights into their biology are leading to more effective treatments, such as the poly ADP-ribose polymerase (PARP) inhibitors in conjunction with new combinations of cytotoxic chemotherapy (Anders et al., 2010; Di Cosimo & Baselga, 2010).

Molecular characterization using cDNA microarrays reveals that African American women are more likely to have basal-like tumors and less likely to have luminal A or B tumors than Caucasians, providing strong evidence that some of the disparities are not just due to differences in access to care and in tumor management. In the Carolina Breast Cancer Study of 496 cases (196 African American and 300 non-African American) of invasive

breast cancer, the prevalence of basal-like tumors was significantly higher in African Americans (26%) than in non-African Americans (16%) (Carey et al., 2006). Additionally, this high prevalence of basal-like tumors in African Americans was mainly seen in premenopausal women, irrespective of stage at diagnosis. This study also found that basal-like tumors were more likely to have high nuclear and histological grade, as well as a high mitotic index, than other tumor subtypes, after adjustment for age, race, and stage. Furthermore, the basal (44%) and HER2 (43%) subtypes had a higher percentage of p53 mutations in comparison to luminal subtypes (luminal A, 15%; luminal B, 23%), thereby offering some insights into why early studies showed that African Americans were more likely to have tumors that displayed unfavorable microscopic features. It is currently not known why African Americans are more prone to develop basal-like tumors than Caucasians. It is also not known why luminal A breast cancers predominate in Asian and Caucasian populations, and are more common in postmenopausal than in premenopausal women. However, further study of the mechanisms driving the individual breast cancer subtypes and the environmental exposures that likely modify these processes will lead to improved understanding of this phenomenon.

## BIOLOGY OF COLORECTAL CANCER DISPARITIES

### Incidence and Mortality Rates

Colorectal cancer is the third leading cause of new cancer cases and cancer deaths in both men and women within the United States, with an estimated 141,210 cases expected to occur in 2011. Overall incidence and mortality have decreased in the past two decades as a result of improved screening and improvements in treatment. Screening can lead to the removal of premalignant polyps, thereby decreasing the likelihood that cancer will develop. However, incidence rates are increasing about 2% per year in adults under the age of 50, a population that is not recommended for screening unless in high-risk circumstances (American Cancer Society, 2010). African Americans have the highest age-adjusted incidence and mortality rates of any other racial/ethnic group, whereas Asians/Pacific Islanders and American Indians/Alaska Natives have the lowest rates. Both incidence and mortality rates within African Americans are declining, but the decline has been slower than in Caucasians, leading to an increasing divergence, especially in mortality rates (American Cancer Society, 2009, 2010). For those who get colorectal cancer, African Americans (OR = 1.2), American Indians (OR = 1.2), Hispanics (especially Mexicans, OR = 1.2), and Hawaiians (OR = 1.3) are more likely to die than Caucasians, with the greatest disparity in

risk of death in early-stage cancers (stages I and II), even while adjusting for age, stage, and treatment (African Americans, OR = 1.4; Hispanics, OR=1.4; Hawaiians, OR = 1.4) (Alexander et al., 2004; Chien, Morimoto, Tom, & Li, 2005). In a study of 574 patients (224 African American and 350 Caucasian) from the University of Alabama at Birmingham Hospital and the Birmingham Veterans Affairs Hospital tumor registries, African Americans with high-grade tumors were three times more likely to die of colon cancer within 5 years of surgical resection when compared to Caucasians with high-grade tumors [HR = 3.05, 95% CI (1.32–7.05)], following adjustment for race, gender, age, hospital, stage, and anatomic site. The African Americans and Caucasians within this study had similar proportions of high-grade tumors at diagnosis, a similar prevalence of comorbid conditions, and a similar frequency of deaths due to causes other than colorectal cancer, suggesting that differences in the aggressiveness of the cancers play an important role in the disparate survival outcomes among these populations (Alexander et al., 2005). Furthermore, in a large population study (33,464 Caucasians, 6,024 African Americans, 1,618 Asian/Pacific Islanders, and 911 American Indian/Alaska Natives or other unidentified racial/ethnic groups), patients diagnosed under the age of 50 were more likely to present with distant disease and poorly differentiated tumors and were more likely to be African American (Fairley et al., 2006). SEER data has also shown that the differential in incidence and survival outcome between African American and Caucasian patients is the largest in younger cohorts (under 50 years of age) (Polite, Dignam, & Olopade, 2006). Collectively, these studies suggest that African Americans are developing cancers with more aggressive phenotypes, thereby leading to their escalated rates of colorectal cancer mortality.

### **The Role of Genetics in Colorectal Cancer Disparities**

Approximately 15% of all colorectal cancers occur in people who have an inherited risk for colorectal cancer. The majority of these are due to inherited mutations in one of the DNA mismatch repair genes (*MLH1*, *MSH2*, *PMS2*, and *MSH6*) that lead to the development of Lynch syndrome (Kinzler & Vogelstein, 1996). The changes in DNA mismatch repair that occur in this syndrome can affect particular areas of the DNA called “microsatellites,” leading to a specific type of genomic instability called microsatellite instability (MSI). MSI can also occur in response to acquired changes in DNA repair, but the presence of MSI within colon cancer cells suggests the presence of either inherited defects in DNA mismatch repair enzymes or acquired mistakes in the function of this pathway. A few studies have examined MSI in

colorectal cancers from African Americans and Caucasians to determine if mismatch repair pathway dysfunction is playing a role in the higher rates of young-onset cases and proximally located colon tumors in young African Americans compared to Caucasians. These small studies reported that MSI incidence was more than twofold greater in African Americans when compared to Caucasians (Ashktorab et al., 2005; Ionov, Peinado, Malkhosyan, Shibata, & Perucho, 1993), but larger studies found that the rate in African Americans was approximately 20%, a frequency similar to what has been reported in the U.S. population (Cunningham et al., 2001; Hampel et al., 2005). It remains to be determined whether there are racial differences in the frequency of people harboring defective DNA mismatch repair genes, since not all cases of MSI are due to an inherited defect.

Another genetic syndrome that leads to colorectal cancer is familial adenomatous polyposis (FAP). The syndrome results from an inherited defect in the *APC* gene, and people who inherit defective *APC* develop hundreds of polyps, each with the potential to progress to cancer. Nearly 100% of people who inherit mutant *APC* develop cancer by the time they are in their forties. The large number of polyps that occur in this syndrome make carriers easy to identify, but FAP is sufficiently rare that it does not play a large role in the racial disparities that exist.

Methylenetetrahydrofolate reductase (MTHFR) is an enzyme involved in folate metabolism, which has been inversely linked to colorectal cancer risk (Le Marchand, Wilkens, Kolonel, & Henderson, 2005). Folate is important in making the building blocks for DNA, and folic acid deficiency leads to double-strand chromosome breaks by extensive incorporation of uracil into DNA. This occurs because there is a deficiency of thymidine when folate is low, so its precursor, uracil, is substituted. Folate also plays a functional role in DNA methylation, so patterns of methylation of the genome change during folate deficiency, and this can alter gene expression (Ames, 1999; Goelz, Vogelstein, Hamilton, & Feinberg, 1985). A common polymorphism, C677T, in the MTHFR gene was previously identified and shown to result in a temperature-sensitive enzyme that functions with decreased activity (Weisberg et al., 1998). In a study of 2,843 cases and controls from the Multiethnic Cohort Study, the MTHFR 677TT genotype was associated with a 23% decreased risk of colorectal cancer (Le Marchand et al., 2005). There was an even stronger association at high levels of folate intake. The study also reported differences in the allele frequency among racial/ethnic groups, with the T allele being the lowest in African Americans and Hawaiians when compared to Hispanics, Japanese, and Caucasians. The differences in the frequency of this allele might contribute to the higher incidences of colorectal cancer in Hawaiian and African American populations.

## **Environmental Factors Contributing to Colorectal Cancer Disparities**

The development of colorectal cancer is dependent on the accumulation of multiple changes in the DNA. Irrespective of whether the colorectal cancer is sporadic or in people with genetic risk, the majority of cancers arise in polyps, so that removal of polyps is likely responsible for the decreasing incidence of colorectal cancer that has occurred in recent years. Insights into the steps involved in the development of cancer come from comparing the DNA in colorectal cancer to DNA in polyps and in unaffected colon or rectum. Such studies show that over 90% of polyps contain an acquired change in the *APC* gene (either genetic or epigenetic), and additional changes in the DNA are found when polyps grow very large. Not all polyps progress to cancer, but those that do contain many more genetic changes that are responsible for the ability of cells to invade and metastasize.

Epidemiologic studies have shown that alcohol consumption, smoking, diabetes, obesity, and high meat intake are associated with increased risks of colorectal cancer (Akhter et al., 2007; Gapstur, Potter, & Folsom, 1994; Huxley et al., 2009). These exposures can lead to inappropriate DNA methylation and alkylation that promote carcinogenesis (Cross & Sinha, 2004; Slattery, Schaffer, & Edwards, 1997). Therefore, the dietary and lifestyle patterns that are common to specific racial/ethnic populations may induce altered frequencies and/or spectra in genetic alterations among different populations, leading to variations in cancer risk and clinicopathologic features.

Whole-genome analysis of tumors offers insights into some of the changes that occur in colorectal cancer in different patient populations. When 15 colorectal cancer samples taken from African American patients at Howard University Hospital were compared to a previously published analysis of 22 Caucasian colorectal cancer cases from Germany, many of the genetic changes were similar, but there were a few differences (Ashktorab et al., 2010; Lassmann et al., 2007). The *ATM* gene, whose encoded protein functions in the DNA damage response, was frequently amplified in Caucasian tumors but not in any of the African American tumors. In addition, the *DCC* gene, whose encoded protein functions as a receptor that can induce programmed cell death (Rodrigues, De Wever, Bruyneel, Rooney, & Gespach, 2007), was primarily amplified in Caucasians but deleted in African Americans (Takayama, Miyanishi, Hayashi, Sato, & Niitsu, 2006). They also reported that the *STS* gene, involved in promoting the growth of human breast cancer cells, was deleted in Caucasians and amplified in African Americans (Ashktorab et al., 2010). The functional consequences of these differences are not known, but they indicate that differences exist in the types of changes that occur in tumors from various patients, underscoring the need for characterizing both the causes and the consequences of these differences.

## CONCLUSIONS

Researchers have made tremendous progress in understanding many of the biologic changes that occur in cancer and some of the factors that initiate and perpetuate various forms of cancer. Vaccines, antibiotics, and other interventions are helping reduce some of the cancers that are initiated by infectious agents, and government regulations are reducing exposures to known carcinogens that once were more commonly encountered by the public. Multiple genes that are inherited and lead to increased risk for cancer have been identified, offering the opportunity to screen for people who are at increased risk. Screening for some forms of cancer has improved outcome through identifying cancers before they have spread, and clinical trials have helped define combinations of treatment that improve outcome. Knowledge of how specific genes and biologic processes contribute to tumorigenesis offers the opportunity for developing interventions that reduce risk and/or allow early detection of premalignant and malignant changes. Various forms of cancer are being characterized by some of the specific mutations and changes in gene expression that occur, offering more detailed understanding of biologic similarities and differences in cancers that were previously only characterized by their microscopic appearance. For those who get cancer, specific pathways that are critical to tumor cell survival and growth are now being targeted in many forms of cancer, leading to more effective treatments, with fewer long-term side effects. These and other advances in detection and treatment are responsible for the more than 10 million cancer survivors in the United States today.

Population studies have alerted the nation to the disparities in cancer incidence and mortality rates among the diverse racial/ethnic populations within the United States. Health care access plays a vital role in cancer health disparities, as unequal access plagues many, especially minority and impoverished populations. Biologic factors also contribute to the differences in incidence and outcome of cancer in different racial and ethnic groups. Racial and ethnic classifications do not necessarily align with population ancestry and hence are limited in their ability to identify people who might have some shared genetic background. African Americans are a heterogeneous group with admixture from African, European, and American Indian populations. Asian/Pacific Islander and Hispanic designations include a variety of ancestries within each racial/ethnic construct. To begin to refine our understanding of how genes contribute to tumor risk, researchers have begun to incorporate ancestry informative markers (AIMs) into their analysis of diverse populations, as a method to reduce bias associated with population stratification (Nassir et al., 2009).

Elimination of the disparities that exist in cancer incidence and outcome is an important goal, but it is not sufficient. There are approximately



1.5 million people who get cancer in the United States each year, and more than 550,000 people die of it. Elimination of cancer disparities would have a valuable impact on reducing these numbers. Through knowledge, it should be possible to develop more effective interventions that decrease incidence and mortality from cancer, to benefit people from all racial and ethnic groups.

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