Energy Balance and Cancer 9

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Impact of Energy Balance on Cancer Disparities

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Energy Balance and Cancer

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Preface

Energy Balance and Cancer Disparities

While great progress has been made across the spectrum of cancer research, extending from prevention, diagnosis, and therapy to survivorship, the benefits of these advances have not been realized by all groups. Significant disparities exist due to a variety of factors including age, gender, ethnicity, socioeconomic status, geography, built environment, and others. Since energy balance impacts the entire continuum of cancer care, from prevention through survivorship, groups affected by disparities in energy balance including the complex issues influencing obesity, exercise, sedentary behavior, sleep, insulin resistance, and more may show profound differences in cancer outcomes. Moreover, these disparities may have diverse contributors and consequences in different regions throughout the world.

The goal of this volume is to identify cancer disparities in different groups in the USA and around the world and compare similarities and variations in energy balance to identify commonalities in order to inform further opportunities for transdisciplinary research and interventions. Specific chapters have been included to provide information regarding application of current state-of-the-art strategies to analyze and alter biologic, behavioral, community, and policy effects on energy balance and the disparities that result from barriers that restrict their generalized implementation.

In Chap. 1, Rory Weier, James Fisher, and Electra Paskett (Ohio State University) along with Jesse Plascak (University Washington) discuss the distinctive features of Appalachia and its unique contribution to the burden of obesity, cancer incidence, and mortality in the USA. In Chap. 2, Donald Nicolson and Una Macleod (Hull York Medical School) and David Weller (University Edinburgh) examine socioeconomic factors that determine disparities in lifestyle factors, cancer incidence and outcomes in the United Kingdom.

In Chap. 3, Donna Spruijt-Metz, Lauren Cook, CK Freddy Wen, Robert Garcia, Gillian A. O'Reilly, Jennifer B. Unger, (University Southern California Keck School of Medicine), Selena T. Nguyen-Rodriguez (California State University,

Long Beach), and Ya-Wen Hsu (Chia Nan University of Pharmacy and Science, Taiwan) discuss behavioral influences on racial/ethnic and socioeconomic disparities versus incidence and mortality by cancer sites. Chapter 4, by Kathryn Schmitz (University Pennsylvania), Tanya Agurs-Collins (National Cancer Institute, Marian Neuhouser (Fred Hutchinson Cancer Research Center), Lisa Pollack and Sarah Gehlert (Washington University in St. Louis), reviews the impact of obesity, race, and ethnicity on cancer survivorship, which is particularly important in view of the projected increase in this group of patients. In Chap. 5, Nathan LeBrasseur (Mayo Clinic), Derek Huffman (Albert Einstein College of Medicine), and Gerald Denis (Boston University College of Medicine) discuss the impact of aging on obesity, inflammation, and cancer. They raise the possibility that healthy aging may maintain fitness or protect against these chronic disorders and examine the social determinants of healthy and unhealthy aging. Focusing on specific malignancies with established disparities, in Chap. 6, Graham Colditz, Kari Bohlke, Su-Hsin Chang, and Kenneth Carson (Washington University School of Medicine) review the evidence that obesity, more common in African Americans, and other factors such as lower serum levels of 25-hydroxy vitamin D, may contribute to the significantly higher incidence of Multiple Myeloma. In Chap. 7, Melissa Kang and Temitope Keku (University of North Carolina) discuss single nucleotide polymorphisms (SNPs) that occur in a racially oriented manner, resulting in differences in obesity and inflammatory genes that may contribute to racial disparities in colorectal cancer incidence and survival. Rebecca Hasson (University Michigan) and Michael Goran (University Southern California) in Chap. 8 and Sarah Cohen (EpidStat Institute) and Loren Lipworth (Vanderbilt-Ingram Cancer Center) in Chap. 9 provide comprehensive assessments of racial differences in biological mechanisms linking obesity to cancer with particular focus on insulin resistance, sex steroids, inflammatory mediators, and adipokines. In Chap. 10, Melinda Stolley (University of Illinois at Chicago) analyzes behavioral factors contributing to disparities in breast cancer survival and describes community-based strategies to alter energy balance and decrease disparities. In Chap. 11, Deborah Bowen (University of Washington) and Stacey Zawacki (Boston University) examine differential responsibilities and potential contributions to change neighborhood-based policies that impact the obesogenic environment or, as uniquely defined in this chapter, the inflammatory environment. In the last section, Chap. 12, Debra Haire-Joshu (Washington University) focuses on the important issue of how public and social policy has been and can be used to prevent obesity-related disparities in young children thereby reducing their predisposition to cancer at later stages of life.

This current volume in the series on Energy Balance and Cancer provides a unique transdisciplinary approach to analyze problems associated with disparities in energy balance and cancer in diverse geographic areas and among different ethnicities from a biological, behavioral, socioeconomic, environmental, and policy basis as well as to suggest where and how potential interventions may be helpful. This volume should provide a valuable resource to all investigators, practitioners,

and policy makers dealing with problems of obesity, energy balance, and cancer. It is the first major book dealing with biology, behavior, and policy that contributes to and results from disparities in energy balance and cancer. It should provide a valuable resource to disparity-focused investigators at the molecular, psychosocial, community, and policy levels and serve as an important guide to the broad range of professionals who regularly deal with these issues.

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Chapter 1
Obesity and Cancer in Appalachia

Rory C. Weier, Jesse J. Plascak, James L. Fisher, and Electra D. Paskett

Abstract Appalachia, a diverse, federally designated region that spans 13 states, is home to nearly 25 million residents. It is also an area in which the leading cause of death is cancer and financial and physical access to healthcare are known barriers to regular medical care. Obesity and its risk factors contribute to the region's burden of cancer incidence and mortality. Disparate prevalences of overweight and obesity have been found in Appalachia as early as preschool, and, compared to the rest of the country, parts of Appalachia have higher rates of physical inactivity and lower prevalence of fruit and vegetable consumption. Obesity is related to at least eight types of cancer, of which colorectal cancer and female breast cancer have been the most heavily examined in Appalachia. This report reviews what is known about obesity and cancer in the Appalachian region and provides suggestions for future intervention and research to address Appalachia's cancer and obesity burdens.

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The Relationship Between Overweight and Obesity and Cancer

Body mass index (BMI), a ratio of weight in kilograms (kg) to height in meters (m) squared, is commonly used to categorize body weight. Among adults, overweight is defined as a BMI between 25.0 and 29.9 and obesity is defined as BMI greater than or equal to 30.0 [1]. Among children, overweight is defined as BMI between the 85th and 95th percentiles for children of the same sex and age, and obesity is defined as equal to or greater than the 95th percentile for children of the same sex and age [1].

Overweight and obesity have greatly increased over the past three decades in the USA [2]. Results from the 2009 to 2010 National Health and Nutrition Examination Survey (NHANES) show that 68.7 % of US adults aged 20 years and older are estimated to be overweight or obese, and among children and teens, aged 2–19 years, 17.0 % are estimated to be obese [3]. According to the American Cancer Society, diet, physical activity, and weight status are associated with cancer risk. One-third of the more than 500,000 cancer deaths that occur each year in the USA can be attributed to poor diet and physical inactivity, which are also risk factors for overweight and obesity. Additionally, it is estimated that overweight and obesity are responsible for approximately 14 % of all cancer deaths among men and 20 % of all cancer deaths among women [4].

Epidemiologic and molecular studies in various countries and different settings have provided supporting evidence of a causal relationship between excess adiposity (fat storage) and cancer risk [5, 6]. Adipose tissues are highly metabolically active and produce an array of hormones, growth factors, and signaling molecules fueling inflammation and cellular proliferation that may lead to cancer [5, 6]. According to the National Cancer Institute (NCI) overweight and obesity increases the risk of at least the eight following cancers: esophageal, pancreatic, colorectal, female breast (after menopause), endometrial, kidney, thyroid, and gallbladder cancers [7]. Obesity and physical inactivity may account for approximately 25–30 % of new cases of colon, female breast (postmenopausal), endometrial, kidney, and esophageal cancers [8]. In addition, overweight and obesity *may* increase the risk of several other sites/types of cancer (e.g., prostate, other male genitals, ovary, non-Hodgkin's lymphoma, leukemia, liver, and hemangioma) [7].

A population group suffering from a cancer burden that is significantly higher than that of the general population is defined as a cancer disparity population [9]. The Appalachian population suffers a disproportionate burden of cancer, and cancer risk factors such as obesity. The purpose of this report is to review what is known about obesity and cancer in Appalachia.

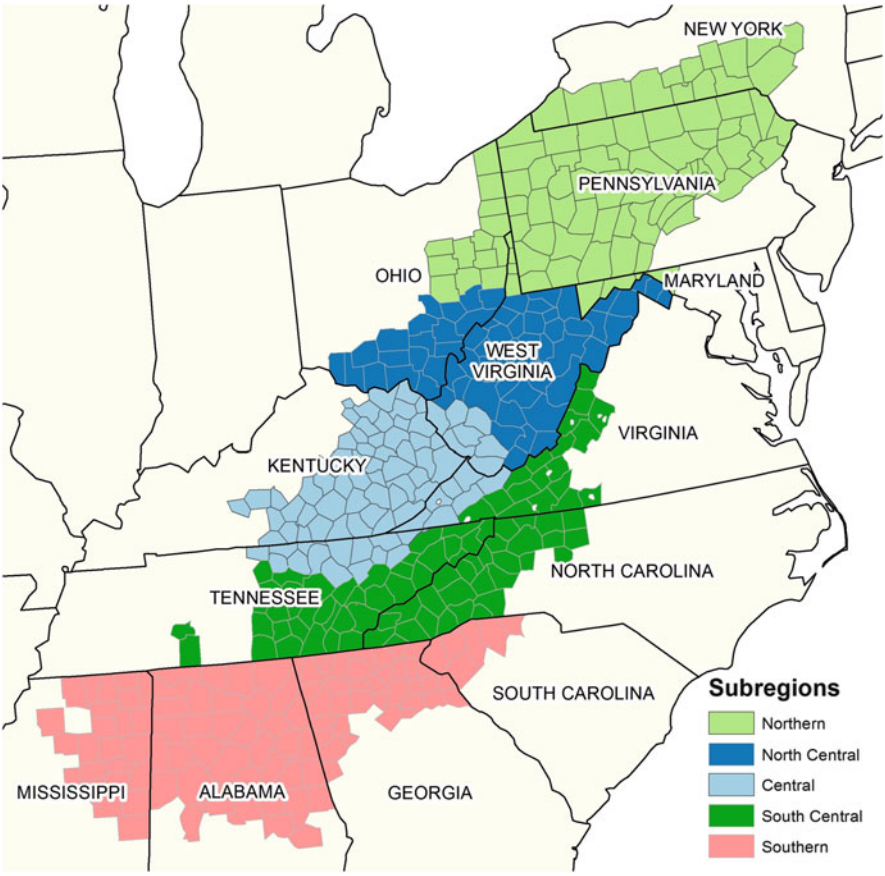

Fig. 1.1 The current Appalachian region of the USA (Adapted from the Appalachia Regional Commission) [12]

The Appalachian Region

Appalachia is a federally designated region of the USA that includes 24.8 million residents living within 420 contiguous counties across 13 states that include some portion of the Appalachian mountains or foothills [10]. In most cases, Appalachian status was given to a county because of lagging socioeconomic indicators [10, 11]. Once designated as "Appalachian" a county is qualified for special government funding and subsidies [10, 11]. The Appalachian Regional Commission (ARC)—a regional economic development agency—has been charged with coordinating programs in the region [10]. The ARC has categorized Appalachian counties into sub regions based on similar demographic and socioeconomic characteristics (Fig. 1.1) [12]. Despite this, subregions are not consistently defined throughout the Appalachian health literature.

The demographic and socioeconomic characteristics vary greatly between regions of Appalachia and non-Appalachia and within Appalachia. According to an analysis of 2007–2011 American Community Survey data, 83.9 % of Appalachian residents, compared to 64.2 % of US residents, were non-Hispanic Whites [13]. Between Appalachian subregions, the percentage of non-Hispanic Whites varied from 70.4 % (Southern) to 95.5 % (Central). The same analysis indicated that 16.5 % of Appalachian residents, compared to 14.6 % of US residents, aged 25 years and older had not attained a high school diploma. However, Northern Appalachia had a percentage of residents not attaining a high school diploma that was lower than that of US residents (11.8 %), while Central Appalachia had the highest percentage (27.2 %). Similarly, the poverty rate among Appalachian residents (16.1 %) is higher than that of the USA (14.3 %) [13]. Again, the Northern Appalachia poverty prevalence of 13.8 % was slightly lower than that of the USA, while all other regions had prevalences that were higher, with the Central Appalachian prevalence of 23.5 % being the highest among the subregions. These regionally dependent demographic and socioeconomic characteristics of Appalachia are important factors that could affect various health outcomes including cancer and risk factors such as obesity.

The Burden of Obesity in Appalachia

An analysis of data from the 2007 Behavioral Risk Factor Surveillance System (BRFSS) indicates that West Virginia and Appalachian counties in Tennessee and Kentucky were among the areas of the USA with the highest prevalence of obesity ($\geq$30.9 %) [14]. Estimates indicate that 81 % of counties in Kentucky, Tennessee, and West Virginia and 77 % in Alabama, Georgia, Louisiana, Mississippi, and South Carolina had obesity prevalences greater than 60 % of all US counties [14]. Many of these counties are located within Appalachia (Fig. 1.2). According to 2004–2007 state BRFSS data, Appalachian regions of Kentucky, Ohio, Pennsylvania, Virginia, and West Virginia had obesity prevalences ranging between 27 % (Pennsylvania) and 34.7 % (Kentucky) among men and 26.0 % (Pennsylvania, Virginia) and 31.7 % (Kentucky) among women [15]. Moreover, in each of these states, except Pennsylvania, the obesity prevalence was greater in the Appalachian region, compared to the non-Appalachian region.

A number of studies have estimated the burden of overweight and obesity among children and adults in Appalachia. There is evidence of disparate rates of overweight and obesity among low-income Appalachian children as early as preschool [16]. The rates of high BMI among nearly 500 preschool-aged children participating in Southeastern Ohio Head Start programs exceeded national estimates [16]. Among a sample of 2,000 children aged 6–11 years participating in a school-based screening program in Southeastern Ohio, the overweight (BMI $\geq$ 85th percentile) and obesity (BMI > 95th percentile) prevalences of (17 %) and (20.9 %), respectively, both significantly exceeded national estimates

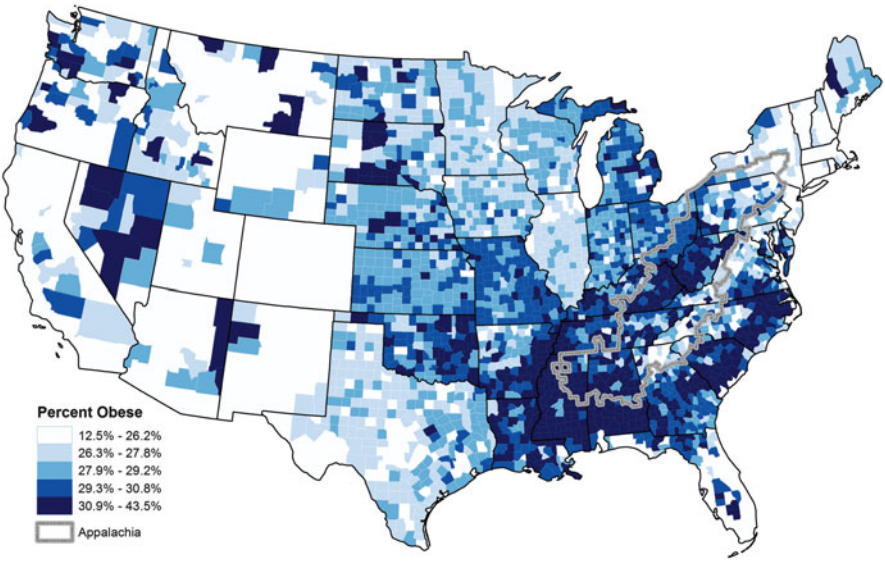

Fig. 1.2 County-level estimates of adult (≥20 years) obesity prevalence, 2007 (Adapted from the Centers for Disease Control and Prevention) [29]

[17]. Additionally, among a sample of over 1,500 Appalachian adults living in West Virginia, 39 % were overweight and 34 % were obese [18]. Despite the high BMI status of this population, 74 % viewed themselves as healthy [18]. Discrepancies between subjective and objective measures of health were also observed among over 200 adults in Appalachian Kentucky. Over 60 % of the sample considered their health to be good, while 75 % were overweight or obese [19]. The observed disconnect between self-reported health and BMI demonstrates the importance of understanding obesity from an Appalachian perspective in order to make progress.

The Burden of Cancer in Appalachia

Nationally and worldwide, the leading cause of death is heart disease [20]. However, within the Appalachian region, the leading cause of death is cancer [21]. Compared to the rest of the country, the Appalachian region had higher incidence rates of cancers diagnosed between 2001 and 2003 [22]. There were also differences between the Northern, Central, and Southern regions of Appalachia. Overall, cancer incidence rates were lowest in the Southern region of Appalachia and were highest in the Central and Northern regions [22]. Similar differences in cancer mortality rates were found using National Center for Health Statistics (NCHS) cancer mortality data from 2003 to 2007 [21]. Compared to the rest of the USA, the mortality rate for all cancers combined was 7 % higher in the 13 states that compromise the

Appalachian region [21]. Within these 13 states, the mortality rate for all cancers combined was 5 % higher in Appalachian counties than in non-Appalachian counties [21].

According to 2003–2007 state BRFSS data, Appalachian regions of Kentucky, Ohio, Pennsylvania, Virginia, and West Virginia had prevalences of tobacco smoking that ranged between 25.9 % (Virginia) and 33.6 % (Kentucky) among men and 25.9 % (Virginia) and 29.0 % (Kentucky) among women [15]. For both genders, the prevalence of smoking was higher in Appalachian regions of the five states [15]. And, for each state, the prevalence was greater than that for the non-Appalachian region. The high prevalence of tobacco smoking in Appalachia undoubtedly underlies some of the cancer differences observed between the Appalachian region and the rest of the USA. However, tobacco use and associated effects do not fully explain these disparities [23, 22]. Obesity also contributes to the region's disparate cancer incidence and mortality. Of the eight cancers related to obesity, colorectal cancer and female breast cancer have been the most heavily studied in Appalachia.

Colorectal Cancer

As the third leading cause of cancer incidence and mortality in the USA, colorectal cancer is estimated to account for 9 % of new cancer cases (73,680) and 9 % of deaths (26,300) among males and 9 % of new cancer cases (69,140) and 9 % of deaths (24,530) among females in 2013 [24]. According to the NCI, high BMI and waist circumference, a measure of abdominal obesity, are more strongly associated with increased colorectal cancer risk among men than women. A potential mechanism that may explain the relationship between obesity and increased risk of colorectal cancer is insulin and insulin-related growth factor levels, which tend to be higher in people who are obese [7].

Across Appalachian regions of Kentucky, Ohio, Pennsylvania, Virginia, and West Virginia, 2001–2006 state cancer registry data indicate that the average annual, age-adjusted incidence rate of colorectal cancer was 56.8 per 100,000 (Virginia) to 70.7 per 100,000 (West Virginia) among men and 39.9 per 100,000 (Virginia) to 52.3 per 100,000 (Kentucky) among women [15]. For both genders, the colorectal cancer incidence rate was higher in the Appalachian region of the states, except for Virginia [15].

An analysis of 2003–2007 NCHS colorectal cancer mortality data indicates that Appalachian regions of 9 of the 13 states experienced colorectal cancer mortality rates that were higher than the national rate [21]. Appalachia Kentucky had the highest colorectal cancer mortality rate (21.6 per 100,000), Appalachia Georgia had the lowest colorectal cancer mortality rate (17 per 100,000), and Ohio was the only state in which the Appalachian region had a significantly higher colorectal cancer mortality rate than the non-Appalachian region (9 %) [21]. Across Appalachian regions of Kentucky, Ohio, Pennsylvania, Virginia, and West Virginia, 2001–2006

state cancer registry data indicate that the average annual age-adjusted rate of colorectal cancer mortality ranged between 21.1 per 100,000 (Virginia) up to 26.06 per 100,000 (West Virginia) among men and 13.2 per 100,000 (Virginia) to 19.0 per 100,000 (Kentucky) among women [15]. For both genders, the colorectal cancer mortality rate was higher in the Appalachian region of the state, except for Virginia [15].

Unlike many other cancers, it is possible to prevent colorectal cancer using screening methods to detect precancerous polyps and prompt their surgical removal [24]. The 3 % annual decline in the rate of colorectal cancer morality nationally between 2000 and 2009 has primarily been attributed to an increase in the prevalence of screening. However, there is evidence of geographic variability in declining colorectal cancer mortality rates and uptake of screening recommendations [25]. In the early 1990s, states in the Northeast and North central region of the USA experienced the highest rates of colorectal cancer. However, in the mid-2000s, the highest rates of colorectal cancer were concentrated along the southern Appalachian region, which may be indicative of low screening rates and late stage diagnoses [25]. According to 2002–2006 state BRFSS data, Appalachian regions of Kentucky, Ohio, Pennsylvania, Virginia, and West Virginia had prevalences of adult colonoscopy or sigmoidoscopy use within the past 5 years ranging from 40.0 % (Ohio) to 66.6 % (Kentucky) [15]. The prevalence of adults having undergone a colonoscopy or sigmoidoscopy within the past 5 years was higher in the non-Appalachian region of the state, except for Kentucky [15]. Furthermore, 2002–2006 state cancer registry data indicate that the proportion of colorectal cancer cases diagnosed late stage ranged from 46.5 % (Ohio) to 54.9 % (Virginia) among men and 46.7 % (Ohio) to 55.2 % (Virginia) among women [15]. Only in Kentucky was the prevalence of late stage colorectal cancer higher among men and women in the Appalachian region of the state [15].

Studies also suggest screening uptake may explain Appalachian and non-Appalachian differences. For example, a 2008 telephone survey of over 1,000 Kentucky adults found that those living in Appalachia were less likely to have received a colonoscopy or sigmoidoscopy within the past 10 years compared with those living outside Appalachia [26].

Female Breast Cancer

As the leading cause of cancer incidence and second leading cause of cancer mortality among women in the USA, breast cancer is estimated to account for 29 % of new cancer cases (232,340) and 14 % of deaths (39,620) among females in 2013 [24]. Although overweight and obesity have been linked to a reduced risk of premenopausal breast cancer, they have also been tied to an increased risk of postmenopausal breast cancer, albeit modest [7]. Increased postmenopausal breast cancer risk is associated with weight gain in adulthood and is most common among women who have never used hormone therapy and whose tumors express estrogen

and progesterone receptors, particularly among white women [7]. A potential mechanism that may explain the relationship between obesity and a modest increase in risk of postmenopausal breast cancer is estrogen levels, which tend to be higher among women who are obese [7]. State cancer registry data from 2002 to 2006 indicate that the average annual age-adjusted female breast cancer incidence rates among Appalachian regions of Kentucky, New York, Ohio, Pennsylvania, Virginia, and West Virginia ranged from 112.2 per 100,000 (Kentucky) to 126.5 per 100,000 (New York) [15]. Only in New York was the breast cancer incidence rate higher among women in the Appalachian region of the state [15].

Breast cancer mortality rates have decreased over the past two decades, a change which has been attributed to a combination of screening and adjuvant treatment [27, 24]. An analysis of 1969–2007 Surveillance, Epidemiology and End Results (SEER) mortality data indicates that the decrease in breast cancer mortality rates occurred at a slower rate in Appalachian counties (17.5 %) compared to non-Appalachian counties in the 13 states (30.5 %) and non-Appalachia US counties across the country (28.3 %), which may suggest a lower prevalence of screening and differences in treatment [28]. Analysis of NCHS breast cancer mortality data from 2003 to 2007 indicates that Appalachian regions of nine of the 13 states experienced breast cancer mortality rates that were higher than the national rate [21]. Unlike colorectal cancer mortality rates, there were no in-state breast cancer mortality rate differences between Appalachian and non-Appalachian regions. The highest breast cancer mortality rate was in Appalachia Virginia (27.0 per 100,000) and the lowest was in Appalachia Georgia (22.3 per 100,000) [21]. State cancer registry data from 2001 to 2006 indicate that the average annual, age-adjusted female breast cancer mortality rates among Appalachian regions of Kentucky, New York, Ohio, Pennsylvania, Virginia, and West Virginia ranged from 23.4 per 100,000 (New York) to 26.6 per 100,000 (Ohio) [15]. Only in Kentucky was the breast cancer mortality rate higher among women in the Appalachian region of the state [15].

According to 2002–2006 state BRFSS data, Appalachian regions of Kentucky, Ohio, Pennsylvania, Virginia, and West Virginia had prevalences of women having underwent a mammogram within the past 3 years of 68.1 % (Kentucky) to 75.0 % (Pennsylvania) [15]. The prevalences were higher in the non-Appalachian regions of the states [15]. Furthermore, 2002–2006 state cancer registry data indicate that the proportion of female breast cancer cases diagnosed late stage ranged from 27.0 % (Ohio) to 36.2 % (Virginia) [15]. Only in Kentucky and Virginia were the prevalences of late stage breast cancer diagnoses higher among women in the Appalachian region of the state [15]. Studies also suggest that screening uptake may explain Appalachian and non-Appalachian differences. For example, a 2008 telephone survey of nearly 700 Kentucky adult women found that those living in Appalachia were less likely to receive regular mammograms than those living outside Appalachia [26].

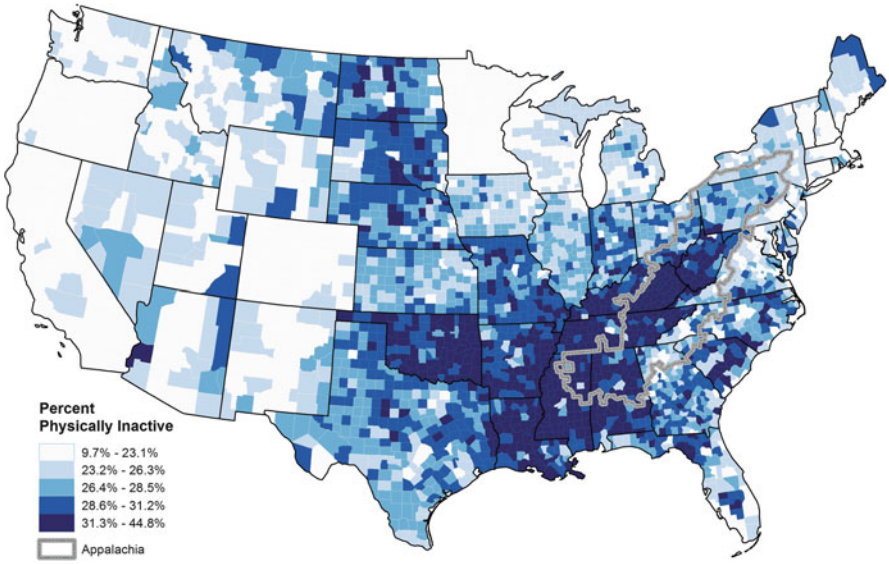

Fig. 1.3 County-level estimates of adult (≥20 years) physical inactivity prevalence, 2008 (Adapted from the Centers for Disease Control and Prevention) [29]

Risk Factors for Overweight and Obesity and Cancer: Physical Inactivity

An analysis of data from the 2008 BRFSS indicates that prevalences of leisure-time physical inactivity are highest in counties of the Southern and Appalachian regions of the USA [29]. Among the six states in which 70 % of counties had physical inactivity prevalences greater than or equal to 29.2 %, four are part of the Appalachian region (i.e., Alabama, Kentucky, Mississippi, and Tennessee) [29]. State BRFSS data from 2003 to 2007 indicate that the prevalence of no physical activity in the past month among Appalachian regions of Kentucky, Ohio, Pennsylvania, Virginia, and West Virginia ranged from 24 % (Pennsylvania) to 36.8 % (Kentucky) among men and 29.0 % (Pennsylvania) to 41.1 %(Kentucky) among women [15]. For both genders, the prevalences of no physical activity in the past month were higher in the Appalachian regions of the states [15] (Fig. 1.3). A study of 1,000 high school students in Southern Ohio found that only 5 % met the Centers for Disease Control and Prevention (CDC) recommendation of 60 min of moderate physical activity per day whereas 28 % and 78 % reported zero days of moderate and vigorous activity, respectively [30]. Among a church-based sample of over 1,200 adults in the Ohio Valley region of West Virginia, 48 % did not exercise on a regular basis each week whereas 42 % exercised 5 or more days per week for a total of 150 or more minutes [31]. Among over 200 adults in Appalachian Kentucky, 60 % viewed their health as good, just as 60 % reported no physical activity in the previous week [19].

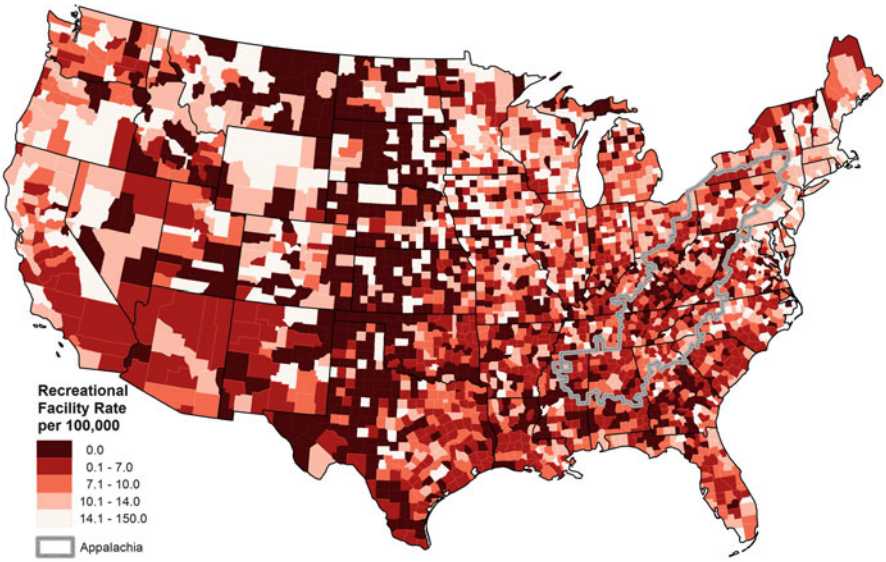

Fig. 1.4 County-level recreational facility rate per 100,000 population, 2008 (Adapted from the University of Wisconsin Population Health Institute and Robert Wood Johnson Foundation) [59]

Non-Appalachia focused research has suggested a number of determinants of physical activity behavior at both the individual level (e.g., limited time and financial resources, competing priorities and lack of knowledge) [32] and the environmental level (e.g., limited access to recreational facilities and sparse programming and activities) [33]. Many of these factors have been echoed across studies in Appalachia [34, 35, 31]. Among samples of Appalachia residents, participation in physical activity is influenced by transportation realities, such as long travel distances, poor road conditions, and limited transportation options [34]. A lack of local physical activity opportunities, sometimes due to low attendance to previously held programming and closure of recreational facilities within a reasonable distance, may also negatively affect physical activity participation [34]. As demonstrated in Fig. 1.4, access to recreational facilities is varied across the Appalachian region.

Perceptions of exercise and physical activity influence behavior among the Appalachian population. Focus groups conducted among Appalachian youth aged 8–17 years in Kentucky found that "physical activity" is viewed more positively than "exercise" among this population [35]. Reasons included that "exercise" is an activity that is planned for a specific duration and purpose and is often a requirement in school, whereas "physical activity" is less formal and more enjoyable because it is conducted at one's leisure [35]. Although exercise was viewed more positively across focus groups of over 110 adults in Appalachia Kentucky, the adults also viewed physical activity as a less structured activity that could be translated into exercise [34]. Common forms of physical activity among a

church-based sample of over 1,200 adults in the Ohio Valley region of West Virginia were low intensity activities conducted in or around the home (e.g., work around the home, gardening, and leisure and brisk walks), whereas, participation in more formal activities (e.g., yoga, aerobics, swimming, sports) was much more infrequent [31]. Therefore, informal opportunities for physical activity may facilitate participation among this population [34, 35].

Risk Factors for Overweight and Obesity and Cancer: Poor Diet

National BRFSS data from 2000 to 2006 indicate that the prevalence of fruit and vegetable consumption was lower in the Mississippi Delta, Appalachian Mountains, and Great Plains compared to the West Coast, Northeast, and parts of the South [36]. State BRFSS data from 2002 to 2007 indicate that the prevalence of inadequate fruit and vegetable consumption among Appalachian regions of Kentucky, Ohio, Pennsylvania, Virginia, and West Virginia ranged from 52 % (Pennsylvania) to 88.9 % (Ohio) among men and 36.0 % (Pennsylvania) to 80.2 % (Kentucky) among women [15]. For both genders, the prevalence of inadequate fruit and vegetable consumption were higher in the Appalachian regions of the states [15]. Access to healthy food is not distributed equally across the country, or in the Appalachian region. A common indicator of access to healthy foods is the US Department of Agriculture Food Measurement Atlas's "low income and low access to store" variable. This variable represents the percentage of people in a given county who are of low income and, in urban areas, live more than one mile from the nearest supermarket or large grocery store or, in rural areas, live more than 10 miles from the nearest supermarket or large grocery store [37]. As demonstrated by Fig. 1.5, this measure shows that limited access to healthy food varies across the Appalachian region.

There is also variation in access to fast food in Appalachia (Fig. 1.6). Although there is mixed evidence about the relationship between access to fast food and health outcomes, fast-food establishments are known to offer items than are more calorically dense and nutritionally poor than meals prepared within the home [38, 39].

The relationship between diet quality and physical access to grocery stores, supermarkets and fast-food retailers is complicated, and physical access to healthy food does not necessarily result in consumption of a healthy diet. Among a sample of over 1,500 Appalachian adults living in West Virginia, of whom 74 % viewed themselves as healthy, 22 % reported consuming fast food three or more times a week [18]. However, 67 % reported drinking one or more cans of regular soda on a daily basis, which is concerning given that, on average, a 355 ml can of regular soda contains 40 g of sugar and 150 kcal [18]. Similarly, of over 200 adults in Appalachia Kentucky, 60 % viewed their health as good when just over a quarter reported

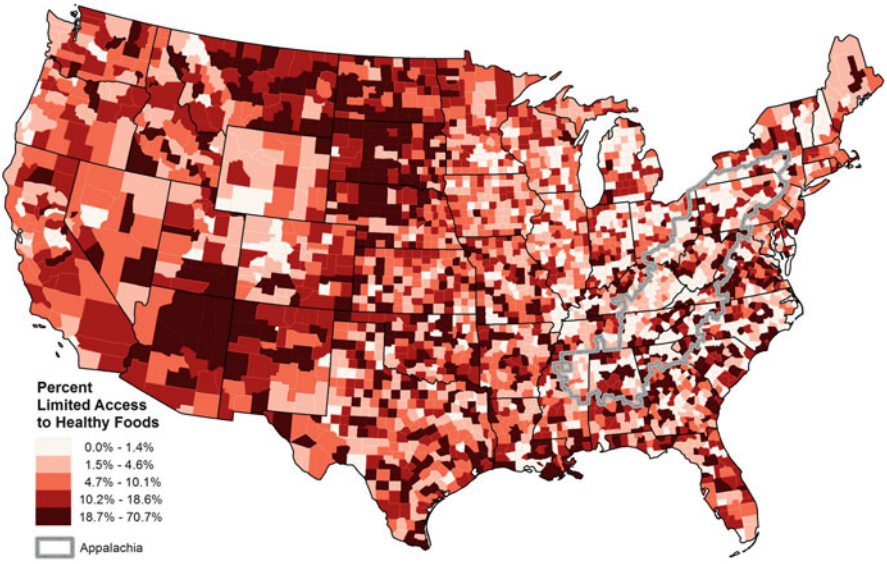

Fig. 1.5 County-level percent of the population that has limited access to healthy foods, 2006 (Adapted from the University of Wisconsin Population Health Institute and Robert Wood Johnson Foundation) [59]

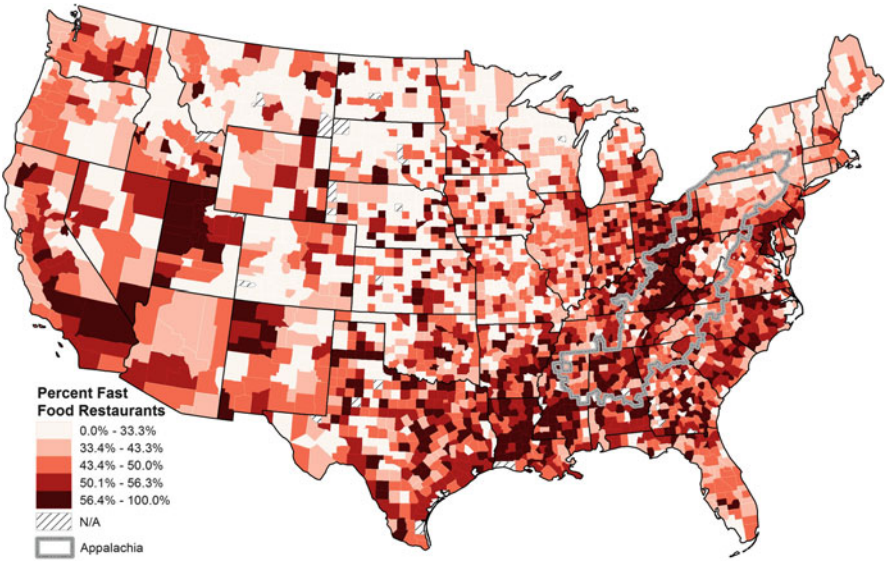

Fig. 1.6 County-level percent of all restaurants that are fast-food establishments, 2009 (Adapted from the University of Wisconsin Population Health Institute and Robert Wood Johnson Foundation) [59]

eating one or fewer daily servings of fruits and vegetables over the previous week [19]. Additionally, over 220 third graders across three Appalachian Ohio counties participating in a school-based dietary screening program did not achieve the recommended dietary intakes of grains, vegetables, fruits, milk, and meats/beans per the MyPyramid for Kids recommendations, the dietary recommendations for children that were current at the time of the study [40, 41]. Alarmingly, almost a fifth of the calories consumed by these children came from sweets, and this proportion was even higher among those of lower socioeconomic status [40].

As in other areas of the country, individual taste preferences and time constraints have been shown to influence diet quality in the Appalachian health literature [35]. However, other factors seem to be more specific to the region [35]. For example, social and familial norms and perceived support appear to greatly influence the food served at social gatherings and in the home as well as the dietary choices made by individuals [42–44]. Given the history of poverty in Appalachia, it is not surprising that cost is a salient determinant of what is purchased and consumed [42]. As with physical activity, diet is also affected by transportation realities in Appalachia [42]. It is also important to note that the region is not as isolated as it once was. As a result, historically common food practices like gardening and preservation are not as necessary as they once were given physical access to modern food retail outlets [45]. For example, compared to Amish adults living in Ohio Appalachia, non-Amish adults were more likely to purchase food outside of the home from grocery stores and restaurants and less likely to grow their own fruits and vegetables and use methods of preservation like canning and pickling [46].

Interventions

Disparate prevalences of overweight and obesity in Appalachia have been found as early as preschool [16, 47, 17, 48]. Consequently, many overweight and obesity interventions implemented in Appalachia have been focused on children, particularly in the context of school [49, 50]. For example, in Northern Tennessee, a school-based physical activity and healthy eating initiative based on the CDC's coordinated school health model was designed by a community coalition and piloted in a rural Appalachian elementary school [49]. Four-year follow-up data demonstrated significant improvements in the daily pedometer steps of students and their selection of healthy cafeteria food items [49]. Although commonly employed to improve academic outcomes, teen mentoring in the school setting is not commonly used in childhood overweight and obesity interventions [50]. A randomized control trial conducted among third and fourth graders in Appalachia participating in an afterschool health promotion program found that children whose program was mentored by teens experienced greater increases in physical activity than those whose program was led by adult instructors [50]. The need to integrate the support

of family, primary care, and school-based efforts to foster long-term behavior changes among children has been noted in the literature [47, 40].

Methods currently being used to overcome barriers to improve access to health care and promote cancer screening across Appalachia offer additional insight into what can be done to address overweight and obesity in the region across age groups. For example, physical access and financial access have been noted as barriers to health care in Appalachia [51, 52]. Mobile health units, such as the Health Wagon, have had success reaching high risk individuals who lack health insurance and/or means of transportation [51]. The Health Wagon provides primary health care to Southwest Virginia's rural Appalachian population through clinics, cancer screening, case management services and telemedicine consultations with specialists that are free of charge [51]. By collaborating with local academic, medical, religious, and nonprofit partners and utilizing existing assistance programs and volunteers, the Health Wagon is able to maximize its limited resources [51]. However, staffing, financial support and coordination of care are just a few of the logistical challenges faced by this and likely other mobile clinics [51]. Despite these challenges, mobile health units may also be useful in the fight against overweight and obesity through the provision of biometric and dietary screening and case management services to individuals facing issues related to financial and physical access.

It is also possible to tailor evidence-based programs to address the region's burden of both overweight and obesity and cancer. Evidence-based programming is at the core of the "Cancer Control Plan, Link, Act, Network with Evidence-based Tools (PLANET)," an effort of the NCI, CDC, American Cancer Society, Substance Abuse and Mental Health Services Administration, Agency for Healthcare Research and Quality, and Commission on Cancer [53]. Featured program areas include breast and colorectal cancer screening, diet/nutrition, obesity, and physical activity. A searchable database of research-tested intervention programs (RTIPs) focused on cancer control is available online at: http://rtips.cancer.gov. An example of a featured program designed outside of Appalachia is StrongWomen, an evidence-based strength training program. This program was successfully modified to address physical activity as well as breast cancer awareness, screening and survivorship among women in Appalachian Pennsylvania [54]. The resulting 12-week program, New STEPS (Strength Through Education, Physical fitness and Support) was implemented using existing community resources and networks, which has afforded the ability for programs to extend beyond the study period [54].

The Appalachia Community Cancer Network (ACCN), a joint effort of the University of Kentucky, The Ohio State University, Pennsylvania State University, Virginia Tech University, and West Virginia University, is currently pursuing a research project in collaboration with over 20 churches in the Appalachian region of Kentucky, Ohio, Pennsylvania, Virginia, and West Virginia [55]. Using a group-randomized study design, half of the churches receive *Walk by Faith*, a dietary and physical activity faith-based intervention program, while the other half receive *Ribbons of Faith*, a comparison condition focused on cancer screening. *Walk by Faith* uses eHealth technology to address individual and environmental level changes to increase physical activity and to improve healthy food choices among

participants [55]. Changes in physical activity levels, diet, and blood pressure will be assessed to determine the effectiveness of the faith-based intervention [55]. The sustainability of the intervention effects will also be tested and the results will be used to disseminate the intervention to the comparison churches, churches located in other Appalachian and rural areas, and the RTIPs Web site.

It is important to note that the selection, adaption and implementation of evidence-based programming to meet the needs of individuals living in Appalachia are not simple or necessarily straight-forward undertakings [56, 57]. The realities of Appalachian communities (e.g., limited community resources, competing time demands for potential participants and staff, reduced access to technology, low rates of participation) may present significant barriers to the success of evidence-based programs, which are often derived from well-funded, highly controlled research settings outside of the region [56, 57].

Suggestions for the Future

In summary, there are disparities in cancer rates, overweight and obesity prevalence, risk factors for overweight and obesity, and interventions in the Appalachian region of the USA. Thus, efforts to develop and test interventions to improve risk factors are urgently needed. Potential interventions that could be implemented in Appalachia to address disparities in obesity include efforts to partner with the USDA-sponsored cooperative extension service agents; focus on the entire family; utilize culturally relevant activities and develop advertisements with a focus on "health" versus "appearance" [34].

In addition, good surveillance data to monitor trends in cancer rates and risk factors are needed. Appalachia-specific health data are limited in terms of both volume and quality [58, 22]. Most notably, there is a lack of public health surveillance efforts that span the entire 13-state Appalachian region. For example, compared to other subregions, the information available on the South Central and Southern regions of Appalachia (e.g., North Carolina, South Carolina, Georgia, Alabama, and Mississippi) is more limited. Despite the efforts of state cancer registries and multi-state collaborations like the ACCN, there is a need for data that captures the heterogeneity of Appalachia. For example, an Appalachian variable could be added to BRFSS and NHANES to facilitate region-wide studies.

To make a difference in overweight and obesity prevalence in Appalachia, culturally appropriate interventions need to be developed, tested, and if effective, disseminated through trusted channels. Lastly, for effective strategies to be adopted the community needs to be involved from the start and take ownership of the problem as well the solution. Efforts are currently underway using community based participatory research (CBPR) strategies and will be able to inform researchers and the community about possible approaches that could be disseminated to reduce disparities in overweight and obesity and cancer rates in Appalachia.

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Chapter 2
Disparities in Cancer Outcomes: A UK Perspective

Donald J. Nicolson, Una Macleod, and David Weller

> *It is the cry of men who feel themselves the victims of blind economic forces beyond their control. . . The feeling of despair and hopelessness that pervades people who feel with justification that they have no real say in shaping or determining their own destinies (Reid 1972).*

Abstract The social problem described by Jimmy Reid in 1972 [1] is still prevalent in the UK in the twenty-first century. Many people who are socio-economically disadvantaged do not have the capacity to influence their freedom, and as a consequence, they do not have control over the destiny of their own health. In this chapter we examine how socially disadvantaged people in the UK are at greater risk of poorer outcomes when they have cancer. That is, socio-economic factors determine disparities in cancer outcomes, incidence, mortality, and survival rates, in the UK.

Keywords The UK • Cancer incidence • Health inequalities • Black report • Acheson report • Marmot review • National Health Service cancer plan • Carstairs deprivation index • Socio-economic status • Inverse care law

Preface

While the focus of this book is Energy Balance and its relation to cancer disparities, this chapter takes a broader look at health inequalities and cancer with a UK perspective; it draws on UK and international research and policy work spanning the last 30 years and more. Energy balance is a key factor in cancer outcomes; the

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UK has a rich literature on health inequalities, and we hope that by examining the multiple contributing factors to cancer outcome disparities, the role of energy balance can be better understood. We have considered "health inequalities" to be synonymous with "disparities" (a term that is more commonly used in the USA). Several UK Governments have commissioned significant documents over the last few decades and these form the principle overview and understanding of health inequalities in the UK. The first of these was the Black Report [2], commissioned in the late 1970s. This illustrated extensive health inequalities in the UK, despite the advent of the National Health Service in 1948. Similarly, two decades later the Acheson Report [3] reported a relationship between health disparities and social class, with the higher social classes having greater decline in mortality than the rest of the population. These landmark reports have added to our understanding of how health inequalities arise from social inequalities.

A more recent report, the Marmot Review [4] noted that health inequalities are a profound social justice issue for the UK; highlighting how there is a social gradient in health and health inequalities, and concluding that addressing health inequalities is a matter of fairness. The Marmot Review also noted that, based on deprivation categories (a score constructed around communities access to resources, relationships in society, income, housing, and employment), people from more deprived backgrounds not only have a higher rate of cancer, but men from the most deprived category have nearly double the risk of cancer than men from the least deprived background. This is a powerful example of the relationship between cancer mortality and level of deprivation.

Alongside these reports on health inequalities, there has been a policy drive to improve cancer outcomes. This was initially formalised in the NHS Cancer Plan in 2000 [5] and the Cancer Reform Strategy in 2007 [6]. These set in place a national cancer programme for England with a focus on saving more lives to ensure that people with cancer got the right support, care, and treatments; that inequalities in health and cancer were tackled; to invest in strong research; and to prepare for the genetics revolution.

Incidence, Mortality, and Survival

Before we examine health inequalities in cancer outcomes, it is necessary to understand the epidemiology of cancer outcomes. The outcomes we are interested in are the rates of newly diagnosed cancers (incidence), the numbers of people dying from cancer (mortality), and the survival rates for people living with a cancer. The data reported in this section have been largely produced by Cancer Research UK, a highly reputable source of cancer statistics in the UK, who make cancer data available on their website (www.cancerresearchuk.org) [6]. Unless otherwise stated, figures below have been obtained from this source.

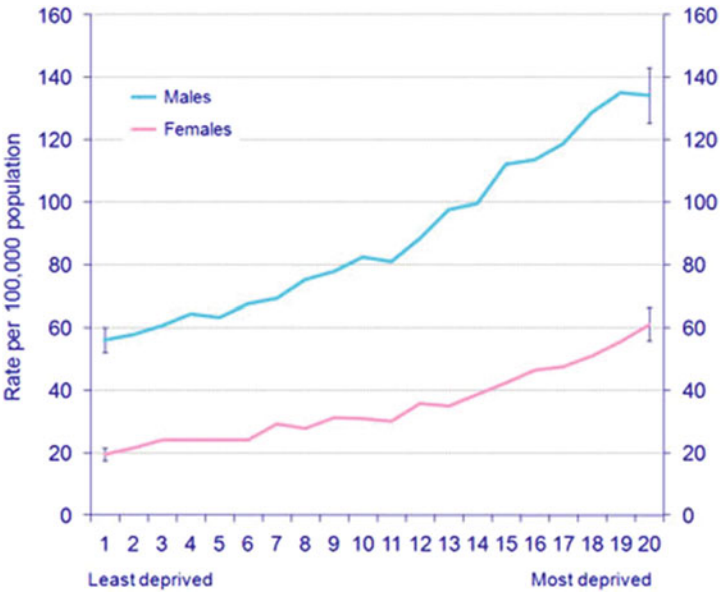

Fig. 2.1 Lung cancer (C33-C34), age-standardised incidence rates by deprivation category, England and Wales, 1993

Incidence of Cancer in the UK

In the UK in 2010, around 325,000 people were newly diagnosed with a cancer. This included a similar number of males and females, around 160,000 each. However when the rates were standardised for age, considerably more men (426 per 100,000) compared to women (374 per 100,000) were newly diagnosed. The incidence of cancer in the UK has steadily risen for men and women since the mid-1970s by 22 %. However, the rate of increase has slowed down from the period 2001–2010, with just a 2 % increase for men and a 6 % increase for women.

Data from 1993 for the incidence of lung cancer showed clear evidence of the impact of deprivation. Two and a half times as many men and three times as many women from the most deprived groups compared to the least deprived groups were diagnosed with lung cancer. Figure 2.1 below shows how the age standardised rates of lung cancer increase across deprivation categories. Although these data are old, more recent work confirms no change [8].

Four types of cancer: breast, lung, bowel, and prostate, accounted for 54 % of all new cases of cancer in 2010. The most commonly diagnosed cancer in men is prostate—one in four cases. The more commonly diagnosed cancer in women is of the breast—just under one in three cases.

Worldwide there were approximately 12.7 million new cases of cancer in 2008. The rate was considerably greater for North America and Europe compared to the developing world (Cancer Research UK).

Scotland has the worse rates of cancer in the UK; reflecting the all-cause mortality gap between Scotland and England which grew from 1981 to 2001 [9]. This is not necessarily determined by social inequalities; the Carstairs deprivation index (a measure of deprivation), declined during the same period [10]. Other factors, such as the "Scottish Effect" (a factor related to living in Scotland, independent of other risk factors) have been proposed to explain poor outcomes in Scotland [11, 12].

Mortality from Cancer in the UK

Around 82,000 men and 75,000 women in the UK died from a cancer between 2007 and 2009, i.e. 427 per 100,000 men, and 371 per 100,000 women [13]. The 157,000 people who died from a cancer in the UK in 2010 accounted for more than one in four (28 %) of all deaths. The most common cause of cancer mortality was due to lung cancer 19,410 cases (24 %) in men; and 15,449 cases (21 %) in women. Death from a cancer becomes more likely with age and is more common for men than women.

In recent years in the UK, more men than women have been newly diagnosed with a cancer. However, overall the rates of newly diagnosed cancers have been falling. More men than women die from a cancer each year in the UK. Deaths from cancer accounted for more than one quarter of all deaths in the UK in 2010. Lung cancer was the most common cause of a cancer death in both men and women. More people are now dying from cancer of the liver than in previous decades.

Mortality rates from cancer have been declining in the UK since the early 1990s. Between 2001 and 2008, there was a 12 % and 9 % decrease in all cancers for men and women respectively. However the rates of cancer mortality from liver cancer have increased in both sexes, which may be due to trends in increased alcohol intake. While deaths from lung cancer have decreased for men by 19 % they have increased for women by 6 % (Cancer Research UK).

Surviving Cancer

Coleman et al. [14] analysed data from population-based cancer registries in six countries for two to four million adults diagnosed with a cancer during 1995–2007 and found survival rates were lower in the UK (and Denmark) than in Australia, Canada, and Sweden.

Rachet et al. [15] have found survival rates for patients with cancer was significantly higher in the most affluent groups compared to the most deprived groups. However, the relationship is complex, due to the interplay between the type of cancer, patient personal factors, and the role of the health service [16].

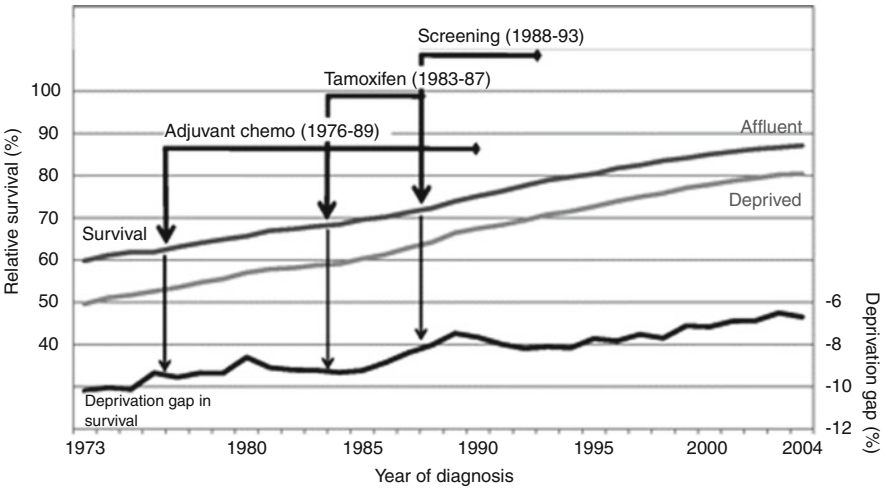

Fig. 2.2 Trends in 5-year relative survival (%) from breast cancer in women in the most affluent and most deprived groups and deprivation gap (%) in survival: 5-year moving average values, England and Wales, 1973–2004. Periods of emergence of evidence about the efficacy of new interventions are denoted on the graph [Reproduced with permission]

Trends in survival differences, by deprivation category, are also complex; Lyratzopoulos and colleagues [17] examined changes in socio-economic inequalities in survival from breast cancer for women, and from rectal cancer for men in England and Wales from 1973 to 2004. They found survival rates increased over this period from 55 % to 85 % for women with breast cancer, while the survival gap between the two deprivation groups narrowed slightly from −10 % to −6 % (Fig. 2.2). For men they found 5-year relative survival rates from rectal cancer improved from 29 % to 53 % between 1973 and 2004; but the survival gap between the two deprivation groups increased from −5 % to −11 % (Fig. 2.3).

These authors conclude that the cause of inequalities in survival rates remains unknown, but may partly reflect differences in clinical management (the "health care factors" hypotheses). If so, socio-economic inequalities should be largely determined by socio-economic differences in the quality of treatment received, with deprived patients more often managed suboptimally.

Coleman et al. [18] clearly highlighted the link between socio-economic disadvantage and poorer cancer outcomes, finding a difference in 1 and 5 year survival rates for all cancers combined when comparing people from deprivation categories between 1986 and 1990. People from the more affluent groups had higher survival rates after diagnosis than people from the most deprived category. The difference remained fairly stable between 1 and 5 year survival; 12.7 % and 11.1 % respectively. Figure 2.4 shows this gap in survival rates.

In a related study, Abdel-Rahman et al. [19] found that compared with data from countries in continental Europe, socio-economic differences in survival in Britain may account for half the avoidable premature mortality from cancers.

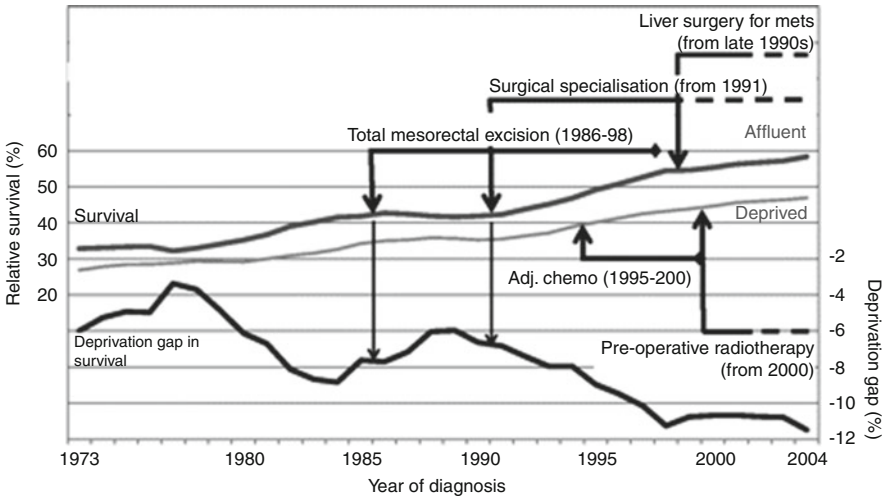

Fig. 2.3 Trends in 5-year relative survival (%) from rectal cancer in men in the most affluent and most deprived groups and deprivation gap (%) in survival: 5-year moving average values, England and Wales, 1973–2004. Periods of emergence of evidence about the efficacy of new interventions are denoted on the graph. Increasing use of flexible sigmoidoscopy occurred throughout the study period, and is not denoted on the graph [Reproduced with permission]

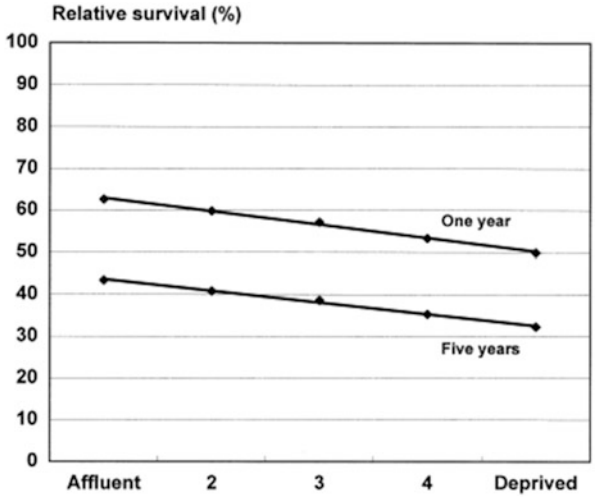

Fig. 2.4 Relative survival rates 1 and 5 years after diagnosis by deprivation category, all cancers combined: England and Wales, adults diagnosed 1986–1990

Explaining Disparities in Health Outcomes

It is estimated that only 5–10 % of cancers are attributable to genetic variation [20]. If this is the case, then most cancers might be preventable if people avoid specific environmental risks, or practise health promoting behaviours. It is thought that about half of all cases of cancer could be prevented by lifestyle changes [21]. This indicates how social and behavioural factors, e.g. gender, ethnic group, income, geographical, education, and social class, are important determinants of cancer.

The Black Report

The Black Report [2] has played a fundamental role in explaining health-care disparities in the UK. It examined four ways to understand health inequalities; they remain a useful framework in understanding disparities in people's cancer outcomes.[1]

1. Artefact: This argument proposes that a relationship between class and health is spurious; that there is no real relationship and that the findings are a product of the way the data were measured. Macintyre [22] suggests this relationship is not straightforward because the level of class influence on illness will depend on how both class and illness are measured. A failing of this hypothesis is that evidence of health inequalities are consistent across populations and periods of time [23], which suggests the finding reflects reality and is not a social construct.
2. Social selection: This model proposes that health determines class [22]; thus health inequalities are thought to produce health-related social inequalities; that is, for example, people with illness tend to suffer downward social mobility from loss of employment and/or income. This is also known as the "reverse causation" or "drift" hypothesis [24]. At best, this model can only partially explain health disparities. For example the link between cancers and education cannot be accounted for by social selection because people have usually completed their education in early adulthood before succumbing to a cancer [24]. There is little evidence to support this theory and it does not have widespread support in the international literature [25].
3. Cultural/behavioural: This model proposes that health damaging behaviours (e.g. smoking, excessive alcohol intake, or poor diet) are more common among the socially disadvantaged. The more extreme version of this argument suggests that individual ignorance, lifestyle choices, and neglect are the cause of illness [26]. Individuals from lower socio-economic status (SES) groups are also

[1] Macintyre [22] noted that each explanation has a "hard" (extreme) and "soft" (moderate) version for explaining the relationship between social class and health.

more likely to be exposed involuntarily to environmental pollutants [27] and occupational hazards [28]; factors which put them at high risk of developing a cancer. This argument however ignores the social context of people's lives and can be said to blame the victims of health inequalities for their poor health, although this argument in itself does not discredit this model. Critics have said that little has been done to disentangle the relationship between social disadvantage and health damaging behaviour [25]. We know there is a relation, but we are unclear why this is.

4. Material/structural: This proposal suggests that health is determined by a person's wealth—at its simplest, whether a person is "rich" or "poor". One such explanation proposes that health status is determined by income inequality; in particular that negative exposure and lack of resources combine to produce health inequalities [29]. A softer version acknowledges that psychosocial and other influences mediate this relationship. Coleman et al. [30] spoke of a "deprivation gap", e.g. the deficit in a cancer outcome between the rich and the poor.

There is clear and considerable evidence showing socio-economically disadvantaged people have significant health problems and poor access to health care. For example there is a gradient in the relationship between class and mortality: as a whole, people from lower classes have a lower life expectancy and die earlier than people from more affluent backgrounds. As we will later show, there is much evidence showing cancer incidence, mortality, and survival are related to social class. The material/structural argument helps explain national and international health disparity at a population level, but it remains a challenge to understand how socio-structural factors influence health inequalities [25], and at an individual level.

SES, Cancer and Pathways

The models discussed in "Incidence of Cancer in the UK" offer generic explanations of health inequalities. Kawachi and Kroenke [24] have sought to explain the mechanism linking SES and cancer by means of two possible pathways. In the first pathway, people from higher SES groups are able to access various resources to help prevent them developing cancer, or improving their outcome following cancer onset. They give the example of people who, through better education, are more "health literate" and consequently better able to understand options for cancer treatments. The second pathway suggests that people with higher SES have a differential exposure to psychosocial mediators (compared to people from poorer backgrounds), which benefits their health outcomes (see below for further details).

Examples of Disparities

Disparities are observed across a range of categories:

- Gender disparity: women have a longer life expectancy than men [31].
- Ethnic group disparity: there is a higher rate of cardiovascular disease in the UK amongst people from South Asia [32].
- Income disparity: people with higher levels of income tend to have better health overall than people with lower incomes [33].
- Geographic disparity: the Scottish city of Glasgow has nearly half of the 10 % most health deprived areas in Scotland [34]. These areas have higher rates of morbidity and mortality than more affluent areas in the same city and elsewhere.
- Education disparity: people with better education opportunities tend to have better health and well-being than people who have not had the same level of education [35].
- Social class disparity: people from lower social classes tend to have poorer health, and receive poorer health care than people from higher social classes [33].

It is important to recognise that individuals can face inequality across a number of these categories.

The Impact of Socio-economic Disadvantage on Cancer Outcomes

Having explored rates of people living with, surviving, and dying from cancer; and examined how socio-economic disadvantage impacts on people's health and access to health care in general; we now examine the evidence that socio-economic disparities impact on cancer outcomes. We consider lifestyle factors, public perception of cancer, issues related to cancer screening, awareness and recognition of cancer, health-care factors, and psychosocial factors.

Lifestyle Risk Factors

People who are socio-economically disadvantaged are often at greater risk of exposure to lifestyle risk factors than people from more affluent backgrounds. This may be seen to reflect a cultural/behavioural explanation for cancer inequalities. Lifestyle is intricately woven with socio-economic conditions and so it does not solely reflect someone's "choices".

1. Tobacco smoking: Smoking is an unequivocal risk factor for cancer and other diseases. For example it is considered to be the main determinant of lung cancer, with 90 % of people with lung cancer having smoked [24]. Smoking is the main cause of difference in morbidity and mortality between wealthy and poor individuals [36]. Accordingly, tackling smoking among people from the lowest socio-economic groups might reduce the incidence of smoking-related cancers and other smoking-related diseases. Much has been done in recent times in the UK to encourage and support people to stop smoking. The Scottish Government banned smoking in public places in 2006, with the rest of the UK doing so a year later. The National Health Service in the UK also runs a "Smokefree" service which offers people who want to stop smoking support via telephone, the Internet, and paper-based materials. However poorer people have less success in stopping smoking than more affluent people [37]. Therefore smoking related health inequalities will likely continue.
2. Poor diet: Poor diet has been linked to around one third of cancer deaths [21]. Diets rich in fats and red meat, high in calories and low in vegetables, are commonly related to lower SES [24]. Diets that have greater amounts of fruit and vegetables are more often consumed by people from an affluent background [38]. People from lower socio-economic backgrounds are at further disadvantaged because of the link between the availability and cost of food [39].
3. Physical activity: Minimal physical activity is related to the risk of several cancers [40], as well as obesity. Recreational physical activity tends to be strongly correlated with higher income households [41]. This is related to lower levels of obesity linked cancers [24]. The affordability and accessibility of recreational physical activity may be beyond many people from poorer backgrounds.
4. Weight and obesity: As expressed in other chapters of this book, there are major disparities in levels of obesity, between different social classes [42]. Given the growing body of evidence linking overweight and obesity with unfavourable cancer outcomes [43], poor dietary and energy balance trends in the UK must play a significant role in cancer disparities. It is suggested that if individuals maintained a healthy body weight, up to 12,000 cases of cancer could be prevented (Cancer Research UK; Cancer and Health Inequalities: an introduction to current evidence). People from lower socio-economic backgrounds, because they are more likely to be obese, are disadvantaged and so at greater risk of acquiring a cancer. Being obese increases the risk of several cancers, including cancer of the uterus, kidney, or colon [44]. Obesity levels in the UK have trebled over the last 20 years [21], indicating that this is a recent risk factor.
5. Alcohol consumption: Excessive alcohol intake is related to various diseases, including liver disease, heart disease, stroke, and cancers of the liver and the head and neck [21]. While the evidence of a link between alcohol and illnesses is clear, there is no conclusive evidence that people from a disadvantaged background are more at risk of misusing alcohol. It is thought in the UK that this is because excessive alcohol intake has no class pattern—in contrast to smoking [21].

Public Perceptions of Cancer

People's perceptions of cancer are probably relevant in their decisions to take screening tests for cancer in the absence of symptoms of cancer, or to attend for care when they develop symptoms. Dein [45] noted that beliefs about cancer can determine the perception of risk of developing cancer, and therefore have implications for the perceived urgency for patients to participate in screening, their decisions about treatment, and emotional responses to the disease.

It is not only the perception of someone's risk of cancer that can impact on their outcome, but their opinion of the likelihood that treatment would be successful [46]. For example, Powe & Finnie [47] have spoken of "Cancer Fatalism", where death from cancer is considered inevitable. This can be seen to reflect the observation by Susan Sontag [48] that some people held the belief that "cancer equals death". It is not difficult to see that if someone perceived this, she/he may not appreciate an urgency or benefit from early diagnosis and treatment, because they would not perceive any benefits from this.

Screening for Cancer

There are three national screening campaigns in the UK: for breast, bowel, and cervical cancer. These are available through the National Health Service, which is funded by taxation and so the tests are free to everyone. While there is no economic barrier to their uptake, other factors intervene for each cancer screened.

There are socio-economic differences in who is screened, with poorer people less likely to take up screening. Moser et al. [49] found a correlation between "indicators of wealth" (e.g. an owner occupied house, or a household with a car), and women having had breast screening. Women, who lived in a bought house or lived in a household with one or more cars, were more likely to have had a mammogram than women living in rented accommodation and not having a car. Reduced uptake of cervical screening has also been found among lower socio-economic groups [50]. Moss et al. [51] found people from lower SES less often took up the opportunity for bowel cancer screening compared to people from higher SES, despite it being free at the point of access. They proposed that great effort would be necessary to avoid significant disparities in screening uptake between deprived and wealthy people.

Despite the best efforts of national screening programmes to promote equitable uptake of screening, significant inequalities exist across all the programmes; the reasons for this are complex [51], and resistant to interventions. Consequently, cancer screening has the potential to enhance disparities in cancer outcome.

Awareness and Recognition of Cancer

There is a great deal of interest in the UK in awareness and recognition of cancer by patients and family doctors. In countries with strong primary health-care systems, such as the UK, family practice is typically the first point of contact for the majority of patients. In order for timely diagnosis to take place people need to recognise that their symptoms may be serious and so worthy of contacting a doctor, and then the doctor needs to recognise these symptoms as potential cancer symptoms [53].

If people do not present as early as possible with cancer symptoms, an opportunity may be lost to diagnose and treat the cancer early (and, potentially, improve survival). A link between prolonged diagnostic intervals and deprivation is challenging to prove; although we know that there are differences in stage of diagnosis for many cancers, based on whether someone is from a deprived or better-off background, [54] this may not be because there was any delay in presenting with symptoms. Rather, the nature of the illness may be such that the symptoms duration was short. There is, nevertheless, a policy drive in the UK to seek to ensure that patients recognise symptoms as early as possible and for practitioners to refer appropriately [55].

Systematic reviews of the evidence have been carried out to seek to understand the factors associated with timely recognition of cancer by patients and family doctors [53]. These reviews have concluded that, for many cancers, non-recognition of symptom seriousness is the main patient-related factor resulting in increased time to presentation. There is strong evidence of an association between older age and patient delay for breast cancer, between lower SES and delay for upper gastrointestinal and urological cancers and between lower education level and delay for breast and colorectal cancers [53]. Fear of cancer is a contributor to delayed presentation, while sanctioning of help seeking by others can be a powerful mediator of reduced time to presentation [53].

These findings have resulted in an interest in awareness of cancer, even though it is clear that awareness is insufficient in and of itself. The evidence does, however, suggest that many people appear to have very limited knowledge about cancers. This may be based on how they are asked about cancers. For example, a study examined the awareness of cancer of patients from both an affluent residential and deprived inner-city area in the same city in the North of England, and found that people had very poor open recall, but better prompted recognition [56].

On the whole people tend to have poor awareness about the warning signs of cancer for all symptoms (except lumps and swelling). Robb et al. [57] asked people to freely recall and then to recognise a set of cancer symptoms, and found recognition, which studies of memory have shown to be a more effective means of retrieval of information, was much higher for cancer symptoms, e.g. mole, lump, or swelling, than free recall. This was a general finding across the population: in particular men, younger people, people from an ethnic minority, and people from the lower end of the socio-economic spectrum had poorer awareness.

Further, it appears that people from ethnic minorities, who are often amongst the most socially disadvantaged, have poor awareness of the warning signs for cancers [58]—these authors suggest poor understanding of English may be a contributing factor, as people from ethnic minorities in the UK have higher levels of deprivation.

Evidence on cancer disparities has prompted considerable policy interest and activity regarding early detection of cancer. In England, a key programme is the National Awareness and Early Diagnosis Initiative (NAEDI) [55]; in Scotland there is a similar initiative—the Detect Cancer Early programme. Both these programmes seek to join up expertise from the NHS, the academic sector and the NHS in order to improve cancer survival outcomes (The Scottish Government. Detect cancer early. http://www.scotland.gov.uk/Topics/Health/Services/Cancer/Detect-Cancer-Early; accessed Sept 2013) [59].

Health Service Factors

So far, we have shown how a person's cancer outcomes are disadvantaged by socio-economic factors. However, the patient can also be disadvantaged through poor provision and/or poor quality of health services. Julian Tudor Hart [60] proposed the Inverse Care Law; this states that the accessibility of good medical care is inclined to vary inversely with the need for it by the population. Thus, people with cancer from poorer backgrounds may be disadvantaged by the poor availability of good quality care as much as by their own personal circumstances.

The first important health service factor is the response of the family doctor when a patient presents himself/herself with a new symptom. The evidence for factors associated with delay by family doctors is mixed [53]. In family practice many patients present with symptoms that may be indicative of cancer, but diagnostic tests later exclude cancer. On the other hand, family doctors assigning a diagnosis other than cancer to a set of symptoms can introduce delay in the pathway to referral [53].

Some work has also considered whether patients from poorer regions experience different care once diagnosed with cancer than those from better neighbourhoods and in general this has been found not to be the case [61]. However the presence of other coexisting illnesses occurring more commonly in socio-economically deprived patients may in part explain the poorer outcomes.

An individual with cancer receives care across several stages, from when they first present with their symptoms to a health-care professional, through living with cancer and then either surviving or dying from cancer. Lewis et al. [62] noted how SES impacts on four dimensions of access to palliative care: its availability, affordability, accessibility, and acceptability. Broadly speaking, palliative care is less available to people from the lower social classes and is less affordable for them; they have less access to it, and they are less accepting of it.

While care is free at the point of delivery to all in the UK, differences in care remain. Raine et al. [63] found patients from deprived areas, older people, and

women were more likely to be admitted as emergencies for their cancer. People living in deprived areas and males were less likely to receive their preferred surgical procedures for cancers. They also found that older people were more likely to receive their preferred surgical procedure for rectal cancer but less likely to receive breast conserving surgery and lung cancer resection.

Psychosocial Factors

As we have shown, the evidence points to people from poor backgrounds being differentially exposed to environmental stressors compared to people from more affluent backgrounds. This adversely affects their health outcomes in general. White and Macleod [64] have noted three psychological consequences from having cancer: the patient can experience depression; the patient can feel anxiety, fear, and panic; or if the patient has a cancer that spreads to the brain, she/he can suffer neuropsychiatric problems.

A follow-up study of women with breast cancer showed that affluent women were more likely to have received information from their hospital specialist and from a breast care nurse than deprived women, but deprived women had poorer SF-36 scores (Short-Form 36, self-reported survey of health status) than affluent women, and reported greater anxiety about money, other health problems, and family problems [65]. In a recent study of cancer survivors in England, individuals from most socio-economically deprived areas reported lower quality-of-life scores [66].

Conclusion

People with cancer from disadvantaged socio-economic backgrounds have poorer health in general, poor access to health care, and poorer outcomes. The reasons for this are undoubtedly multifactorial; in this chapter we have emphasised that the relationship between inequalities and cancer is complex and probably not unidirectional. People from lower SES groups may be in a poorer position to cope with hardship resulting from living with cancer, while people from a more affluent background will have the resources and knowledge to cope with cancer. In other words, understanding context is key.

Because socio-economic inequalities can determine people's health in general and particularly for cancer, people from poorer backgrounds do not always have access to the same quality of care as more affluent people. Reflecting Wilkinson and Pickett [67] we argue that political efforts need to be made to rebalance social and health inequalities. Heath [68] has likewise argued the need to confront causes of health inequalities. Reducing disparities is difficult; there was hope that the NHS Cancer Plan [5], with a number of measures focused on deprived sectors of the

population, would improve cancer survival rates and reduce disparities. While it resulted in a decrease in the deprivation gap for cancer outcomes at 1 year, this was not maintained, and the reason for this is unclear [15]. It may be that changes enacted around this time needed longer to impact on morbidity and mortality from a cancer. Or perhaps social class (and resultant social inequalities) are so well entrenched within society and so less responsive to policy initiatives.

The problem of health inequalities was recognised in 1997 by the UK Secretary of State for Health Frank Dobson, He stated that:

> Inequality in health is the worst inequality of all. There is no more serious inequality than knowing that you'll die sooner because you're badly off. (Dobson and Department of Health 1997) [69].

Health inequalities prevail in the UK and have a significant impact on people with a cancer. To ensure that everyone has the best possible outcome from a cancer, regardless of whether they are affluent or poor, will probably require great effort at a national policy level.

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Chapter 3
Behavioral Differences Leading to Disparities in Energy Balance and Cancer

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Abstract The patterns of racial/ethnic, gender, and socio-demographic disparities in cancer incidence patterns are complex. While susceptibility, exposure, environment, access to and attitudes towards screening and medical treatment influence cancer incidence and mortality, there are strong behavioral influences on racial/ethnic and socioeconomic disparities in incidence and mortality by cancer site. These behaviors are intertwined with culture and acculturation. In this chapter, we discuss disparities in four central areas of behavior that are related to both energy balance and cancer. These include dietary intake (broken down by key nutrients), disparities in physical activity and sedentary behavior, disparities in sleep, and disparities in smoking.

Keywords Racial/ethnic disparities • Socioeconomic disparities • Diet • Physical activity • Sleep • Smoking • Sugar consumption • Red meat consumption • Fish consumption • Dietary fat • Fruit and vegetable consumption

Introduction

Racial/ethnic and socioeconomic disparities in cancer screening, incidence, treatment, and mortality are both glaring and complex. For all cancer sites combined, African-American men have a 14 % higher incidence rate and a 33 % higher death rate than white men, whereas African-American women have a 6 % lower incidence rate but a 16 % higher death rate than white women [1]. However, specific cancers are more prevalent in particular groups. For instance, stomach and liver cancer incidence and death rates are twice as high in Asian Americans/Pacific Islanders as in Whites [2]. Another example is that kidney cancer incidence and death rates are the highest among American Indians/Alaskan Natives, which may reflect the high prevalence of obesity and smoking in this population [3]. In some cases, equal treatment for similar disease and tumor status has been shown to yield similar outcomes between racial/ethnic minorities and Whites [4, 5]. Nonetheless, racial disparities continue to exist in cancer treatment [4, 5]. Several systemic and doctor-related barriers contribute to these differences, as do factors that influence patient freedom of choice, decision-making, and ultimately, patient behaviors.

Broad disparities between subgroups within racial and ethnic groupings reflect possible differences in exposure, susceptibility, and access, but also between cultures and behaviors. For instance, the incidence rate for invasive cervical cancer, much of which is preventable by screening, is four times higher among Vietnamese women than in all Asian American/Pacific Islander populations combined. Another example of subgroup disparities is the regional influence on cancer rates among some American Indian populations, which increases with proximity to reservations [6].

The strong socioeconomic gradients in cancer incidence differ by racial/ethnic group, gender, country/region and type of cancer [7]. For instance, in the USA, lung cancer incidence is associated with markers of lower socioeconomic status in

Whites, Blacks, and Asians but with markers of higher socioeconomic status in Hispanics. One study in California Hispanics found that higher neighborhood socioeconomic status was associated with increased lung cancer incidence in women, but weakly associated in men, and ever-smoking rates were higher with increased acculturation [8].

Thus, although susceptibility, exposure, environment, access to and attitudes towards screening and medical treatment influence cancer incidence and mortality, there are strong behavioral influences on racial/ethnic and socioeconomic disparities in incidence and mortality by cancer site. These behaviors are intertwined with culture, acculturation, and socioeconomic status [9]. The links and mechanisms between energy balance-related behaviors and cancer have been discussed previously [10]. In this chapter, we discuss disparities in four central areas of behavior that are related to both energy balance and cancer. These include dietary intake (broken down by key nutrients), disparities in physical activity and sedentary behavior, disparities in sleep, and disparities in smoking.

Racial/Ethnic and Socioeconomic Disparities in Dietary Intake

Sugar Intake

Much research aimed at elucidating dietary contributions to energy balance has focused on the role of dietary sugar, particularly added sugar. There is substantial evidence that excess sugar intake contributes to positive energy balance [11, 12]. However, the contribution of sugar intake to positive energy balance may depend upon whether calories from sugar replace other calories or add to them [13]. Additionally, the form in which added sugar is consumed may contribute differentially to energy balance. There is evidence that energy consumed from beverages, such as soda and fruit juice, is regulated by different mechanisms than energy consumed from food, such that energy consumed from beverages may lead to a greater positive energy balance [13, 14]. This is supported by experimental studies that have shown a causal association between consumption of sugar-sweetened beverages and weight gain [15–17]. One potential explanation for the contribution of sugar-sweetened beverages to positive energy balance is that consumption of these beverages leads to extra energy intake before adequate feedback is provided by physiological satiety signals [18]. Given that most of the added sugar consumed by Americans is in the form of sugar-sweetened beverages, the contribution of sugar-sweetened beverages to positive energy balance is a particularly important public health concern [13, 19].

Dietary sugar has also received attention for its potential contribution to increased risk for certain types of cancer. High intake of sugar-laden foods may be associated with increased risk for pancreatic cancer [20, 21]. Added sugar intake

has also been associated with increased risk for colorectal cancer [22–24]. The increased risk for these types of cancers may be explained by the impact that dietary sugars have on insulin sensitivity, body fat distribution, and the concentration of growth factors that can contribute to the growth of cancers [25].

There are notable differences in sugar consumption across ethnicities and socioeconomic strata, but studies provide mixed evidence about which racial/ethnic groups consume the highest amounts of added sugar. In one recent study among a nationally representative sample of preschool-aged children, Hispanic children consumed less added sugar than all other ethnic groups, while non-Hispanic black and non-Hispanic white children consumed the most added sugar [26]. However, evidence indicates that the diets of low socioeconomic status Hispanic children exceed guidelines for added sugar intake [27]. Findings are similarly mixed for adults. A recent study using dietary data from a nationally representative sample of adults indicated that Hispanics consumed less added sugar than all other ethnicities except for Asian-Americans [28]. In this sample, non-Hispanic Blacks had the highest added sugar intake, followed by American Indian/Alaskan Natives and non-Hispanic Whites [28]. However, there is also evidence that Hispanics in particular consume high amounts of sugar-sweetened beverages [29]. There is more consistent evidence of an association between socioeconomic status and dietary sugar intake. A number of studies have indicated that individuals with low income and low education consume more sugar than individuals from higher socioeconomic backgrounds [28, 30, 31].

Acculturation and food cost may provide explanations for the differences in sugar consumptions between racial/ethnic and socioeconomic groups. While there are mixed findings from studies regarding the relative sugar consumption of Hispanics in the USA, studies on acculturated Hispanics provide more consistent findings. Hispanic individuals who are more acculturated to US culture have been consistently shown to have higher sugar intake than other racial/ethnic groups [32–34]. This indicates that acculturation status may explain the differences in findings of studies on sugar intake among Hispanics. The higher sugar intake exemplified by groups from lower socioeconomic strata may be explained by the difference in cost of high energy, low nutrient dense foods versus low energy, high nutrient dense foods [28]. Foods with high energy density but low nutrient density, such as those high in added sugars, are typically less expensive than foods with low energy density but high nutrient density, such as fruits and vegetables [28, 35, 36]. Added sugar intake has been shown to be directly related to the amount of income one has to spend on food [12], so individuals from low socioeconomic status groups are particularly vulnerable to consuming diets that are high in added sugar.

Beneficial Dietary Fats and Proteins

Although findings are inconsistent [37, 38], evidence suggest that consumption of omega-3 polyunsaturated fatty acids (PUFA, found in fatty fish like salmon,

sardines, and herring) may be protective of various cancers by altering the carcinogenic process [39], especially those that are hormone-related [38]. A major limitation of this area of research is that total fish intake is often examined as a risk factor, and lean fish such as cod or halibut may not offer the same health benefits [38] (methodological limitations will also likely bias findings towards null). Some specific ethnic groups have a rich history of consuming diets high in fish and marine mammals, such as the Inuit (natives of Alaska, Canada, and Greenland) [40], yet these individuals have a higher risk for all cancers, except breast and prostate cancer, than non-Inuits [41]. The protective effects of a native diet are likely mitigated once native cultures adopt a more Western diet with smaller amounts of these potentially protective foods [42].

Similarly, an assessment of dietary intake by varying ethnic groups in Hawaii and Los Angeles found that relative to Whites, Japanese-Americans and Native Hawaiians consumed the greatest quantities of fish, whereas African-Americans and especially Latinos had lower consumption [43]. Given the relationship between socioeconomic status and ethnicity, it is likely that the lack of fish consumption is due to cost, as this was identified as a barrier to consumption in Belgian adults [44]. Perceived inconvenience was also identified as a barrier in another European study [45]. Yet a study of fishing and subsequent consumption in South Carolina found that African-Americans consumed more fish than Whites, as did those who did not finish high school (it should be noted that this study was conducted in an area with a fishing advisory due to high fish mercury content) [46]. Given this evidence, it is likely that fish availability and accessibility (indicated by proximity to coasts and rivers and/or historical prominence in the diet of certain regional groups) are highly predictive of intake.

It should also be briefly noted that soy products (specific isoflavones contained in these foods) have also emerged as protective for breast cancer among Asian women [47], and possibly for prostate cancer, although the evidence is not so strong [48]. This protective relationship has not been observed with those following a Western diet, possibly due to the predominant use of soy as an additive rather than whole food [47].

Deleterious Dietary Fats and Proteins

Similar to findings on fish and PUFA intake, studies examining the impact of red meat consumption on various cancers are mixed, with stronger support for the impact on certain cancers (such as esophageal) than others (including prostate, gastric, pancreatic, and colorectal cancers) [49–56]. There are two components of red meat that make this a risk factor: higher levels of saturated fat [57, 58], and frequent use with cooking methods (such as char-grilling) than may impart carcinogens into the food [59].

Data from the Los Angeles/Hawaii multiethnic cohort indicate that Latinos consume about 30 % more red meat than African-Americans and Whites

[43]. NHANES (National Health and Nutrition Examination Survey) data also show that Latinos consume the greatest amounts of red meat, although this is not statistically higher than other ethnic groups [60]. Studies of meat intake and acculturation indicate that Latinos with the lowest US assimilation had the lowest avoidance of foods high in saturated fats, relative to more assimilated Latinos and Whites [61]; and that less assimilated Latinos were more likely to eat meat, relative to more assimilated Latinos [62]. Qualitative data suggest that Latina mothers find it more easy to procure red meat in the US relative to their home countries [63], so perhaps this higher degree of intake in this lower assimilated group is due to the interaction of accessibility and cultural value placed on meat intake (as a symbol of prosperity, as in many parts of the developing world) [64]. A separate qualitative study found that Latina mothers perceived meat to be a healthy food type [65], so it is possible that higher assimilated Latinos decrease intake of red meat given a gain in knowledge of potential negative healthy effects. Supporting this hypothesis, NHANES data indicate that both the perceived benefit of diet quality and use of food labels are negatively associated with red meat intake [66].

Whole Grains, Fruits, and Vegetables

Fruit and vegetable (FV) intake is strongly associated with cancer prevention, especially those related to the gastrointestinal system, lungs, and pancreas [67, 68]. Raw FV are the most beneficial, likely because they have the greatest concentration of antioxidants, including vitamins, minerals, and polyphenols [67]. Another protective component of FV is fiber, which has been found to be beneficial for several different types of cancers [69–73]. Whole grain products, which are also high in fiber, have also been shown to reduce cancer risk [74, 75].

A comparison of FV intake between different ethnic groups found that relative to Whites, African-Americans consumed approximately 1 serving/day less of FV, and Mexican Americans consumed about 0.3 servings/day less than Whites per day, with the majority of this disparity attributable to differences in intake of vegetables [76]. After adjusting for neighborhood SES, the difference between African-Americans and Whites remained [76]. NHANES data also indicate that African-Americans are less likely to consume the recommended number of FV servings/day, compared to Whites [77]. However, other neighborhood factors (adjusting for socioeconomic variables) may still contribute to this disparity. A study in Brooklyn, NY found that supermarkets were located in one third of the predominantly White US census tracts, while predominantly African-American census tracks had no supermarkets, and had less fresh produce available [78]. Similarly, in a study of African-American and Latina women eligible for the Women, Infants and Children (WIC) supplemental nutrition program, it was found that Latina women and children consumed a significantly greater amount of whole grains, compared to African-Americans [79]. This difference could be attributable to the lower levels of US assimilation among the Latina women (and likely manifested in a higher intake

of corn tortillas, a dietary staple), or possibly because they were significantly more likely to be married or living with a partner (perhaps attributable to cultural or religious values, which could enhance social support; it is unclear if this was controlled for in analyses) [79].

Racial/Ethnic and Socioeconomic Disparities in Physical Activity and Energy Balance

Evidence indicates that regular physical activity is protective against several types of cancer, including breast, colon, endometrium, prostate, and pancreatic cancer [25, 80–83]. In fact, the American Cancer Society points to physical activity as one of the most important modifiable determinants of caner [25]. Physical activity reduces the risk of cancer through several direct and indirect mechanisms, including body weight and energy balance regulation, immune system functioning, and regulation of sex hormones, insulin, and prostaglandins [25, 84, 85]. Physical activity plays an important role in energy balance because the movements of skeletal muscles during physical activity result in energy expenditure [86]. The intensity, duration, and frequency of physical activity all affect the extent to which physical activity contributes to energy balance [87]. For example, vigorous intensity activities (>6.0 metabolic equivalents or METs, a metric for estimating energy expenditure during physical activity) lead to greater energy expenditure than moderate-intensity activities (3.0–6.0 METs) carried out over the same duration and frequency [87]. National guidelines suggest that adults accrue at least 150 min a week of moderate-intensity, or 75 min a week of vigorous-intensity aerobic physical activity [88].

Although physical activity engagement provides great promise for preventing cancer incidence and recurrence, there are disparities in physical activity among many groups, especially ethnic minority communities. Disparities in physical activity engagement can be attributed to environmental and individual factors. Physical features in the built environment, including but not limited to streetlights, infrastructure that facilitates active transportation, and park availability, predict physical activity levels. The skewed availability of these features in areas with high ethnic minority density and/or low socioeconomic status (SES) may put minority populations at a disadvantage for opportunities to engage in physical activity [89]. There is also a wide array of individual level factors that influence physical activity, including perceived neighborhood safety [90, 91], psychosocial barriers [92]. While these factors influence behavior at an individual level, the interaction between individual factors and the environment also contribute to disparities in individual physical activity engagement. In the following section, we present examples illustrating the intertwined relationship between neighborhood environment and individual behavior.

Moderate and Vigorous Physical Activity (MVPA)

Physical activity engagement differs across age and gender. A cross-sectional study using NHANES data highlighted the differences in time spent in MVPA across gender and age by finding that females are less active than males and, overall, MVPA engagement declines with increasing age [93]. The lower physical activity levels observed among females are believed to be influenced by cultural and psychosocial factors, for example, body image issues, especially among ethnic minority groups [94]. Challenges that limit physical activity participation in culturally and linguistically diverse groups include: cultural and religious beliefs, issues within social relationships, socioeconomic status, environmental barriers, and culture-related perceptions of physical activity outcomes. Several strategies to overcome these challenges have been suggested, including culturally sensitive programs, education sessions addressing healthy behavior, and improving access to environments that promote physical activity both at work and in the community.

Occupation and Physical Activity

Within the context of one's occupation, socioeconomic status and environmental factors can interact to influence physical activity. Certain physical activities associated with low-wage, labor-intensive occupations qualify as MVPA. According to Troiano et al., despite the decline in MVPA with increasing age demonstrated in the overall population, Hispanic and African-American males exhibit higher activity levels than non-Hispanic white males [93]. This may be because labor-intensive jobs are more prevalent among African-American and Hispanic males than non-Hispanic white males [92]. While low-wage, labor intensive jobs may have a positive impact on physical activity for workers, their family members, especially children and adolescents, may experience negative effects on physical activity because such families have a higher likelihood of living in low socioeconomic neighborhoods [95].

Access to Physical Activity Facilities

A body of literature has documented the disparities in access to physical activity facilities influence MVPA. From an ecological perspective, however, factors that influence disparities in MVPA engagement may not be applicable only to ethnic minorities. Studies from various parts of the world indicate that affluent neighborhoods have better access to physical activity facilities than low SES neighborhoods [95–98]. Whether neighborhood demographics is a better predictor of physical

activity engagement than other factors that can be applicable to all ethnic backgrounds, such as socioeconomic status, is not well understood.

Leisure Time or Recreational Physical Activity

Leisure time physical activity (LTPA) engagement is also influenced by multiple factors. LTPA encompasses activities that people engage in during discretionary time. Examples of such activities include: gardening, walking, and recreational sports such as cycling. Like MVPA, LTPA engagement is also influenced largely by socioeconomic position both in an individual and an ecological perspective. Similar to how occupation influences disparities in activity engagement, time constraints due to work schedule and lack of energy after work also hinder adults with labor-intensive occupations from engaging in LTPA [99]. From an ecological perspective LTPA engagement is influenced by the SES of one's neighborhood. Features that are associated with lower SES neighborhoods, such as high crime rate, limited streetlights, and increased traffic density negatively impact PA engagements [90, 91].

Sedentary Behavior

Increasing attention has been paid to reducing sedentary behavior, as sedentary behavior is not simply a "lack of physical activity". However, there is no clear evidence that there are disparities in sedentary behavior among individuals from different ethnic and SES groups [100]. This may be because there is increasingly universal access to activities that promote sedentary behavior, such as television watching and video game playing. Environmental features that negatively impact physical activity engagement are also found to be associated with increased likelihood of time spent in sedentary behaviors [90].

Racial/Ethnic and Socioeconomic Disparities in Sleep, Obesity, and Cancer

Sleep is important for restoring physical and mental health. A growing body of literature indicates that inadequate sleep increases the risk of a range of chronic diseases including obesity [101, 102], diabetes [103], and hypertension [104, 105]. The associations between sleep duration and obesity may differ by age group. Based on a meta-analysis in children and adolescents ($\leq$18 years) [101], it was summarized that short sleep duration was inversely related to risks of

childhood overweight/obesity in pediatric population (OR: 1.58, 95 % CI: 1.26, 1.98) [101]. A recent prospective cohort study supports these findings, showing that short sleep among 0–4 year olds led to a subsequent 80 % increased odds of overweight or obesity [106]. Among adults, however, sleep duration was shown to have U-shaped associations with obesity [107, 108], suggesting that both short and long sleep duration were associated with concurrent and future obesity and weight gain.

Inadequate sleep is a risk factor for not only obesity, diabetes, and CVD [109, 110], but also to some types of cancer. Individuals with less than 6 h per night had an almost 50 % increase in risk of colorectal adenomas (OR = 1.47; 95 % CI = 1.05–2.06) as compared with individuals sleeping at least 7 h per night [111]. According to a meta-analysis on the relationship between sleep duration and cancer risk [112], there was a positive association between long sleep duration and colorectal cancer, and an inverse relationship with incidence of hormone related cancers like those in the breast.

Ethnic and SES Differences in Sleep

Considering the multiple deleterious effects of poor sleep, exploration of demographic patterns may shed light on methods to increase healthful sleep. Race/ethnic and socioeconomic factors may play a substantial role in sleep patterns and related disease. For example, in a sample of multiethnic US adults, insufficient sleep was related to increased odds of diabetes in all races, except non-Hispanic Blacks [113]. This again highlights the complexity of the impact of sleep on health; further compounding these intricacies is the difficulty in disentangling the influence of race/ethnicity versus socioeconomic status (SES).

In an epidemiological review, Bixler [114] highlights a body of research indicating low SES as a culprit for short sleep. In a 34-year longitudinal study of residents from Alameda County, CA, low SES led to fewer than 7 h of sleep, and short sleep was more common for African-Americans and Hispanics, as well as those with less education and lower SES (adjusting for other health factors related to poor sleep) [115]. A cross-sectional study on a national sample of US adults found that non-Hispanic Blacks were at increased odds for both short and long sleep, attenuated after controlling for SES, but remained significant [116]. Mexicans had increased odds for long sleep, although that association became non-significant after adjusting for SES. The authors speculated that these high risk sleep patterns may be attributable to substantial stressors experienced by urban minorities, and they conclude these differences in sleep may contribute to overall health disparities experienced by minorities [116]. Patel and colleagues [117] reported that poverty and race also contributed to poor sleep quality, and that employment and education mediated this relationship, highlighting that poorer individuals were most vulnerable.

Similar to the aforementioned study, a national study of over one-hundred thousand Americans found that education, employment and SES were inversely associated with sleep complaints [118]. Interestingly, this research showed Black and Hispanic women had fewer sleep complaints (e.g., trouble falling asleep, staying asleep, or sleeping too much) than their White counterparts, but these differences were not observed in men. Interaction analyses revealed more detailed patterns: the employment-sleep complaint association was inverse for African-American men (e.g., homemakers reported fewer sleep complaints compared to the combined male group); the positive income-sleep complaint relationship held for Hispanic men reporting less than $50,000 annual income; multiracial men had higher complaints if they were in the low SES group; non-college graduate Asian and Other women reported significantly increased sleep complaints and multiracial women showed a similar pattern; in contrast, Latina women were less likely to report complaints if they did not finish high school [118]. Goodin, McGuire and Smith [119], found ethnicity to be a moderator, reporting that lower perceived social status (perception of SES) was related to reduced sleep quality in Asians and African-Americans, but not Caucasians. Again, these findings illustrate the intricacies among ethnicity and SES factors in their influence on sleep.

These patterns are also seen in youth populations. A diary study of a nationally representative sample of children and adolescents found that Asian children (aged 5–11 years) and African-American adolescents (12–19 years old) reported shorter sleep durations during the week, which African-American and Hispanic adolescents also engaged in fewer hours of sleep on the weekend [120]. Crosby, LeBourgeois, and Harsh [121] found differences in sleep distribution by race in children as young as 3 years old. Caretaker reports indicated that 2–8 year old Black children napped more often, had shorter sleep durations, less sleep during the week than on weekends compared to their non-Hispanic white counterparts.

Understanding why these disparities occur may help to identify methods to improve sleep for ethnic minorities and people with low SES. Hicken and colleagues [122] found that Black adults experienced higher levels of sleep difficulties than Whites, and that this was fully mediated by racism-related vigilance, a marker of racially salient chronic stress. Although a similar pattern was found for Hispanics, it was not statistically significant. The authors suggest that racial discrimination plays a significant role in ethnic health disparities [122]. Tomfohr et al. [123] found that African-Americans experience more time in lighter sleep stages (sleep architecture) than their Caucasian counterparts, and that increased perceived discrimination was a partial mediator of these differences.

Family interactions and stressors may be responsible for sleep disturbance among youth. A study of urban Hispanic American infants and children (aged 6–48 months) found that frequent all-night cosleeping was more prevalent among minority families (21 %) than white American urban children (6 %); this practice was also associated with single parents and living in multiple households [124], which may be markers of lower SES. A longitudinal study found that marital conflict reported later sleep disruption in children, and that this association was

stronger among African-American children and those from families of lower SES [125].

Substantial research shows the significant negative impact of poor sleep on health, including positive energy balance, obesity, and cancer. However, research identifying determinants of poor sleep is limited. Reducing sleep disparities could help the field of health promotion progress toward equalizing health outcomes for all.

Racial/Ethnic and Socioeconomic Disparities in Smoking

Adult Current Smokers

The prevalence of smoking in the USA has declined since the first Surgeon General's Report documented the health hazards of smoking in 1964. When the report: *Smoking and Health*, was released approximately 43 % of the US adult population were current smokers [126]. Fifty years later the prevalence of adult current smokers has decreased to 19 % [126, 127]. These advances are remarkable but we have hit a plateau and the rates have not decreased significantly in recent years. In 2011, over 43 million adults reported as current cigarette smokers, of whom 77.3 % smoked daily and 22.2 % smoked intermittently [126, 127]. Furthermore, deaths from smoking and tobacco use remain the number one preventable killer of US adults [126, 127]. Cigarette smoking has also led to annual financial losses such as the $96 billion lost to direct medical expenses and $97 billion lost in productivity [126–129]. Important for this review, smoking is related to negative energy balance [130] making smoking an attractive tool for weight loss, while quitting smoking is related to weight gain [131]. Maternal smoking has also been shown to predict offspring obesity [132].

Large disparities in smoking and tobacco use remain for the racial and ethnic groups; these are further exacerbated when broken down by socioeconomic status (SES) and region [126, 129]. Prevalence of current smokers in 2011 was highest amongst the American Indians and Alaska Natives (31.5 %), followed by African-Americans (24.2 %), Hispanics (17.0 %), and the group with the lowest rate were Asians (14.9 %) [126, 127]. The prevalence of smoking in non-Hispanic Whites for the same year was 22.6 % [127]. While the differences in prevalence rates might be lower for most of the groups and non-significantly higher for African-Americans, racial and ethnic minorities carry most of the burden of tobacco related diseases [133], including lung cancer, other cancers, and cardiovascular disease. African-American males have shown a higher incidence of lung cancer (122.8 per 100,000) compared to non-Hispanic Whites (81.5 per 100,000) [134]. The other racial groups show much lower incidence; Asian Americans (61.2), American Indian/Alaska Native (49.8), and Hispanics (47.2) [134, 135].

Paradoxically, although racial and ethnic minorities are more likely to die from tobacco-related diseases, they are also more likely to report as intermittent or light smokers [133]. African-Americans, for example, show higher rates of lung cancer but only 8.0 % report as heavy smokers, 25 or more cigarettes per day, compared to non-Hispanic Whites (28.3 %) [136]. In a recent study Trinidad and colleagues found that among racial and ethnic minorities who had any history of smoking behavior there were significantly higher rates of current intermittent smoking than non-Hispanic Whites (8.5 %): African-Americans (15.9 %), Asian Americans (16.1 %), and Hispanics (20.8 %) [133]. The 1998 Surgeon General's report on racial and ethnic minority smoking provides a breakdown of the number of cigarettes consumed per day for four groups: African-Americans, American Indian/Alaska Natives, Asians, and Hispanics. The report shows that the prevalence of consuming 25 or more cigarettes has declined since 1976 and the proportion of smokers who consume 15 or fewer cigarettes per day has been increasing [137]. While this data show signs of progress, tobacco-related disparities persist [126, 127, 133, 138–140].

Adult Smoking Cessation

Recent data from the National Health Interview Surveys show that 68.8 % of adult smokers would like to quit [141]. The same data show that in the previous year: 52.4 % attempted to quit by ceasing to smoke by 1 or more days, 6.2 % had recently quit, 48.3 % had a physician advise them to quit, and 31.7 % had used either medications or a counseling service to assist in their attempt to quit [141]. Smokers between the age of 25 and 64 all showed increased rates of quit attempts from 2001 to 2010 [141]. Quit attempts are most common among younger smokers and college graduates [141]. When cessation statistics are broken down by race and ethnicity we get a clearer picture of where we should focus our efforts.

In 2010, 75.6 % of African-Americans reported interest in quitting smoking which was higher than non-Hispanic Whites (69.1 %) and Hispanics (61.0 %) [141, 142]. Furthermore, attempts at smoking cessation were higher for African-Americans (59.1 %) than those of non-Hispanic Whites (50.7 %), Hispanics (56.5 %), and other non-Hispanic races (53.8 %) [141, 142]. This and other evidence shows that African-Americans and Hispanics are more likely to make cessation attempts, but investigation into cessation success rates paints a different picture. The quit ratio (percentage of lifetime smokers who have stopped) in 2000 was lower for African-Americans (37.5 %) and Hispanics (42.9 %) as compared to their non-Hispanic White counterparts (50.4 %) [142]. These differences can be attributed to many factors such as SES, education, access to health care, quality of health care, type of health insurance, smoking behaviors, access to cessation resources, and perceptions of evidence-based cessation methods [134, 141, 142].

One of the leading hypotheses as to why some racial/ethnic minority groups do not succeed in cessation is the higher prevalence of menthol cigarettes [141,

143]. Menthol cigarettes anesthetize the throat and allow the smoker to inhale more nicotine per puff, leading to increased nicotine dependence [143]. The low use of evidence-based cessation programs is another prominent factor in racial/ethnic disparities in successful smoking cessation [141]. The rates of use for cessation counseling were lower for Hispanics (15.9 %) and African-Americans (21.6 %) than for non-Hispanic Whites (36.1 %) [141]. Racial/ethnic minorities are also shown to be less likely to be advised by a physician to stop smoking or about the health consequences [133, 144]. Nicotine replacement therapy has been shown as a promising method to increase success in smoking cessation attempts but also has low uptake by racial/ethnic minorities due to low prescription rates and utilization [133, 142]. There is plenty of evidence that shows the success of these and other interventions to increase the success of quit attempts [144]. There is also, however, a lack of evidence-based programs and outreach intended for racial/ethnic minorities decreasing chances of success [144]. Future research needs to be dedicated to creating targeted and culturally appropriate cessation interventions for these vulnerable populations.

Youth Tobacco Use

The significance of youth tobacco use has garnered attention from investigators and the Surgeon General. The use of tobacco among youth in the USA is of importance since 80 % of adult smokers report initiation before the age of 18 and 99 % before age 26 [128, 145]. It is estimated that over 3,800 youth under the age of 18 begin smoking each day in the USA [128]. In 2012 the prevalence for current tobacco use in middle school students was 6.7 % and 23.3 % for those in high school [145]. Youth also engage in cigar use with 2.8 % of middle school students reporting use and 12.6 % of high school students [145]. The use of cigars by youth can be explained by the popularity of small cigars, cigarillos, by this group and their lower price compared to cigarettes [145]. Youth tobacco use has shown a similar pattern as adults in that the progress has stalled in recent years [128, 145]. In the master settlement with the USA and several state governments the tobacco companies were obligated to create prevention programs for youth but their efforts have not shown any documented evidence of success [128]. Since the master settlement, however, tobacco companies have increased their efforts to reduce prices as they are aware that youth are more price conscious than adults [128, 145]. It also been shown that tobacco companies focus such strategies in areas high with racial/ethnic minorities [128].

Overall tobacco use for middle school students was higher in 2012 among Hispanics (10.5 %) than non-Hispanic Whites (5.1 %), African-Americans (7.7 %), and all other non-Hispanic groups (3.1 %) [145]. Among high school students, African-Americans (22.6 %) and Hispanics (22.5 %) had similar current tobacco prevalence while non-Hispanic Whites (24.6 %) had the highest prevalence [145]. Cigarette use in high school students was highest among non-Hispanic

Whites (15.4 %) and cigar use was highest among African-Americans (16.7 %) [128, 145]. Concurrent tobacco product use is prevalent across all racial groups in high school [128, 145]. Furthermore, over half of current Hispanic female tobacco users report of using more than one type of tobacco product on a regular basis [128]. In terms of susceptibility it has been shown that youth of Mexican descent are more vulnerable to initiate smoking than other youths [146]. These statistics show the need to better fund prevention programs for youth in order to prevent the premature deaths of one in three current young smokers [128].

Youth Tobacco Cessation

Smoking cessation is a rare occurrence in youth and young adults (16–24 years); only 4 % per year quit smoking [147]. The rates for attempts to quit, however, are higher for youth (58 %) than for adults (52.4 %) [147]. Youth and young adults between 16 and 24 years of age were more likely to attempt to quit without assistance [147]. Only 20 % of current youth smokers sought advice from a nurse or physician prior to their quit attempts, with females (24.9 %) being more likely to seek the help than males (15.6 %) [147]. The only two groups of current high school smokers who showed differences in attempts to quit were African-Americans (68.1 %) and Hispanics (54.1 %) compared to non-Hispanic Whites (62.8 %) [148]. In general there is limited data on youth cessation with even less for racial/ethnic minorities; therefore it is important that future research address this gap. Public health officials also need to create and adequately fund prevention and intervention programs that are both relevant and appropriate for all groups of youth.

New and Emerging Tobacco Products

Since the groundbreaking Surgeon General's Report on Smoking in 1964 there have been many advances but now we must adapt our efforts to include new and emerging tobacco products. Products such as electronic cigarettes and hookah are gaining in popularity especially among youth [145]. Tobacco companies have noticed this gain in popularity for e-cigarettes and have responded by increasing smokeless tobacco product marketing by 277 % compared to 48 % increase for cigarettes [126]. Over 6 % of adults in the USA, including 21 % of current smokers, have tried e-cigarettes [138]. From 2011 to 2012 there were significant increases in e-cigarette use among middle (0.6–1.1 %) and high school students (1.5–2.8 %) [149]. Hookah use also increased among high school student from 2011 (4.1 %) to 2012 (5.4 %) [145]. E-cigarettes are more popular among current high school non-Hispanic White (3.4 %) tobacco users, followed by Hispanics (2.7 %), other non-Hispanic groups (2.2 %), and African-Americans (1.1 %) [145].

While the statistics for e-cigarettes and other emerging products are low in comparison to traditional cigarettes, public health officials and researchers need to investigate the health consequences of such products. Little is currently know about these new products and currently most are not regulated by the Food and Drug Administration. The lack of regulation allows tobacco companies to make claims about the use of these products for harm reduction or smoking cessation without the need for scientific review. Claims such as health benefits could be detrimental especially for our vulnerable populations such as racial/ethnic minorities by making it easier to fall unto nicotine dependence and harder to achieve cessation [150].

Some Brief Conclusions

This overview of four central behavioral domains that influence both energy balance and cancer shows clear racial/ethnic disparities in all four areas, although patterns are not always straightforward. It is clear that, in the USA, racial/ethnic "minorities" are at higher risk for poor diet, exercise, sleep and smoking behaviors, at higher risk for obesity, and at higher risk for most cancers, than their white counterparts. Mechanisms for these disparities likely differ according to a complicated network of influences from cell to society, from genes to cultural views on the specific behaviors. However, some commonalities can be noted.

Socioeconomic Status and Health Behavior

In each of the sections above, the inverse relationships between low socioeconomic status and unhealthy behaviors related to energy balance and cancer have been demonstrated empirically. The underlying mechanisms for these relationships remain unclear. In the USA, racial/ethnic minorities are disproportionately represented in lower socioeconomic strata [151], but even after correction for race/ethnicity, socioeconomic differences in health-related behaviors persist [152]. There is no doubt that gaps in socioeconomic status impact access to insurance, adequate health care, healthy food, and safe places to exercise, among many other important needs related to attaining and maintaining a healthy energy balance. However, unlike disparities in many other components of health, disparities in health behaviors appear to involve something *more* than the ability to use income to purchase good health [152].

Stress: One Possible Missing Link

Stress has been related to poor sleep [116], unhealthy eating patterns [153], lower physical activity and increased sedentary time [154], and the initiation and maintenance of smoking [155]. Research has shown that low socioeconomic status and minority status are strongly related to increased stress. For example, in a population of 3,105 adults (34 % white), Sternthal et al. [156] found significant racial differences in exposure to eight stress domains, e.g., acute life events, employment, financial, life discrimination, job discrimination, relationship, early life, and community stressors.

Although disentangling the roles of race/ethnicity and socioeconomic status in health behaviors remains complex [157], there exist acute disparities in energy-balance and cancer-related behaviors. There are also racial/ethnic differences in stress, as well as a socioeconomic gradient in stress and stressful experiences. The documented interrelationships between these core behaviors and stress highlight the role that social stressors uniquely experienced by minority populations may play in existing health disparities. Considering public health's mandate to achieve health equity for our communities, efforts must be put into reducing the stressors associated with poverty and racism. These efforts may help to ameliorate the racial/ethnic and socioeconomic disparities in energy balance and cancer in the USA.

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Chapter 4
Impact of Obesity, Race, and Ethnicity on Cancer Survivorship

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Abstract It is estimated that between 1971 and 2002, the population of cancer survivors grew from approximately three million to ten million. Currently, it is estimated that there are over 13.7 million cancer survivors in the USA and this number is expected to increase to 18 million by 2022. The seminal Institute of Medicine's report on cancer survivorship that outlines the need to develop strategies to address the unique issues faced by this growing clinical population was published 8 years ago. However, long-term cancer survivors are still a relatively new clinical population in the field of oncology, borne of successes in improved cancer screening and treatment approaches. There continues to be a need to define and clarify the factors that contribute significantly to outcomes in cancer survivors

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in order to develop effective and efficient intervention strategies. Within this chapter we address the independent and interactive contributions of two issues thought to substantively influence the length and quality of cancer survivorship: obesity and race/ethnicity.

Keywords Cancer survivorship • Breast cancer survival • Endometrial cancer survival • Colorectal cancer survival • Prostate cancer survival • Adverse treatment effects • Poverty • Affordable care act • Prevention and public health fund • Quality of life • Obesity • Patient Protection and Affordable Health Care Act • Cancer-related fatigue

Introduction

From 1971 to 2002, the number of cancer survivors in the USA has grown from three million to ten million [1], and the number of survivors is expected to reach 18 million by 2022 [2]. This growth has occurred over the same decades during which the prevalence of obesity has increased as well. The prevalence of overweight (BMI = 25.0–29.9 kg/m^2) and obesity (BMI $\geq$ 30.0 kg/m^2) in the USA rose from 13.5 % in the 1960s to 35.9 % in 2010 [2, 3]. Data from the 2007 Health Information National Trends Survey (HINTS) indicate that cancer survivors are no more or less likely to be obese than those who have not experienced cancer [4]. However, the combined experience of cancer and obesity may influence the length and quality of life after completing treatments for common cancers, including breast, colon, prostate, and endometrial cancer [5]. In section "Obesity and Cancer" of this chapter, we review this evidence.

The racial and ethnic diversity in the USA has also shifted over the same decades during which the cancer survivorship population has grown. In 1970, when there were approximately three million cancer survivors living in the USA, 11.1 % of the country's population identified their race or ethnicity as African American, 4.4 % as Hispanic, 0.8 % as Asian, and 87.7 % as non-Hispanic White [7]. By 2010, when there were over 12 million cancer survivors, 13.6 % of the US population identified their race or ethnicity as African American, 16.3 % as Hispanic, 4.9 % as Asian, and 72.4 % as non-Hispanic White. Incidence of cancer does vary by race and ethnicity [8]. Social, economic, behavioral, health access, and other differences might be expected to contribute to variability regarding the burden of cancer across race or ethnicity. In section "Race/Ethnicity and Cancer" of this chapter, we review the evidence that survival after diagnosis and adverse effects of cancer treatment vary by race and ethnicity for four common cancer diagnoses (breast, colon, prostate, and endometrial).

Finally, it can also be observed that prevalence of obesity varies by race and ethnicity, with a higher prevalence of obesity among ethnic and racial minorities in the USA [4]. The racial and ethnic groups for whom cancer survival is worse are the same groups in which obesity is more prevalent, including African Americans and

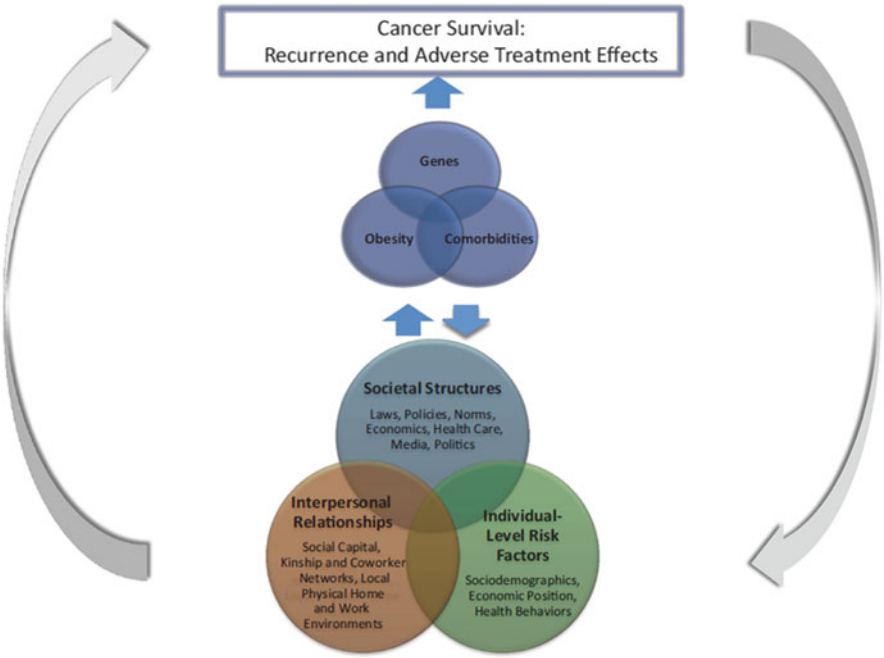

Fig. 4.1 Framework for the combined influence of race and obesity on cancer survivorship. The *bottom* Venn diagram represents distal determinants of disparate cancer survival outcomes. Disparities in these underlying social and physical determinants are embodied and expressed through biological responses and genetic pathways, which lead to disparities in risk for obesity and comorbidities. In the *top* Venn diagram, differential genes, obesity, and comorbidities then lead more proximally to disparities in survivorship outcomes. All of these relationships operate in a feedback loop of biological–social–physical environment interactions, making it difficult to disentangle which of the underlying or mediating factors are the greatest contributors to disparities in survivorship

Native American/Pacific Islanders [3, 9]. It could be hypothesized that the disparities by race and ethnicity for cancer survival and treatment outcomes are explained, in part, by disparities in obesity and related comorbidities. A framework for discussing these complexities has been proposed (Fig. 4.1) [6]. Disparities in underlying social and physical determinants are embodied and expressed through biological responses and genetic pathways, which may lead to disparities in risk for cancer, obesity, and comorbidities. Differential risk in obesity and comorbidities may then lead to disparities in cancer survivorship outcomes. All of these relationships operate in a feedback loop of biological–environmental interactions. In section "Future Directions and Summary" of this chapter we review the limited evidence available on this topic and draw from evidence on this interaction of obesity with race/ethnicity for predicting other health outcomes (such as heart disease) to speculate further about the significance of these factors to outcomes among cancer survivors. Section "Future Directions and Summary" also includes

commentary on the potential influence of the roll out of the 2010 Patient Protection and Affordable Health Care Act on these issues. The chapter concludes with a summary and comments about possible future directions for better understanding the interactive effects of obesity and race/ethnicity on cancer survivorship in a manner that will lead to expediency with regard to maximizing the health of cancer survivors while minimizing disparities in these outcomes by obesity and race or ethnicity.

Obesity and Cancer

Obesity and Survival/Mortality

Obesity is increasingly recognized as a risk factor for poor survival for many cancers, but particularly so for breast, prostate, endometrial, and colorectal cancers [10–13]. In many published studies the risk of cancer-specific mortality is as much as two times higher for obese patients compared to nonobese patients making treatment of the obese cancer patient a particularly important clinical issue [11, 14, 15]. Obesity is associated with all-cause mortality as well. For example, among endometrial cancer patients, obesity and diabetes at diagnosis are associated with all-cause but not cancer-specific mortality, suggesting the need to address these comorbidities to reduce the burden of mortality in this cancer survivorship population [16]. Another emerging and recognized problem is that many patients may enter cancer treatment at a normal weight, but may gain a significant amount of weight during therapy. This treatment-related weight gain phenomena has been linked to female breast cancer patients receiving systemic adjuvant chemotherapy [12]. However, the causes of weight gain after cancer treatment are not fully understood. Hypothesized causes include a combination of changed diet, reduced physical activity, or altered metabolism that may accompany after exposure to the chemotherapy [12, 17]. It is not yet known whether these patients who gain weight while undergoing treatment have the same mortality risk as those who are obese at the time of diagnosis [18, 19]. Nonetheless, this weight gain during treatment phenomena should be carefully monitored by clinicians with referrals to appropriate weight management plans [12].

Numerous factors have been identified as contributing to the increased mortality rate in obese cancer patients. Many of these patients will have multiple comorbidities. Managing diabetes, cardiovascular issues (including prior stroke or stroke risk), metabolic syndrome, and multitudes of other obesity-related diseases is a clinical challenge from the perspective of polypharmacy and drug–drug interactions. In addition, many obese patients will be viewed as surgical risks due to concurrent poor cardiovascular or respiratory health and as a result, treatment plans must be altered from approaches known to be most effective, as necessary. Further, for those who are able to undergo surgery, clean surgical margins can be very

difficult to attain in the obese patient due to the large fat pad around the tumor and surrounding tissue. Obese patients also tend to have disordered metabolism even in the absence of a diagnosis of diabetes or prediabetes. Low levels of adiponectin and high levels of insulin (or C-peptide), IGF-1, glucose, adipose-derived inflammatory factors, cytokines, and other metabolic markers are very common in obese individuals and each of these has been associated with increased risk of cancer-specific mortality [18–21]. Many of the molecules that tend to be higher in obese people (even those without cancer) have direct links to the carcinogenic process by upregulating critical pathways such as mTOR and PI3K and by influencing the local inflammatory environment [22]. Modest evidence exists to suggest that genetic variation in the synthesis or metabolism of certain fatty acids or lipid-related compounds may influence the relationship between obesity and survival [23, 24]. More work is needed to better understand these complex relationships.

Recent and very intriguing data suggests that the tumor phenotype or the tumor microenvironment may be very different for patients who are obese compared to nonobese patients [22, 25, 26]. A recent study examined breast tissue from 30 normal weight and overweight/obese women undergoing surgery for breast cancer [26]. Among the findings, they reported higher aromatase expression in the breast tissue of obese women with subsequent greater local synthesis of estrogen in the breast. They also reported more crown-like structures in the breast tissue from obese women, which is also an indicator of greater levels of local inflammation. Other studies have shown that adipocytes that comprise the tumor microenvironment actively recruit macrophages similar to the peripheral circulation. The macrophages then promote neovascularization and angiogenesis, which sets up the patient for risk of metastasis [22]. Data are suggestive, but by no means definitive, that obese colorectal cancer patients may have tumors with a distinct pathologic phenotype that could be driven by the underlying obesity-driven metabolic disturbances [25, 27].

A critical link to the intersection between obesity and racial/ethnic cancer-related health disparities is that since African Americans and Hispanics have the highest rates of obesity in the USA [4], their body habitus already puts them at disproportionate risk of cancer-related mortality compared to Caucasians. Still, not all studies support an interaction between race and obesity with respect to cancer survival [11], so clearly additional work is needed in order to formulate the most appropriate treatment protocols.

Obesity and Persistent Adverse Treatment Effects

Cancer patients who are obese at diagnosis may require specialized treatment plans and management strategies. It has been observed that obese endometrial cancer patients experience greater loss of blood and longer surgical times than nonobese patients [28].

A persistent question facing clinicians is whether obese cancer patients should receive different chemotherapy doses based on body weight. There has been a long history of controversy on this topic where on the one hand it is thought that obese patients may be underdosed if drug doses are not based on actual body weight while on the other hand the risk of toxicities may be elevated with higher doses. A recent systematic review and meta-analysis had shed some light on this critical clinical issue [29]. Hourdequin et al. reviewed 12 studies that included cohort studies and clinical trials for a variety of cancers. Details of their methods including selection criteria for inclusion in the meta-analysis and patient inclusion criteria are reported in their publication [29]. The prespecified primary outcome was grade 3–4 hematologic toxic effect (on a scale of 1–4) while secondary outcomes included standard blood counts (leukocytes, platelets, hemoglobin), neutropenia, and overall survival. The overall pooled results showed that when chemotherapy doses were based on actual body weight, grade 3–4 hematologic toxic effects were 27 % lower in obese patients compared to nonobese patients [29]. The authors concluded that their evidence suggests that full-dosing based on actual body weight is safe and without clear evidence for risk of excess toxicity. Still, because other studies suggest incomplete pathologic response to chemotherapy among obese patients [30], other reasons besides chemotherapy dosing may be important to examine in future studies.

A relatively new but growing area of clinical and scientific concern is persistent adverse treatment effects from cancer. Below we review the empirical evidence on the association of obesity and common persistent adverse effects of cancer treatment, including lymphedema, quality of life, functional health, cancer related fatigue, chemotherapy induced peripheral neuropathy, and cardiotoxicity.

Lymphedema

Cancer treatments, including removal of lymph nodes and radiation therapy, can damage the lymph system, resulting in a chronic, sometimes progressive condition called lymphedema. Lymphedema is commonly characterized by swelling of the affected body part. However, the swelling associated with lymphedema is distinct from other types of edema due to the enrichment of protein in the accumulation of lymph fluid. This accumulation of protein rich fluid, accompanied by the role of the lymph system in inflammatory and immune responses, sometimes results in lymphedema becoming a systemic issue. Ongoing symptom monitoring is recommended to avoid lymphedema onset and progression [31]. Obesity has been consistently associated with both onset and worsening of lymphedema after breast cancer. Prospective studies report odds ratios of 2.93–3.6 for risk of lymphedema among obese versus normal-weight women [32–35]. There is also evidence of a dose–response relationship between excess weight and lymphedema risk, with an OR of 1.08 for each additional BMI unit above the normal weight category (95 % CIs 1.05–1.12 [32] and 1.0004–1.165 [33]). Further, there is evidence that body fat is associated with lymphedema across a broad range of BMIs. For example, in a study

conducted in Hong Kong, higher BMI was noted in breast cancer patients with lymphedema compared to matched controls, even though BMI was low in both groups (22.9 ± 3.6 kg/m^2 for cases vs. 21.8 ± 3.1 kg/m^2 for controls) [36]. One pilot study demonstrated weight loss to reduce lymphedema among overweight breast cancer survivors [37] and a larger study on this topic is ongoing within the Penn Transdisciplinary Research on Energetics and Cancer (TREC) Survivor Center (U54-CA155850 to Schmitz).

Evidence linking obesity with lymphedema is more scant beyond breast cancer. Several studies report no association of BMI and incident lower extremity lymphedema among cervical cancer survivors [38–40], while one other prospective cohort study among cervical cancer survivors found that low BMI (<18.5 kg/m^2) was associated with increased frequency of lymphedema [41]. Finally, in a cross-sectional survey study of 243 Australian women, lymphedema risk was 2.7-fold higher among overweight compared to normal weight endometrial cancer survivors (95 % CI: 1.0–7.5) [38].

Quality of Life and Functional Health

Obesity has been associated with lower physical and functional well-being and poorer quality of life among endometrial cancer [42, 43], breast cancer [44], prostate cancer [45–47], and colorectal cancer survivors [48]. Two other studies with heterogeneous samples of cancer survivors (e.g., breast, colorectal, prostate, bladder, uterine, and melanoma) have also demonstrated reduced quality of life among obese versus nonobese participants [49, 50]. Obesity is also associated with higher prevalence and severity of site-specific symptoms, such as incontinence in prostate cancer survivors [46, 51]. Both cancer [52–54] and obesity [55–57] have been found to be independently associated with functional health. However, the differential impact of cancer and its treatments on functional status among obese versus nonobese survivors remains to be elucidated.

Cancer Related Fatigue (CRF)

Obesity has been positively associated with CRF for a number of cancer sites, including breast [58–61] and endometrial cancers [62]. Factors predicting clinically significant CRF include a BMI > 25 kg/m^2, weight gain, physical inactivity, and low physical functioning [60, 63], and severity of fatigue symptoms is associated with higher BMI [63].

Peripheral Neuropathy and Cardiotoxicity

Very little information is available regarding the potential relationship between obesity and peripheral neuropathy. Three studies have observed no association

between obesity and chemotherapy induced peripheral neuropathy after breast cancer [64, 65] and multiple myeloma [66]. However, determining the independent effect of obesity on neuropathy may be challenging, given obesity is also a strong risk factor for diabetes, which is also associated with neuropathy [67]. Because obesity is already a strong risk factor for cardiovascular disease and late effects of chemotherapy may not appear for many years after treatment completion, it is difficult to determine the specific role of obesity in treatment-related cardiac toxicities. Other sources of increased cardiovascular risk, such as weight gain after chemotherapy among breast cancer survivors [68], further complicate the clinical picture. The relationships between excess pretreatment weight, weight gain after treatment, and treatment-related cardiovascular outcomes have not been extensively studied.

As survival from many of the common cancers (i.e., breast, prostate, colorectal) continues to increase, it is critical to evaluate whether any late effects differ for obese versus normal weight patients. Treatment protocols and effective strategies for total patient care will need to be developed so as to treat the late effects from cancer treatment concurrent with treatment to achieve and maintain a healthy weight.

Obesity and the Economics of Survivorship

Health-care costs in the USA are elevated in comparison to other western nations and cancer treatment is no exception to the health-care spending crisis [69]. In 2010, costs for cancer diagnosis, treatment and survival were estimated to be $124.6 billion [70]. These expenditures vary by cancer site where the greatest direct medical costs are for breast, colorectal, lung, and prostate cancers for solid tumors and lymphoma for hematologic cancers [70, 71]. Other expenditures that some may consider hidden include lost productivity and the value of life lost [72, 73]. Bradley and colleagues reported that as many as a third of cancer patients are unable to return to work after the diagnosis and of those who do return, duties must often be limited or task reassignments must be made [73]. Yabroff et al. estimated that by 2020, the value of life lost due to cancer will reach a staggering $1,472.5 billion [72]. Other hidden costs include the loss of productivity of care givers who often must use family medical leave to care for the cancer patient [72, 73]. Over the next several decades, these figures are expected to increase commensurate with the aging population. One study in Washington state reported that cancer patients were 2.65 times more likely to file for bankruptcy compared to non-cancer patients [74] underscoring the fact that a cancer diagnosis often becomes an economic crisis for patients and their families [70, 75]. Many of these critical issues were highlighted (including systematic reviews of site-specific cancers) in an August 2013 Monograph of the Journal of the National Cancer Institute (JNCI Monographs Volume 2013, Issue 46).

While cancer is costly to all patients, an important question is whether subsets of patients, including those who are obese prior to diagnosis share a disproportionate burden of cancer health-care expenditures. For overweight and obese cancer patients, prognosis is worse compared to normal weight patients. However, it is unclear whether these disparities are due to lower health-care access or utilization, lack of follow-up for suspicious findings from screening tests, lower adherence to adjuvant therapies, lack of referrals to medical oncologists, presentation with more advanced disease, or biological differences in tumors or responses to therapies [76–79]. In addition, patients who are overweight or obese may have comorbid conditions (e.g., diabetes, hypertension, dyslipidemia) that need concurrent treatment [15]. Treatments of these concurrent conditions add to the overall economic burden of cancer. The economic disparities that accompany the racial and body habitus disparities in regard to cancer treatment and survival constitutes a problem that has multiple causes and will require a highly coordinated and multilevel approach to the solution [71].

It will be particularly important to monitor the effects of the 2010 Patient Protection and Affordable Health Care Act on the economic challenges for those who are overweight or obese at the time of a cancer diagnosis. An important component of the Affordable Health Care Act is the expansion of the Medicaid Program. One might intuitively think that this expansion will lead to greater access to cancer screenings and treatment that might otherwise be delayed without access to health-care services. Finally, as summarized in an Institute of Medicine Workshop Summary [69] that was specifically focused on delivering affordable cancer care in the twenty-first century, scientists, clinicians, and policy makers must all work together to construct treatment strategies and insurance reimbursement strategies for affordable and effective cancer care, perhaps particularly for those who have experienced health-care disparities in the past.

Race/Ethnicity and Cancer

Race/Ethnicity and Survival/Mortality

It is widely recognized that cancer survival and mortality disparities persist by race and ethnicity. For some cancers, African Americans and Hispanics have a worse disease-free survival than other racial/ethnic groups [80–82]. These disparities are associated with advanced stage of disease, tumor characteristics, comorbidities, suboptimal treatment, obesity, lack of or type of medical insurance, access to high-quality medical care, and low socioeconomic status (SES) [80, 82–86]. For those diagnosed with cancer between 2002 and 2008, the 5-year survival rates from all cancers were 69 %, 65 %, and 65 % for non-Hispanic Whites, Hispanics, and African Americans, respectively [87]. Disparities among racial and ethnic groups

have existed for decades, even as overall cancer mortality rates for most cancers have been declining.

Breast Cancer

Breast cancer is the second leading cause of cancer-related death in women. Cancer mortality rates have been declining for the past two decades. However, comparable benefits of these declines have not been equally shared among all racial and ethnic groups. For example, SEER data on 5-year breast cancer survivor rates, using data on women diagnosed with breast cancer between 2002 and 2008, illustrates the disparity among non-Hispanic Whites (92 %), Hispanics (86 %) and African Americans (78 %) [87]. A recent study examined BC survival using SEER-Medicare population data between the years 1991–2005 for 16 SEER sites and found a 12.9 % absolute difference in survival between African Americans and non-Hispanic Whites ($p < 0.001$), which was attenuated, but still significant after matching on presentation characteristics and types of treatment [88]. In this study, cancer-related causes accounted for approximately 2/3 of the difference in 5-year all-cause mortality between African Americans and non-Hispanic Whites. Studies also suggest that the racial disparity in survival and mortality does not discriminate between younger and older breast cancer survivors. African American adolescent and young adult women also have worse survival rates compared to non-Hispanic Whites and Hispanics [89, 90]. It was reported that in a comparison of African American and non-Hispanic White women 60–64 years of age, African American women with luminal A/p53− tumors were reported to have higher all-cause mortality (HR 2.22; 95 %; CI: 1.30–3.79) and breast cancer-specific mortality (HR 1.89; 95 % CI: 0.93, 3.86) [91]. Similar results were reported for older women with Triple Negative Breast Cancer [92]. Data from Southwest Oncology Group (SWOG) phase III trials from 1974 to 2001 found that African American patients with early-stage, premenopausal and postmenopausal breast cancer had significantly worse overall survival than non-Hispanic White patients (HR = 1.41, 95 % CI: 1.10–1.82 and HR = 1.49, 95 % CI: 1.28–1.73), respectfully, after adjusting for stage, demographic and socioeconomic factors, tumor characteristics, and treatment [93].

Hispanics compared to non-Hispanic Whites have higher breast cancer mortality rates [94, 95]. There also is heterogeneity in survival within Hispanic subgroups. When examining Hispanic subgroups, one study revealed that Hispanic-blacks have significantly higher BC-specific mortality compared to Hispanic Whites (HR = 1.4; 95 %: CI: 1.1–1.7) [96], and among Hispanic Whites, Puerto Rican women had the highest risk (HR 1.7, 95 % CI: 1.3–2.1) [95]. Banegas et al. [96] reported that regardless of Hispanic origin, African American women experienced worse breast cancer survival compared to Hispanic and non-Hispanic white women. A meta-analysis of 20 studies completed through 2005 identified African American ethnicity as an independent predictor of higher mortality among breast cancer

survivors, including overall survival (HR 1.27; 95 % CI: 1.18–1.38), and breast cancer-specific survival (HR 1.19, 95 % CI, 1.10–1.29) [97].

Endometrial Cancer

Mortality rates for endometrial cancers have declined in the past decades, although there are still racial disparities in both mortality and survival. African American women have lower survival rates for endometrial cancer compared with Hispanics and non-Hispanic White women [98, 99]. A retrospective analysis of data from four Gynecologic Oncology Groups (GOG) randomized treatment trials found that African American women with endometrial cancer had worse overall survival compared with non-Hispanic White women, after adjusting for tumor characteristics and treatment (1.26, 95 % CI: 1.06–1.51) [100]. Others have reported significantly worse survival for African Americans compared to non-Hispanic Whites (HR 1.94) and no significant differences in survival between Hispanics and non-Hispanic Whites [101]. Survival from endometrial cancer was examined in a study in Puerto Rico that revealed African Americans and Puerto Ricans had the lowest rates of survival when compared to non-Hispanic Whites (56.8 % for African Americans, 63.1 % for Puerto Ricans, 78.4 % for non-Hispanic Whites and 79.5 % of US Hispanics [102].

Colorectal Cancer

Colorectal cancer (CRC) remains the third most common cause of cancer-related death in both men and women. The racial disparity in CRC mortality has widened, with 53 % higher mortality in African American men and 46 % higher mortality in African American women compared with non-Hispanic White men and women [80]. Several studies have documented higher CRC mortality for African Americans compared to non-Hispanic Whites [103–105]. A study of resected stage II and stage III colon cancer revealed that African American patients experienced worse overall survival (HR = 1.22, 95 % CI: 1.11–1.34) and recurrence-free survival (HR = 1.14, 95%CI: 1.04–1.24) compared to non-Hispanic Whites [105]. A review of 16 SEER data registries linked to the Medicare database, adjusted for several risk factors including SES, tumor characteristics, treatment, and comorbidities, found that African Americans had a significantly higher risk of CRC death (HR = 1.24; 95 % CI: 1.14, 1.35) compared with non-Hispanic Whites [106]. In this study, Hispanic women had a lower risk of death than non-Hispanic Whites, in the adjusted model. Temporal trends in survival revealed that young Hispanics (20–49 years) improved their 1-year CRC survival from 86 % in 1993–1997 to 91 % in 2003–2007 [107]. Soto-Salgado and colleagues [108] examined CRC mortality in Puerto Rico and revealed that African American women and non-Hispanic White women age >50 years had an increased risk of death from CRC compared with Puerto Rican women. In addition, Puerto Rican women had a similar risk of death compared to US Hispanics, but a lower mortality rate

compared to African American women; whereas, the CRC risk was higher for non-Hispanic White men ≥ 60 and US Hispanic men ≥ 80 than Puerto Rican men [108]. The overall 5-year survival from proximal colon cancer was reported as 39.7 % for African Americans, 43.1 % for non-Hispanic Whites, and 46.7 % for Hispanics [109]. An interaction between race and age may influence CRC survival. One study reported that younger African American women (<50 years) with advanced stage proximal tumors had worse survival compared to age-matched non-Hispanic Whites, whereas older African American men had a worse survival compared to older non-Hispanic White men [110]. It should be noted that there were no significant differences in cancer specific and overall survival CRC between African American and non-Hispanic White women enrolled in the Women Health Initiative study [111]. The investigators suggested that equal access to medical care and uniform tumor characteristics may have contributed to this outcome.

Prostate Cancer

Prostate cancer is the second leading cause of cancer-related death in men. Approximately one in six men will be diagnosed with prostate cancer during their lifetime, with increased risk during each decade of life. Several studies have documented an increased mortality among African American and Hispanic men with prostate cancer compared to non-Hispanic Whites [84, 106, 112, 113]. One study reported that Puerto Rican men had a higher mortality than did US Hispanic and non-Hispanic Whites, but lower rates compared to African American men [108]. In recent years, deaths from prostate cancer have narrowed between African Americans and non-Hispanic Whites, but the disparity still exists [80]. One study estimated that the mortality gap for prostate cancer-specific mortality was 1,320 more cases per 100,000 for African American compared with non-Hispanic Whites men [84]. Another study reported that African American men had a higher risk of mortality (HR = 1.23, 95 % CI: 1.04–1.47) relative to non-Hispanic White men, despite treatment on the same protocols [114]. Albain et al. [93] reported similar findings, showing higher mortality among African American men compared to non-Hispanic Whites (HR = 1.19, 95 % CL: 1.05–1.35), after adjustment for all other available factors [93, 114]. Also, the 10-year overall survival estimates were lower for African Americans. However, two meta-analyses had different findings. A meta-analysis of 48 studies found that African American men had lower prostate cancer-specific survival (RR = 1.13, 95 % CI: 1.00–1.27) and recurrence (RR = 1.25, 95 % CI: 1.11–1.41), but no difference in overall survival, after adjustment for clinical predictors and SES [115]. This analysis included several studies from the same registry with overlapping time periods. Sridhar and colleagues [116] conducted a meta-analysis of published studies from 1968 to 2007 and corrected for this methodological concern by including only one publication from the same cancer registry. They found a significant increased risk of mortality among African American men compared with non-Hispanic Whites, but after adjusting for age, clinical, and demographic variables, this association was not significant.

Race/Ethnicity and Persistent Adverse Treatment Effects

Currently, there are 13.7 million cancer survivors in the USA, and this number is expected to risk by 31 % by 2022 [2]. Cancer survivors may have long-term psychological and physical impairments and incidence and severity of these impairments differs by race and ethnicity.

Lymphedema

Racial/ethnic differences are associated with arm lymphedema [32, 117]. The Pathways Study, a prospective cohort of breast cancer survivors found that the risk of transient and persistent lymphedema was higher among African Americans compared to non-Hispanic Whites (HR = 1.93, 95 % CI: 1.00–3.71), adjusting for potentially confounding factors [118]. In this study, advanced stage of cancer, chemotherapy, and radiation therapy were independently associated with the increased risk of arm lymphedema. Others reported greater swelling in non-white women compared with non-Hispanic Whites [119, 120]. Arm lymphedema was studied in 494 African American and non-Hispanic White women with in situ to stage III-A primary breast cancer [32]. African Americans compared to non-Hispanic Whites had a higher prevalence of arm lymphedema (28 % vs. 21 %), but race was not significant in an analysis adjusted for obesity and hypertension [32]. This study also revealed that comorbidities (i.e., hypertension), obesity, surgery, and receipt of chemotherapy were associated with developing lymphedema [32]. Moreover, there appears to be racial differences in the formal diagnoses of lymphedema. In a population-based study of 450 breast cancer survivors, African American women were significantly more likely to have undiagnosed lymphedema than breast cancer survivors of other racial/ethnicity groups (OR = 2.7, 95 % CI: 0.81–0.98) [121]. Additional research investigating the influence of race and ethnicity on lymphedema in other cancer populations is needed.

Quality of Life and Functional Health

Minority cancer survivors experience lower health-related quality of life (HRQOL) than non-Hispanic Whites. One study examined mental health-QOL and physical health-QOL outcomes among 248 African American and 244 non-Hispanic White cancer survivors with a history of breast, prostate, and colorectal cancers [122]. African Americans had significantly poorer mental health-QOL compared to non-Hispanic Whites, after adjusting for SES, clinical, and psychosocial factors. In this study, the authors reported that race moderated the effect of perceived social support, with African Americans reporting higher mental health-QOL if they had high social support.

African American breast cancer survivors report poorer physical functioning and general health, and poorer physical and social well-being compared to non-Hispanic White survivors [123, 124]. African Americans had lower HRQOL outcomes due to higher levels of stress and worry related to recurrence and financial concerns [125–127]. One study found that in a military health-care system, African American women with breast cancer exhibited more physical impairments ≥12 months post-surgery [117]. Fu and colleagues [128] reported that Hispanic women with stage 0-III breast cancer were more likely to report depression, chemotherapy-related symptoms, and pain-related symptoms compared to non-Hispanic Whites, each of which impact QOL. In a multiethnic sample of breast cancer survivors, Hispanic women reported the lowest HRQOL, such as higher physical and emotional burden and socio-ecologic strain, compared to other racial groups [129].

Studies also suggest that the type of treatment and stage of disease can impact QOL in prostate cancer survivors [130]. Palmer and colleagues [131] examined treatment decision making and post-treatment QOL scores among African American men recently treated for prostate cancer. African American prostate cancer survivors reported lower QOL scores for urinary incontinence, sexual function, and bother, but higher scores for bowel and hormonal functions [131]. Another study among prostate cancer survivors found that non-Hispanic Whites reported significantly greater QOL than African American and Hispanic men [132]. The relationship between ethnicity and QOL was partially mediated by SES, medical comorbidity, and health behaviors (e.g., sleep functioning and physical activity) [132]. A systematic review of the literature suggests that Hispanics report poorer mental, physical, and social QOL relative to non-Hispanics [133].

A study that examined differences in QOL in 182 non-Hispanic Whites and 98 Hispanic breast cancer survivors found that Hispanics reported significantly lower levels of total perceived social support and QOL compared to non-Hispanic Whites [134]. In a study that examined physical health and obesity in African Americans, Hispanic-Americans, Asian-Americans, and non-Hispanic White cancer survivors, racial and ethnic differences were identified, with African American and Hispanic-American survivors reporting significantly lower physical health scores compared to Asian-American and non-Hispanic White survivors [135]. In addition, African American survivors had the highest rates of obesity, which was associated with lower physical function scores compared to nonobese survivors [135].

Cancer-Related Fatigue

African American and Hispanic breast cancer survivors report high rates of cancer-related fatigue (CRF) and depression [119, 136]. When comparing African American breast cancer survivors with African American female controls, one study found that breast cancer survivors experience more CRF, worse hot flashes, and worse sleep quality [137]. Pain-related symptoms also were reported to be

much higher among Hispanic women and elderly women [119, 128]. Factors predicting clinically significant CRF include a BMI > 25 kg/m^2, weight gain, physical inactivity, and low physical functioning [60, 63]. In addition, the severity of fatigue symptoms is associated with increasing BMI [63]. There is a paucity of research on racial differences in CRF. One study examined CRF in African American and non-Hispanic White women, but did not find significant differences between the two groups [126]. Taken together, these findings highlight the important role of race/ethnicity and obesity on poorer HRQOL in cancer survivors, which strongly suggests the need to elucidate the mechanisms leading to poorer HRQOL outcomes in racially and ethnically diverse obese populations, as well as research to examine persistent CRF disparities among racial/ethnic groups.

Peripheral Neuropathy and Cardiotoxicity

Few studies are found in the literature that examined racial differences in peripheral neuropathy and cardiotoxicity among cancer patients. Gewandter et al. [138] studied self-reported chemotherapy-induced peripheral neuropathy (CIPN) in 421 cancer survivors participating in a phase III randomized clinical trial. The authors reported that factors associated with functional impairment included non-white race and greater motor neuropathy scores. Hasan and colleagues conducted a retrospective study of African American patient records to examine cardiotoxicity from doxorubicin-based therapy from 1997–2001 [139]. The investigators found a dose-dependent increase risk of cardiotoxicity in this patient population [139]. Another study reported that low to moderate doses of anthracycline-based chemotherapeutic agents were associated with subclinical abnormalities of cardiovascular function, irrespective of race in patients with breast cancer or a hematologic malignancy [140]. However, one study reported slightly higher trastuzumab-associated cardiac safety events among African Americans (10.9 vs. 7.9) compared to non-Hispanic Whites [86]. Research is needed to examine racial/ethnic differences for peripheral neuropathy and cardiotoxicity related to cancer treatments.

Race/Ethnicity and Economic Impact of Survivorship

Improvements in cancer therapy have led to increases in the cost of treatment, often causing a financial burden for patients and their families. To address this issue, the American Society of Clinical Oncology (ASCO) Cost of Care Task Force developed a Guidance Statement on the Cost of Cancer Care to highlight salient issues to clinicians, provide recommendations, and to identify relevant policy issues [141]. The financial burden associated with treatment is compounded by inadequate insurance coverage, job loss, or the inability to work, as well as higher insurance premiums.

A reported consequence of treatment in breast cancer survivors includes changes in motivation to work, productivity and quality of work, and missed days of work [142]. Racial/ethnicity disparities add another layer of complexity to the cost of treatment. African American and Hispanic survivors who are more often uninsured or receiving Medicaid are likely to present with advanced-stage cancer at diagnosis, live in areas with lower high school graduation rates, and have lower median incomes [143]. As a result of their diagnoses, survivors report increases in insurance premiums at 3 and 6 months from baseline [142].

Private insurance and managed care payer status is associated with improved 5-year overall survival compared to patients with Medicaid, Medicare, or were uninsured/self-pay [144]. For example, African American men with prostate cancer, who tend to receive care from hospitals with higher proportions of African Americans and higher Medicaid admissions, have lower rates of definitive treatment [145], which can impact survival.

Job loss also has been associated with receiving chemotherapy, comorbidities, and a lack of employment support (e.g., paid sick leave and flexible schedules). To illustrate, African American and Hispanic women are more likely to stop working or lose their jobs when compared with non-Hispanic Whites after a cancer diagnosis and during treatment [146, 147]. One study reported that Hispanic women had the highest prevalence of job loss (24.1 %) compared to African Americans (10.1 %), and non-Hispanic Whites (6.9 %) [147]. Another study showed that African American women compared with non-Hispanic White women are more than twice as likely to lose a job due to their diagnoses (6.6 % vs. 2.7 %) [148] and have difficulty paying bills [147].

Race/ethnicity is associated with a higher proportion of income spent on out-of-pocket health-care costs. African Americans often reside in households with a yearly median household income $<$ \$35,000, which is negatively associated with lower likelihood of receiving proper treatment and worse survival [144]. Minority breast cancer survivors with yearly incomes $\leq$ \$20,000 and between \$20,001 and \$40,000 have higher out-of-pocket costs compared with non-Hispanic Whites, 31.4 % versus 12.6 % and 19.5 % versus 8.7 %, respectively [148]. In addition, African Americans are more likely to receive chemotherapy than non-Hispanic White cancer survivors and the cost of chemotherapy treatment significantly impacts the proportion of out-of-pocket costs compared to women not receiving chemotherapy [149]. When examining costs associated with prostate cancer care, African Americans have both higher and incremental costs compared to non-Hispanic Whites [150].

Interaction of Obesity and Race/Ethnicity for Outcomes After a Cancer Diagnosis

Little is known about racial and ethnic differences and obesity's impact on cancer survivorship. Complex theories, models, and frameworks have been developed, and studies have been conducted to try and link the combined influence of race and obesity on cancer survivorship. While incremental progress has been made, the current status of the literature has addressed only fragments of the framework in Fig. 4.1. For example, studies have analyzed underlying social and physical determinants such as the influence of nativity and neighborhoods [151] on cancer survivorship without addressing the impact of obesity. Other studies have considered the impact of obesity [152] or comorbidities [153, 154] on cancer survivorship, but have looked in depth at more distal determinants. What is known is mostly specific to breast cancer, and even there, some of the research findings are inconsistent.

Three large multiethnic cohort studies illustrate this variation. Conroy et al., in a multiethnic prospective cohort study of African American, Native Hawaiian, Japanese American, Latino, and Caucasian women, examined the relationship between self-reported, pre-diagnostic BMI (body mass index (BMI) (weight (kg)/height $(m)^2$) and breast cancer survival [152]. Additionally, they examined whether the association between BMI and risk for breast cancer-specific mortality varied by ethnicity. The study found that while obese women had a modest increased risk of breast cancer-specific mortality, ethnic-specific trends were inconclusive [2]. For example, they found that obese women (BMI ≥ 30 kg/m^2) relative to women of high-normal weight (BMI 25.0–29.9 kg/m^2) had a higher risk of breast cancer-specific mortality (HR = 1.45; 95 % CI: 1.05, 2.00), across all ethnic groups except Native Hawaiian. Though ethnic-specific trends were inconclusive, obese Caucasian and Japanese American women had a slightly elevated risk of breast cancer-specific mortality compared with other ethnic groups [152].

Two more recent studies have moved closer to accurately representing the complex relationship between race/ethnicity, obesity, and cancer survivorship by including demographics and lifestyle factors on a larger number of ethnically diverse groups. The California Breast Cancer Survivorship Consortium (CBCSC) combined self-reported interview data regarding demographics and lifestyle factors (e.g., family history of breast cancer, parity, smoking, alcohol consumption) from six California-based breast-cancer epidemiologic studies with amassed cancer registry data on clinical characteristics and mortality [155]. Between 1993 and 2007, a multiethnic cohort of 12,210 women (6,501 non-Latina Whites, 2,060 African Americans, 2,032 Latinas, 1,505 Asian Americans, and 112 other race/ethnicity) were diagnosed with breast cancer. African Americans had higher rates of breast cancer-specific mortality compared with non-Latina Whites (HR = 1.13; 95 % CI: 0.97, 1.33). But, the breast cancer-specific mortality rates in Latinas (HR = 0.84; 95 % CI: 0.70, 1.00) and Asian Americans (HR = 0.60; 95 % CI: 0.37, 0.97) were lower than in non-Latina Whites. In a separate study, and in contrast to

findings from the aforementioned CBCSC paper, Kwan et al. further investigated these disparities in survival outcomes by race/ethnicity, accounting for obesity status, and found ethnic variation [156]. Kwan et al. evaluated the association between body size measurements (BMI and waist–hip ratio (WHR)) and breast cancer-specific mortality after breast cancer diagnosis by race/ethnicity using data from questionnaires and the California Cancer Registry between 1993 and 2007, with follow-up through 2009. In the data, 11,351 breast cancer patients were identified. Compared with normal weight (BMI = 18.5–24.9), morbid obesity (BMI $\geq$ 40) was associated with having an increased risk of breast cancer mortality in non-Latina Whites (HR = 1.43, 95 % CI: 0.84, 2.43) and in Latinas (HR = 2.26, 95 % CI: 1.23, 4.15), though these differences were not statistically significant. No BMI–mortality associations were present in African Americans or Asian Americans. High WHR was associated with breast cancer mortality in Asian Americans (HR = 2.21, 95 % CI: 1.21, 4.03; p for trend = 0.01), but no associations were seen in African Americans, Latinas, or non-Latina Whites. This study demonstrates that obesity and body fat distribution impact cancer survivorship, and this association varies by race/ethnicity. While this study allowed for comparisons of some important determinants in the feedback loop of disparities in cancer survivorship outcomes within and across multiple racial/ethnic groups, additional studies are needed to understand why degree of obesity or body fat distribution at breast cancer diagnosis differentially affects cancer survivorship by race/ethnicity [156].

Due to the limited and incomplete evidence available on the biological-environmental interactions of race/ethnicity, obesity, and cancer survivorship, we draw from evidence of these interactions for predicting other, more well-known health outcomes (i.e., heart disease) to learn and speculate about the significance of these factors to outcomes among cancer survivors. Similar to cancer survivorship, patterns of cardiovascular disease (CVD) and mortality vary by race/ethnicity even after controlling for established risk factors for poor prognosis [157, 158]. In a more recent prospective multiethnic cohort study of adult men and women living in Hawaii and California, Henderson et al. examined the mortality rates from acute myocardial infarction and other heart disease in five racial groups—African American, Native Hawaiians, Japanese Americans, Latinos, and Whites—to investigate whether the observed differences in CVD mortality could be explained by differences in the prevalence of established CVD risk factors [159]. Relative risks for mortality were calculated accounting for established CVD risk factors (BMI, hypertension, diabetes, smoking, alcohol consumption, physical activity, education level, diet, and factors specific to women including type and age at menopause and hormone replacement therapy use), and the authors found that these risk factors explained a large portion of the racial and ethnic variation in risk for acute myocardial infarction and other heart disease mortality. The authors suggested that the unexplained excess risk of mortality in African American women and Native Hawaiians, and the lower than expected risk of mortality in Japanese-Americans and Latinos, compared with Whites, are due to unequal distributions of unmeasured factors: environmental, social or cultural, and genetic risk [159].

The studies reviewed here explore the connections between different ethnic groups and covariates of interest, such as reproductive, lifestyle, sociodemographic, and other cancer-specific (or cardiovascular-specific) risk factors. Additionally, the authors speculate about ways we could improve studies to better understand the impact of obesity on the racial/ethnic variation on risk of mortality. Conroy et al. suggested that larger sample sizes of ethnically diverse groups are needed to definitively evaluate ethnic-specific trends in mortality [152]. Kwan et al. suggested that multiple measurements of obesity are needed to better understand the racial/ethnic differences in body composition and mortality [156]. And Henderson et al. alluded to the significance of unmeasured environmental factors, social or cultural factors, and genetic risk factors [159], which is also recommended in Fig. 4.1 [6]. It might also be true that our theoretical models have advanced far beyond the methodologies being employed [160]. If this is the case, further advances in methodology might be needed to analyze data with complex patterns of variability, especially nested sources of variability [160] as suggested by Fig. 4.1 [6], in order to identify the interactions of combined influences of race/ethnicity, obesity, and cancer survivorship.

The studies reviewed in both cancer and cardiovascular disease strongly suggest that social environmental and cultural factors that have heretofore not been included in analyses might help to explain why degree of obesity or body fat distribution differentially affects cancer survivorship by race/ethnicity. A number of social and cultural factors have been posited to explain differences by race/ethnicity in the USA. We know for example that racial and ethnic minorities are more likely than non-Hispanic Whites to live in poverty [161]. The poverty rate in non-Hispanic Whites was 9.9 % in 2010, compared to 27.4 % and 26.6 % for African Americans and Hispanics, respectively [161].

Poverty and geographic location predispose racial and ethnic minorities to consume foods that are less healthful and more obesogenic. A number of studies have found that lower SES and predominantly African American neighborhoods have fewer supermarkets, more fast-food restaurants, and lower access to fresh fruits and vegetables [162, 163]. Likewise, the nature of the built environment in lower socioeconomic and predominantly African American neighborhoods impedes physical activity [164].

Racial and ethnic minorities may also experience a disproportionate burden of cancer health-care expenditures by virtue of their higher rates of obesity-related comorbid conditions and higher rates of poverty. These comorbidities may pose further limits to physical activity, as well as limits on treatment options for cancer [165]. In addition, the added costs of treating comorbid conditions such as heart disease likely influence decisions and timing to seek treatment among racial and ethnic minorities, resulting in decreased survivorship.

The Affordable Care Act (ACA), through its provisions for expanded health-care coverage for persons living below the federal poverty line through the expansion of Medicaid coverage, increased attention to the social determinants of health through its newly established Prevention and Public Health Fund, and increased linkage to community services holds promise for decreasing cancer disparities by race and

ethnicity. Increasing access to treatment should decrease the disproportionate burden of cancer care among racial and ethnic minorities and ensure that social and culture components of health are better attended to by moving the focus of treatment from acute care to community settings. One billion new dollars will become available between Fiscal Year 2012 and Fiscal Year 2017 through the Prevention and Public Health Fund, which can be used to implement community programs to address obesity. Some of these funds are targeted specifically to Medicaid beneficiaries to implement, evaluate, and disseminate preventive health activities through community transformation grants.

Future Directions and Summary

Intervention dollars for reducing the burden of cancer are limited. To make best use of these dollars, it is important that intervention efforts be used as efficiently as possible. Unpacking the complexities of the relationships of obesity, race/ethnicity, and cancer will enable interventions to reduce the burden of cancer to be most effective. We have presented empirical evidence supporting a role for both obesity and race/ethnicity for outcomes after a cancer diagnosis. Further, evidence from heart disease has been used to speculate that upstream influences such as poverty, unavailability of healthy food and low access to physical activity may underlie the combined influence of race/ethnicity and obesity on cancer health disparities. Additional observational research may assist with further clarifying intervention targets, particularly if large multiethnic cohorts can be assembled to clarify remaining questions regarding the independent and interactive roles of obesity and race/ethnicity on the burden of cancer survivorship. Interventions to reduce racial and ethnic disparities among cancer survivors could be targeted upstream, toward addressing poverty, access to health care, and access to healthy foods and physical activity. Concurrently, downstream interventions that are both effective and feasible for improving the length and quality of cancer survival across BMI and racial and ethnic categories also need to be evaluated, perhaps in the context of the rollout of the Affordable Care Act and the Prevention and Public Health Fund. It can be noted that the majority of cancer survivorship interventions focus on Caucasian survivors, so establishing effectiveness and feasibility among racially diverse populations with a broad range of BMI profiles would helpful, given the increasing diversity of the US population.

In summary, the USA has become more racially and ethnically diverse during the same decades in which we have also experienced a sharp rise in obesity prevalence. Obesity prevalence is strongly correlated with race and ethnicity. It is possible that the disparities in cancer survivorship noted by race and ethnicity are due, in part, to differences in obesity. Obesity may be a marker for upstream influences on cancer survivorship such as economic and health access differences by race and ethnicity. It is speculated that obesity contributes to disparities for cancer survivorship outcomes through upstream influences such as poverty and

access to health care and lifestyle interventions. Both upstream (system level) and downstream (individual level) interventions for obesity can be better targeted to be effective and feasible to improve outcomes in cancer survivors across a broad spectrum of BMI levels and racial and ethnic groups.

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Chapter 5
The Biology of Aging: Role in Cancer, Metabolic Dysfunction, and Health Disparities

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Abstract Aging is the primary cause of the majority of chronic diseases and disabling conditions. However, some individuals depart from the recognized patterns. Certain "at-risk" or "frail" individuals demonstrate premature aging, with increased cellular senescence, inflammation, early onset of diabetes, cardiovascular disease and cancer, and reductions in the ability to perform activities of daily living; whereas other "protected" or "fit" individuals appear to undergo a protracted period of health despite increasing years, remaining physically active senior citizens without chronic pain, disability, or frailty. Significant effort is being expended to understand this spectrum of aging phenotypes, with the goal of identifying the most important interventions or preventive steps that will preserve a "healthy aging" that maximizes lifespan without pain and chronic problems. We discuss health disparities that influence unhealthy aging, with a focus on interacting mechanisms in cancer, inflammation, and obesity.

Keywords Aging • Disparities • Cancer • Energy balance • Inflammation • Insulin resistance • Senescence

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The Scope of Unhealthy Aging as a Public Health Issue

When sapless age and weak unable limbs
Should bring thy father to his drooping chair. *William Shakespeare. Henry VI, Part I*

The depredations and pains of aging have been apparent to all societies since humans developed agriculture. In the shift from hunter-gatherer cultures to agrarian, pastoral cultures, humans reduced their risk of early mortality from causes related to war, wounding during a nomadic hunt, and starvation or exposure to harsh weather. These developments allowed humans to live long enough to manifest the familiar health consequences of aging, including frailty, osteoporosis, dementia, cancer, and a variety of other chronic diseases. Frailty in the elderly has been defined as the presence of three or more of the following: reduced walking speed, self-reported exhaustion, poor grip strength, recent weight loss, and low levels of physical activity [66]. However, even in ancient societies, there are recorded differences in the ways in which people experienced these complications of old age, with some men and women avoiding long, gradual chronic declines in mobility and strength, maintaining active and healthy lives until just before a natural death. Attention has long centered on the question of how to "live well" and to preserve faculties for as long as possible. For example, much folk wisdom has accumulated about how to best preserve cognitive function during aging, but trustworthy recommendations and mechanism remain obscure. Without such mechanism, the development of rational therapy for cognitive decline will be difficult or impossible. Recent commentary has drawn a distinction between "lifespan" and "health span." In this chapter, we will explore new areas of research that seek to define the factors that preserve health span, and discuss preventive and treatment strategies for aging to maximize health in diverse activities of daily living among the elderly. After delineating the scope of the problem of unhealthy aging, we will discuss six topic areas: cancer as a disease of aging; age-related changes in body composition; inflammatory mechanisms and aging; obesity, inflammation, and cancer in unhealthy aging; social determinants of healthy and unhealthy aging; and therapeutic opportunities including several behavioral strategies.

The medical significance and urgency of this research is apparent when we consider the number of older Americans and their growing representation in the population. The US Centers for Disease Control, in its report The State of Aging and Health in America 2013, noted that the number of Americans aged 65 years or older will double during the next 25 years to about 72 million individuals. By 2030, older adults will account for 20 % of the US population [34]. Between 2000 and 2011, many Southern and Western US states experienced a significant increase in their population aged 65 years and older (Fig. 5.1). Among the Western states, Nevada experienced the largest percentage increase (53.1 %), followed by Arizona (37.3 %), Idaho (37.28 %), Colorado (37.23 %), Utah (35.28 %), New Mexico (32.61 %), Texas (30.21 %), and Washington (30.15 %). Nationally, most of these older Americans (81 %) live in cities, a geographic distribution that has implications for disparities in physical activity and interactions with the built environment.

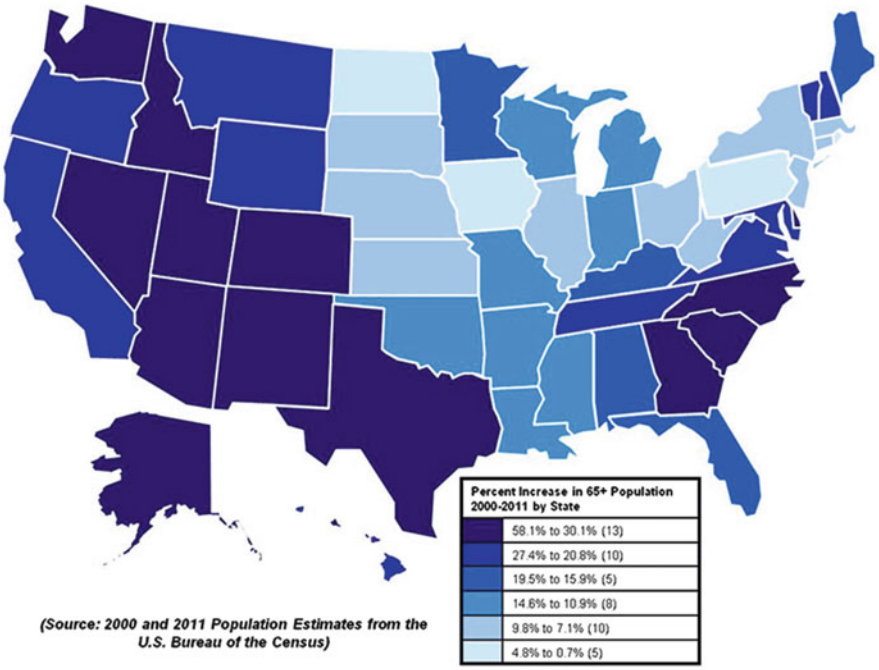

Fig. 5.1 Percent increase in number of Americans aged 65 years from 2000 to 2011. Data were obtained from: http://www.aoa.gov/Aging_Statistics/Profile/2012/8.aspx

Multiple chronic diseases are associated with aging, and the health care costs arising from this increased number of older adults will have a significant economic impact. Recent data from the Administration on Aging of the US Department of Health and Human Services has been used to compile a portrait of older Americans (aged 65 years and older) and issues of quality of life and health that affect them (Fig. 5.2). Disability of some kind was reported by 35 % of males and 38 % of females in 2011. Respondents that were institutionalized were excluded from the sample.

The historical lack of comprehensive health care for aging Americans and their expected chronic morbidities greatly complicates the economics and public policy issues. Without improvements in preventive medicine, such as reductions in obesity, smoking, alcohol abuse, and physical inactivity, it has been estimated that the major chronic diseases of "unhealthy aging" will accrue a cumulative economic impact of $1.6 trillion between 2007 and 2023 [47]. Multiple chronic conditions in older Americans include arthritis, asthma, chronic respiratory conditions, diabetes, heart disease, human immunodeficiency virus infection and hypertension [178], as well as some kinds of cancer. The prevalence of these conditions as comorbidities also increases with age [182, 191]. Significantly, some combinations of conditions, or clusters, of chronic conditions have synergistic interactions, but others do not

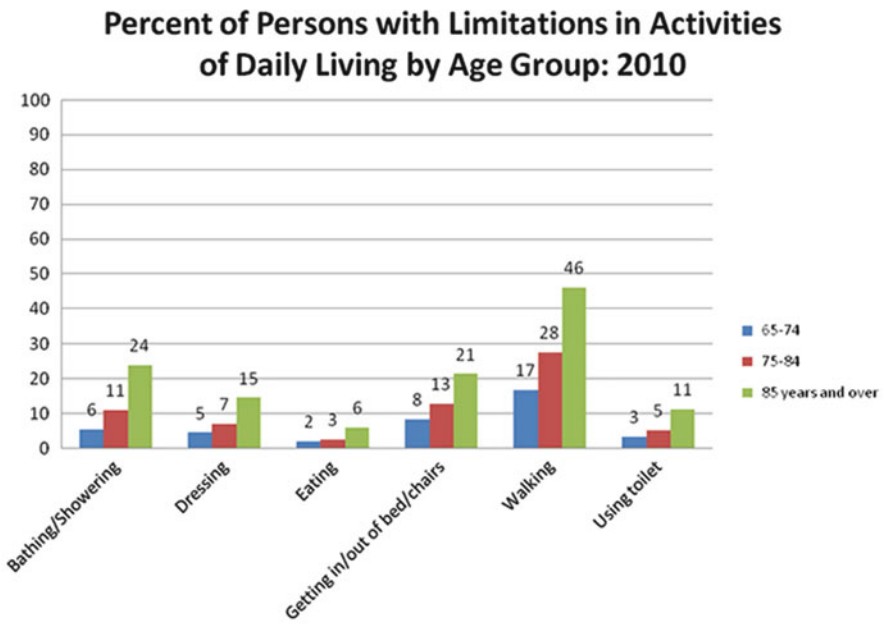

Fig. 5.2 Percent of Americans aged 65 years and older with limitations in activities of daily living, by age group in 2010. Data were obtained from: http://www.aoa.gov/Aging_Statistics/Profile/2012/16.aspx

[177]. It is also troubling that combinations of such chronic comorbidities are also characteristic of, and exacerbated by, unhealthy aging and frailty [178]. Consideration of underlying mechanism and the most effective intervention and prevention strategies is urgently required during this unfortunate era of declining public health expenditure and increasing disparities in health care delivery, because failures of political will and inadequate fiscal planning for anticipated increases in multiple chronic diseases in the aging US population will guarantee increased suffering and avoidable early mortality among older Americans. Discredited economic "austerity" policies in European, Latin American, and Asian economies that drastically curtail spending on health care for the elderly ensure that this pain will be global. No political excuse for inaction, or worse, the slashing of public health care spending, is acceptable when we have adequate scientific and medical knowledge to create cost-effective interventions now that will greatly improve this dire situation.

Cancer as a Disease of Aging

Molecular studies have provided a convincing link between the normal production of oxidative radicals (superoxide, hydroxyl radical and hydrogen peroxide), DNA damage in somatic cells, and gradually accumulating error in the genomic DNA of

those cells that is improperly repaired. These accumulated errors have long been thought to be a primary cause of the molecular and cellular phenotypes we associate with unhealthy aging, including mutations linked to cancer [3]. These results have supported a rationale to recommend the consumption of dietary antioxidants to prevent aging and cancer. It is problematic that the postulated mechanisms are not sufficient to explain diverse cancers of childhood, which are in any case beyond the scope of this chapter.

Genetic and genomic instability is a well-recognized feature of cancer, and chromosomal abnormalities are thought to accumulate when mitotic checkpoints, as well as the machinery that enable proper chromosome segregation at mitosis, begin to fail. The resultant aneuploidy has been linked to aging in the case of increased risk of trisomy associated with female reproductive aging [145]. Instability in chromosome integrity and number has been suggested to be a general characteristic of aging [11], which may also help explain the rise in cancers with age in humans as mitotic regulation declines.

Additional research has developed links between mechanisms of senescence and aging. There is now a convincing body of evidence that cellular senescence is a fundamental mechanism of aging (reviewed in [148, 175]). Senescent cells have lost the ability to divide in response to stimuli that increase the risk of malignant transformation [117]. Senescence is a process that was selected through evolution to assure early life fitness by protection from cancer, but has unselected and undesirable consequences later in life. This evolutionary theme is referred to as *antagonistic pleiotropy*.

Senescence is sometimes considered to be a somatic defense mechanism against the oncogenic risks of mitosis [38]. Once a somatic cell has exited the cell cycle into a permanent post-mitotic state, the risks of genetic errors and mutations through DNA replication are ablated. Failures of function among cell cycle checkpoint proteins, such as p53, which has been famously termed the principal "gatekeeper" of genomic integrity [125], have implications for apoptosis and senescence. Deletion or functional inactivation of p53 and other tumor suppressor proteins is a hallmark of many cancers. The p53 protein has been shown to interact with a number of important transcription factors and co-regulators, including BRD7 [51], which possesses a bromodomain motif that recognizes motifs possessing acetylated lysine residues in proteins. The BRD7 protein also interacts with other tumor suppressor proteins such as BRCA1 [76]. The BRD family of proteins, a newly described group of chromatin-binding transcriptional co-regulators, has raised the profile of epigenetic mechanisms in the control of cancer [43, 17], senescence, apoptosis, and aging.

In addition to mitogenic signals, age-related DNA damage and mutations, telomere shortening, protein aggregation, and increased concentrations of reactive oxygen species also promote senescence [98, 116, 167]. As a result, the abundance of senescent cells increases in multiple tissues with advancing age [78, 154, 175, 183]. These cells secrete numerous biologically active molecules that are collectively referred to as the *senescence-associated secretory phenotype*, or SASP. Cytokines are an abundant component of the SASP and implicate senescent cells in the

etiology of age-related inflammation. Cytokines and other components of the SASP, including growth factors and proteinases, disturb tissue architecture and perturb the functionality of neighboring cells [33]. Ultimately, these events culminate in tissue dysfunction and age-related pathologies.

Recent data suggest that elimination of senescent cells from a mouse model of accelerated aging delays the onset of multiple age-related phenotypes, including cataracts, muscle loss, lordokyphosis, and reduced physical performance [10]. The extent to which cellular senescence and the SASP underlie cancer, diabetes, atherosclerosis, frailty, and other age-related conditions in the context of conventional aging is an important area for investigation. It is tempting to speculate that interventions to prevent the accumulation of senescent cells or suppress the SASP would extend health span and compress late-life morbidity, and that interventions to augment the clearance of senescent cells would retard the progression of age-related conditions and associated disabilities. Disparities related to senescence-associated complications of aging have not been extensively studied. Potentially, lifestyle choices related to nutrition, physical activity, tobacco, and alcohol could affect the accumulation and clearance of senescent cells.

Age-Related Changes in Body Composition

In humans, aging is characterized by increased adiposity, which typically develops between the third and seventh decades of life. This phenotype is further exaggerated by the age-related decline in subcutaneous adipose tissue, leading to a redistribution of fat to the intra-abdominal region and ectopically in tissues such as skeletal muscle, bone marrow, and liver [61]. These unfavorable changes in body fat distribution, and particularly visceral fat accretion, have been found to predict more strongly all-cause [22, 94, 159] and disease-specific mortality risk [108] than measures of general obesity, such as body mass index (BMI). Indeed, studies in humans utilizing either imaging techniques (i.e., X-ray computed tomography and magnetic resonance imaging) or other anthropometric approaches to estimate intra-abdominal fat, such as waist-to-hip ratio, have found that estimates of abdominal obesity are a strong and independent predictor of several site-specific cancers, including colon [103, 140], esophageal [166], liver [153], and prostate [147]. For example, Moore et al. [140] found that waist circumference (a good measure of visceral fat accumulation) was a stronger predictor of colon cancer risk than BMI in both middle aged (30–54 years old) and older men and women (55–79 years old).

The underlying pathophysiology that links visceral adiposity to increased cancer risk and mortality is not entirely clear, but is likely to be multifactorial [90]. Visceral fat has been closely linked to the development of insulin resistance, dyslipidemias, and subsequent risk for type 2 diabetes, cardiovascular disease, and stroke [87]. Likewise, insulin resistance, which results in hyperinsulinemia, is also thought to promote cancer development due to the proliferative potential of insulin, and by suppressing circulating insulin-like growth factor (IGF) BP-1 and IGFBP-2 levels,

leading to greater bioavailable circulating IGF-1. Visceral adipose tissue is also biologically distinct from other fat depots. In rodents, which demonstrate many of the metabolic manifestations of aging observed in humans, visceral fat has a more exaggerated gene expression profile and secretory capacity of cytokines and chemokines than other fat depots, including greater leptin, tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, IL-18, and plasminogen activation inhibitor-1 expression [9], which can be further provoked by nutrients [53–55].

Aged adipose tissue has also been shown to harbor a significant number of senescent cells [10], which can result in SASP as discussed above. Remarkably, selective clearance of p16Ink4a-expressing cells in mice, many of which were found in adipose tissue, delayed the onset of age-related pathologies [10]. Likewise, surgical removal of visceral fat in rodents has been shown to improve lifespan [143] and protect against the development of intestinal tumors [88]. Thus, given the close association between inflammation and diseases of aging (discussed in more detail below), the chronic, low-grade, pro-inflammatory state, which is associated with age-related visceral fat accretion and accumulation of senescent cells in fat, could be an important mechanism linking aging and obesity with aging and cancer risk.

Whereas the relationship between general and abdominal obesity and disease during middle and late-middle age has been clear, there has been some confusion regarding the role of excess adiposity in older adults with some studies showing a negative effect, no effect, or even a protective effect of fat mass. One important consideration when examining older adults is that many people at advanced ages are in fact abdominally obese, with greater ectopic fat stores, despite a seemingly normal BMI, a phenomena that can decrease the utility of BMI as a predictor of disease risk in older adults [165]. Furthermore, one must exercise caution when examining this relationship at advanced ages due to confounding, including the decline in fat mass that often coincides with late-life illness and disease. However, in weight-stable adults >75 years of age, higher BMI is predictive of greater mortality risk, and this relationship is stronger in males than females [165]. The nature and mechanisms of disparities in visceral fat deposition among older adults are insufficiently studied.

Sarcopenia, the age-related decline in muscle quantity and quality, represents a second major change in body composition commonly observed with aging [29]. The causes of sarcopenia are multifactorial, but the pro-inflammatory state associated with aging and obesity appears to contribute to the decline in skeletal muscle mass and function [29]. The loss of skeletal muscle mass with age has broad health implications, including a decline in physical function, onset of frailty, and increased disability among older adults [56]. Skeletal muscle is also a major site of glucose disposal in humans, and sarcopenia has been linked to insulin resistance [105], which can contribute to a more rapid onset of many other age-related diseases, including cancer. Furthermore, worsened insulin sensitivity in muscle is believed to contribute to the decline in skeletal muscle function, reduced protein synthesis rates, and accelerated skeletal muscle loss [120], placing insulin resistance in a vicious cycle of skeletal muscle decline and metabolic dysfunction.

Although it is not difficult to envision how age-related changes in skeletal muscle mass and function could contribute indirectly to cancer risk and other diseases, recent evidence has uncovered a possible direct role whereby skeletal muscle could modulate cancer risk. Specifically, similar to adipose tissue, skeletal muscle is now recognized as an endocrine organ, due to the secretion of numerous myokines, such as brain-derived neurotrophic factor, IL-6, and irisin, among others, in response to contraction [157, 179]. Indeed, Aoi et al. recently identified a novel myokine, secreted protein acidic and rich in cysteine (SPARC), which is secreted from skeletal muscle in response to exercise, has pro-apoptotic effects, and is necessary for the inhibition of intestinal tumorigenesis with exercise in mice [6]. Thus, sarcopenia along with reduced physical activity with age could lead to declines in myokines, such as SPARC [146], and embody an important link between skeletal muscle, aging, and cancer. Thus, visceral fat accrual and loss of skeletal muscle mass with aging represent two major phenotypic changes in humans that can predispose older adults to carcinogenesis. The mechanism (s) linking these shifts in body composition to cancer risk are not entirely known, but are likely multifaceted, encompassing both direct and indirect effects.

Inflammatory Mechanisms and Aging

It is widely appreciated that human aging is usually associated with an increase in the number and gravity of different chronic conditions that affect the geriatric individual. Similar patterns have been observed in rodent models of aging. Recent commentary has focused on prevention and treatment to reduce the number and severity of these conditions, thereby maximizing the length of time a healthy and active individual enjoys before death, and minimizing the end-stage conditions and interval that immediately precede natural death. Rapid, steep decline can be considered to be an aging ideal for humans. But which processes matter most? Which diseases are the most debilitating and what are the mechanisms that converge to create “comorbidities of aging”? What are the critical environmental and population factors that influence disparities among older adults? Do we have sufficient evidence to recommend priorities for geriatric patients that will have the greatest benefit to preserve daily functioning?

Preliminary and published evidence from our laboratories suggests that persistent, sterile, unresolved, chronic inflammation is one of the central causes of “unhealthy” aging that is associated with an increased number and severity of comorbidities, particularly cancer and type 2 diabetes. The immune system, in both its innate and adaptive arms, helps regulate all organ systems and controls responses to diverse exposures. We have discussed hypotheses that low-level, long-lasting inflammation may account for several comorbidities that affect apparently unrelated organ systems [43]. Low grade, sterile inflammation has been implicated in the specific features of frailty associated with aging in humans [58, 102, 123, 185]. Elevated levels in blood of pro-inflammatory cytokines, such as IL-6 and markers

of monocyte activation, have been linked to frailty in geriatric patients [39, 99]. Furthermore, the premature aging phenotypes associated with persistent Human Immunodeficiency Virus (HIV) infection have been linked to chronic inflammation [8, 155, 192, 193]. As discussed above, the role of chronic, sterile inflammation in aging phenotypes has been reviewed recently and associated with senescence [148, 175].

Several animal models have also identified systemic inflammation as a culprit in pathologies associated with aging. For example, very recent work [28] has shown that inflammasome hyperactivity causes aging mice to develop systemic inflammation (neutrophilia, elevated leukocyte counts, splenomegaly, and leukocytosis of organs that are dependent on IL-1β and IL-18 for different stages of pathology). Additional animal models to probe these mechanisms are urgently needed.

Most seriously from the point of view of mortality risk, an aged immune system is less able to develop a robust response of adaptive immune to influenza immunization. During 1976–2007, estimates of annual influenza-associated deaths from respiratory and circulatory causes (including pneumonia and influenza causes) ranged from 3,349 in 1986–1987 to 48,614 in 2003–2004; approximately 90 % of influenza-associated deaths occur among adults aged ≥65 years [176]. Furthermore, seasonal influenza is implicated in excess mortality from cardiovascular diseases, stroke, diabetes, and pneumonia in older adults [134].

Diminished T cell function may offer a critical mechanism that links increased vulnerability to virus infection and decreased immune surveillance of cryptic cancers in geriatric patients. Specifically, thymic involution with age, dramatic decreases in naïve and memory T cell populations, and reduced numbers of $CD8^+$ T cells that infiltrate tumors, support a tolerogenic environment in which tumors grow well [128]. An increased ratio of anergic or functionally defective T cells to competent T cells in peripheral tissues could cause the tasks of tumor surveillance to fail in geriatric patients. Insufficient tumor surveillance in the aging individual opens the door to tumor growth and progression; thus cancers are indeed properly considered a disease of aging. In support of this idea, research in mouse models has shown that failure of immune surveillance of premalignant, senescent hepatocytes, which are normally cleared by $CD4^+$ T cells, leads to development of hepatocellular carcinomas [104]. Additional evidence points to declines in anti-inflammatory cytokines (IL-10 and transforming growth factor (TGF)-β) and adipokines (particularly adiponectin) associated with aging phenotypes.

The greatly increased prevalence of obesity, which in its metabolic complications particularly affects older Americans, represents a grave new threat to the health of hundreds of millions of people worldwide, although the impact will be felt greatest in the USA [60]. Among adults, overweight (BMI ≥ 25.0–29.9), obesity (BMI ≥ 30.0–39.9), and morbid obesity (BMI ≥ 40.0) manifest progressively serious complications, including insulin resistance, hypertension, cardiovascular disease, and type 2 diabetes [72, 180]. The interaction among obesity, chronic inflammation in insulin resistance, and inflammation-associated complications of aging define an important health disparity among older adults, as discussed below.

Many chronic inflammatory diseases of aging appear to be linked through abnormal metabolism. Some of the most significant examples are metabolic syndrome and type 2 diabetes, which are associated with glucose intolerance and insulin-resistant obesity that greatly increase in prevalence among older adults. Insulin resistance, metabolic syndrome, and type 2 diabetes are properly considered as diseases of unresolved chronic inflammation [149]. Obese, metabolically abnormal patients exhibit serum profiles characterized by elevated concentrations of pro-inflammatory cytokines (e.g., IL-1β, TNF-α, IL-6, IL-12, IL-18) [115], as well as acute phase proteins, such as C-reactive protein (CRP) [101], and decreased concentrations of anti-inflammatory, cardioprotective adipokines (e.g., high molecular weight adiponectin). This kind of chronic inflammation is both systemic [14, 27] and local, in white adipose tissue. Insulin-resistant adipose tissue, particularly in the visceral fat depots discussed above, is infiltrated by pro-inflammatory $CD68^+$ macrophages that produce TNF-α, which has long been known to induce insulin resistance in adipocytes directly [84]. These cellular and molecular features have been observed both in humans and in rodent models of obesity [188, 194], and affect T cell function [111].

Furthermore, type 2 diabetes in adult humans is associated with an increased ratio of pro- to anti-inflammatory T cells in peripheral blood [96]. B cells from adult type 2 diabetes patients, unlike B cells from nondiabetic donor controls, fail to secrete the generally anti-inflammatory cytokine IL-10 in response to stimulation through various Toll-Like Receptors [95]. Finally, new results have shown that B cells likely play a pathogenic role by promoting polarization of T cells towards increased production of pro-inflammatory cytokines [42]. These factors can improve over time after intentional weight loss and treatment with anti-inflammatory drugs [149]. We have discussed these mechanisms and interrelationships in detail [45, 149]. However, these specific immune mechanisms have never been studied in geriatric adults, geriatric obese adults, or geriatric type 2 diabetic adults. It is reasonable to speculate that failures of T cell function and tumor surveillance, B cell function, or failures of anti-inflammatory homeostasis in the immune system combine in unfortunate ways with declining metabolic health, increasing obesity, declining physical activity, and increasing chronic inflammation, to promote many comorbidities of aging such as insulin resistance, obesity-associated cancers, and frailty.

Finally, identification of at-risk older adults, particularly vulnerable individuals who experience stigma or race-based, class-based disparities, is important to public health goals. We propose some possible relationships among inflammatory, metabolic, and stress status and the comorbidities of obesity that may affect health disparities (Fig. 5.3). It will be essential to identify and to quantify the most important relationships in order to evaluate the success of short-term and long-term interventions in clinical trials. These interdisciplinary issues are not well studied, nor are optimal interventions defined that would reverse the hypothesized clustering effect of inflammation and other stressors on the underlying chronic conditions.

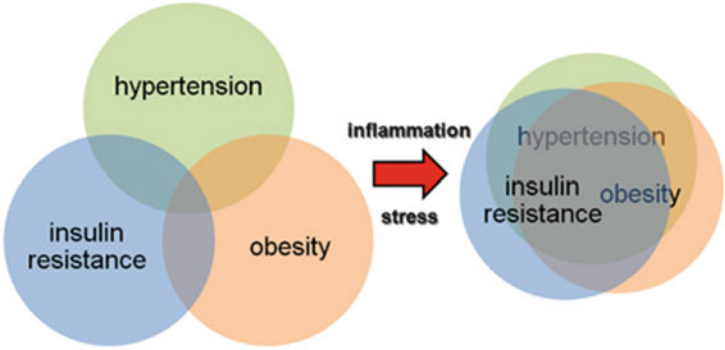

Fig. 5.3 Model for interactions among critical variables in aging: inflammatory, metabolic, and stress status. This scheme suggests testable hypotheses for how comorbidities might arise under conditions of "unhealthy aging" that compromise health span in older adults. Many conditions of aging do not occur in isolation; thus, single disease-focused therapies likely have limited utility to treat patients with complex and interacting diseases. The interacting problems can only be conceptualized properly from an interdisciplinary perspective

Obesity, Inflammation, and Cancer in Unhealthy Aging

As the obesity epidemic worsens, the incidence of cardiovascular disease, type 2 diabetes, and "obesity-associated cancer" is expected to increase. American Cancer Society epidemiologists first brought the problem of obesity-associated cancer to worldwide attention 10 years ago [30, 31]. Elevated levels of leptin, insulin, and IGF-1 found in obese, insulin-resistant patients have been linked to obesity-associated cancer [67, 70]. However, recent evidence suggests that, for certain obesity-associated cancers, metabolic status is important for risk, whereas insulin levels are not [100]. Abundant evidence also links unresolved, chronic inflammation to cancer [107], and more aggressive properties of tumor cells in insulin-resistant obesity [69, 91, 93]. Pro-inflammatory cytokines that are frequently elevated in "metabolically unhealthy" obesity, such as IL-6, are implicated in dangerous shifts in the properties of breast cancer cells [162, 172, 186]. Unresolved inflammation is independently associated with colon cancer in patients with inflammatory bowel diseases [114], which supports the idea that the inflammatory nature of insulin-resistant obesity is a critical mechanism that promotes certain obesity-associated cancers. Obesity-associated inflammation has been implicated in adverse outcomes in breast cancer in postmenopausal women, colon cancer in both men and women, and several other obesity-associated cancers. However, we do not yet know if specific cytokine and adipokine profiles are associated with increased risk for some obesity-associated cancers, but not others. Identification of these profiles is essential before targeted chemopreventive agents can be developed to supersede the broad-spectrum anti-inflammatory agents currently available.

Significantly, it appears that not all obesity conveys the same disease risks: recent data show that immunometabolic status stratifies cardiovascular disease risk in obesity [14, 74, 189]. For most subjects, as obesity increases, metabolic health declines. We have shown in animal models that inflammation [187] and the presence in adipose tissue of "crown-like structures" of CD68+, pro-inflammatory macrophages [36] are associated with metabolic status [44]. Similarly, in "metabolically abnormal" obese humans, crown-like structures in inflamed adipose tissue are associated with cardiovascular risk [7] and breast cancer risk [142].

Interestingly, there is an informative group of humans that appear to bend the rules of metabolism in obesity [46]. "Metabolically healthy but obese" persons [164], who account for about one quarter of obese adults, are overweight/obese but show relatively normal blood parameters [171] and are protected from cardiometabolic risk [20, 21]. They also lack crown-like structures in white adipose tissue [112]. The mechanistic relationship between cardiovascular risk and elevated insulin in obesity has been difficult to study because many factors, including inflammation, tend to co-vary in human subjects. The "metabolically healthy" obese phenotype may be useful to deconvolute some of the relevant variables. Cardiovascular risk in "metabolically healthy" obese women has been shown to be intermediate between lean and healthy women, and "metabolically abnormal" obese women [130]. Critically, "metabolically healthy" obese adults have diminished risks for cancer mortality compared to "metabolically abnormal" obese adults [32, 196]. Specific adipocyte [150, 151], adipose tissue distribution [184], and immunological features, particularly a reduced inflammatory profile [16, 44, 106, 113] and elevated adiponectin [1], separate "metabolically healthy" obese individuals from the obese and insulin-resistant general population, but the molecular mechanisms that uncouple obesity from cancer risks in this context are not well understood. We suspect that this cancer protection is primarily attributable to the attenuated inflammatory profile [16, 17, 44, 45].

The details of the cytokine signal transduction pathways critical for obesity-associated cancer progression are not well established for *any* of the obesity-associated cancers, nor is it understood why some obese adults become inflamed while others do not. Furthermore, it is not known whether the "metabolically healthy" obese state is stable among older obese adults, or whether there is a genetic or epigenetic component to the phenotype that influences cancer risk. Neither is it known whether there are unique qualities to unresolved, chronic inflammation among older obese adults that differ from younger obese adults, or whether the aforementioned multiple, chronic, inflammatory diseases that often accompany unhealthy aging influence risk for obesity-associated cancers in older adults. In many cases, the necessary observational work is incomplete or sample sizes are too small to enable statistically robust conclusions to be drawn about the role of such comorbidities in cancer risk among older adults. This area of investigation is urgently in need of further effort and better mechanistic understanding, in view of the prevalence of unhealthy aging and obesity among older humans and the potential role of health disparities in exacerbating these risks.

Social Determinants of Healthy and Unhealthy Aging

> We don't stop playing because we grow old; we grow old because we stop playing. *George Bernard Shaw*

Groundbreaking studies in cultural anthropology have compared the social context in which senility and mental confusion arise in "Western" cultures and in India, suggesting that the role of supportive family structures must be considered. Elderly people in traditional Indian joint family arrangements were well cared for and asserted to be protected from development of dementia [37]. Forms of dementia in elderly humans can arise through an accumulation of neurofibrillary tangles, as in Alzheimer's disease, or an accumulation of small infarcts in vascular diseases of the brain, as in vascular dementia; but in neither case are these diseases thought of as normal processes of aging. The mechanisms that stratify risks for dementia and other chronic conditions of aging are just beginning to be studied in a comprehensive fashion. These anthropological observations suggest that family structures, measures of social interconnectedness, locus of control, and socioeconomic status play important roles as mediators of biological factors like stress and inflammation, as proposed in Fig. 5.3. Poverty and economic inequality in particular are widely acknowledged to critically affect mortality risks [50, 131].

There is now sufficient evidence to develop a hypothesis that social and environmental factors affect childhood development in ways that influence chronic disease risks, including cancer risks, when the affected children reach geriatric ages. For example, childhood obesity is a major public health problem in the USA that disproportionately affects African American and Hispanic children and children of low socioeconomic status [18, 35]. Cohorts of these racial/ethnic groups who live in environments characterized by high social stress (family and neighborhood) are associated with increased risk of obesity [23, 68, 73]. These stresses also strongly associate with cardiovascular disease and type 2 diabetes, mediated in part by severe or chronic stress on immune processes, which in turn influence physiological stress systems [52]. These stresses in childhood appear to affect health for many years into mature adulthood and beyond [133, 161, 163]. In particular, there is evidence that chronic comorbidities of aging are exacerbated among adults who experienced trauma as children [4, 49], including cancer risks [109]. Psychological trauma therefore also defines an important form of disparity that influences health risks among older adults.

These data considered together implicate social disruption, psychological stress, economic inequality, and early trauma as predisposing factors for chronic diseases that arise as comorbidities in geriatric patients. The rising incidence of obesity and obesity-associated cancer is therefore likely also be worsened by contemporary inequality and sharply diverging socioeconomic status among the wealthy and the poor in modern industrial cultures worldwide. Thus, it is not unreasonable to hypothesize that future cancer disparities will have some of their roots in current socioeconomic disparities. Current political movements and budgetary policies that

will inevitably increase inequality and exacerbate social stress must therefore be vigorously opposed on public health grounds.

Therapeutic Opportunities

Aging is the major underlying risk factor for cancer risk in humans [127]. Identifying effective behavioral and pharmacologic strategies to help prevent cancer incidence and mortality requires a greater understanding of the mechanisms at the cancer-aging interface. Several of the known purported risk factors linking aging to carcinogenesis have been discussed in this chapter. The lifetime accumulation of DNA damage and genome instability induced by oxidative stress and replicative errors, as well as epigenomic changes as a result of environmental cues, have been linked to cancer [181]. Likewise, aging is associated with unfavorable changes in body composition, including increased visceral adiposity [61] and a decline in skeletal muscle mass [56]. These changes are associated with age-related metabolic dysfunction and a pro-inflammatory state [97], both of which can promote tumorigenesis. Aging is also characterized by a deterioration in innate and adaptive immunity, which can increase the likelihood of immune system evasion by a tumor cell [89, 144], as discussed above, and a decline in processes involved in cellular homeostasis [141, 195]. Thus, interventions are needed that can effectively target these processes in middle aged and older adults to break the aging-cancer link.

Behavioral Strategies

Caloric Restriction

It was first shown more than 100 years ago that a reduction in food intake could inhibit tumor formation in rats [173, 174]. Nearly a century later, caloric restriction (CR) remains the most robust intervention for preventing or delaying the onset of disease and extending lifespan [40]. CR results in a multitude of adaptive changes in humans and rodents, including a reduction in body weight, fat, and lean mass, and declines in insulin (and glucose), cytokines, chemokines, thyroid hormone, reproductive hormones, and circulating growth hormone/IGF-1 [13]. CR has also been shown to induce substantial shifts in the transcriptome, metabolome, and proteome, as well as increases in stress hormones such as cortisol (corticosterone in rodents). Collectively, these changes are believed to enhance stress resistance, minimize macromolecular and organelle damage, and improve cellular homeostasis.

Given the near universality of this intervention to improve health status and extend lifespan in animal models, several efforts in recent years have been undertaken to understand the feasibility and potential benefits of CR in humans. These studies have found that ~20–25 % CR is feasible and safe in adults, and reproduces many of the biological effects observed in rodents, including a reduction in body size, blood pressure, and body temperature, as well as several systemic markers including lower thyroid hormone, fasting insulin, low-density lipoprotein (LDL) cholesterol, and core body temperature [62, 64, 77, 122]. However, long-term CR surprisingly did not reduce circulating IGF-1 concentrations unless protein intake was also reduced, highlighting an important difference between humans and rodents regarding this important cancer risk factor [63]. Due to the limitations in performing long-term CR studies in humans to evaluate cancer outcomes, there is no direct evidence as yet that this intervention can effectively reduce cancer risk in humans. However, inference from the overwhelming evidence linking obesity to cancer risk [30] suggests that CR has promise as a therapeutic strategy for cancer prevention and control in humans.

Exercise

The beneficial effects of physical activity on health and function, including lower risk for developing cardiovascular disease, stroke, and cognitive decline, are well documented [59, 65, 129, 156]. Likewise, it has been shown that exercise can modestly improve mean lifespan in rodents [80–83] and life expectancy in humans [121], but unlike CR, does not extend maximum lifespan. Furthermore, compared to CR, the link between exercise and cancer has been less consistent [19]. This result is due in part to the variable nature of exercise interventions employed in preclinical and human studies, including differing modalities (i.e., resistance training, swimming, running), with varying degrees of intensity and duration. Second, most studies have tested the effect of exercise using a mixture of aggressive tumor-bearing mice and cell types (in rodents), as well as a limited number of studies on a range of advanced-stage cancers in humans, from glioma to breast cancer, with mixed results [19]. Furthermore, whereas some trials employ only an exercise intervention, others incorporate a combination strategy of exercise and diet to induce weight loss. Finally, most exercise studies are limited to testing its potential to prevent cancer recurrence, rather than its ability to prevent cancer development. Thus, data on the potential long-term protective effect of exercise in rodents and humans is not totally clear, but there is a growing body of evidence that exercise in humans can lead to improvements in factors associated with cancer risk, such as lowering circulating IGF-1, insulin, and cytokines [137, 139]. Thus, this observation coupled with the existing epidemiologic evidence showing that physical activity is typically associated with lower risk of breast, colon, and prostate cancer [26] suggests that efforts to pursue the optimal exercise prescription for each scenario (site and stage) should continue to be pursued.

Weight Loss

Given the known link between visceral obesity and cancer risk, weight (and abdominal fat) reduction, which is common side effect of CR, may be necessary in order to maximize the beneficial effects of exercise on cancer. Indeed, visceral fat accrual is a common hallmark of aging [61], and cancer occurrence also increases dramatically with age [127]. Thus, it is possible that reducing the amount of total and visceral fat with age via diet and/or exercise may be an important cancer prevention strategy as well as an adjuvant therapy for improving outcomes following a cancer diagnosis. Intervention studies in humans employing a regimen of 20 % CR versus an exercise regimen designed to induce similar reduction in body weight for 1 year reported similar improvements in cardiovascular disease risk factors [64] and reductions in oxidative damage to lymphocytes [79]. Along these lines, results from a Phase II study aimed at inducing >10 % weight loss by diet and exercise in obese postmenopausal women at risk for developing breast cancer were recently published [57]. In this study, the authors report that weight loss led to improvement in a multitude of endpoint markers, including several factors in breast tissue and serum predictive of lower breast cancer risk [57].

Dietary Strategies

The role of diet and dietary factors on cancer risk with aging has been an area of intense study for many years, and a detailed analysis of all the evidence is beyond the scope of this review. In general, diets high in fruit and vegetables, dietary fiber, and plant-based protein coupled with low intakes of saturated fats, red and processed meats, sugar-sweetened foods, and alcohol is the most grounded dietary prescription, based on the evidence, for reducing cancer risk or recurrence [110, 118]. Some evidence exists that specific micronutrient deficiencies with age can increase cancer risk, such as vitamin D, calcium [48], or folic acid [160]. However, over-supplementation of these factors can also lead to complications [132].

In addition, the use of multivitamins is not presently recommended as a strategy to prevent cancer due to a lack of evidence, and in some cases, harmful unintended consequences, such as evidence that long-term supplementation with beta carotene increased lung cancer risk in smokers [2]. Likewise, the issue can also be complicated, such as with omega-3 fatty acids, which have been tied to lower breast cancer risk [24], but increased risk for prostate cancer [25]. Green tea polyphenols, resveratrol, and soy isoflavones as a dietary supplement to reduce cancer risk also continue to be an active area of study with promising effects in the laboratory [85, 86, 136], but evidence that these factors are effective in humans is limiting for several reasons. Among these concerns, the challenge of performing long-term randomized trials for dietary factors that are well controlled and have cancer as an outcome is logistically and financially challenging. Second, it is difficult to

control for confounding effects such as changes in physical activity or body weight with a dietary intervention. Third, it is often problematic to isolate the important effect(s) due to confounding, such as when one dietary component is removed (i.e., refined sugars) and replaced with another (i.e., fruits and vegetables) [158]. Finally, it is difficult to know the dose at which a bioactive component is most beneficial, a methodological concern that has plagued the resveratrol field [41], for example.

Pharmacologic Strategies

The modern era of aging research has ushered in a new genre of research focused on identifying pharmacologic interventions, also termed CR mimetics [15, 92], to treat some manifestations of aging and extend lifespan. Some compounds have produced mixed results, such as resveratrol, the polyphenol first reported to improve survival in mice fed a high-fat diet [5], an observation that could not be replicated on a low-fat diet [138]. Other agents with anti-inflammatory properties, including nordihydroguaiaretic acid and aspirin, led to a significant improvement in survival of male mice [170], but not female mice. Aspirin also reduced cancer incidence in Lynch syndrome patients [12] and extended lifespan in a mouse model of Lynch syndrome [135]. Furthermore, aspirin use has been linked to improved survival in colon cancer patients with *PI3KCA* mutations [152].

Interest is now focused on the potential of other drugs used to treat various age-related ailments, including statins, bisphosphonates, and metformin, as potential therapeutic agents for cancer treatment [71]. For example, the biguanide, metformin, has been shown to increase lifespan in yeast and mice [5], but not in rats [169] or *Drosophila* [168]. Interestingly, metformin, which is commonly prescribed to patients with type 2 diabetes and is well tolerated, has also emerged as an anticancer agent [126]. Specifically, metformin, which is believed to be an activator of 5′-AMP-activated protein kinase (AMPK), has been associated with a ~30 % reduction in lifetime risk of cancer in type 2 diabetics [124]. Metformin is now under intense study in clinical trials, either alone or as an adjuvant therapy.

The most consistent and promising drug thus far, at least from the aging perspective, is the immunosuppressant, rapamycin, which among its many effects inhibits mammalian Target of Rapamycin (mTOR) and consistently extends lifespan in mice, regardless of whether it is started early or late in life [75, 138, 190]. However, rapamycin is unlikely to be used in humans due to numerous side effects, including hyperglycemia, dyslipidemia, immunosuppression, vasospasm, and renal failure [119]. However, the so-called rapalogs, which are under development to safely modulate mTOR activity, could represent an effective strategy in the future to treat diseases of aging, including cancer [119]. Therefore, while a healthy diet and exercise remain the cornerstone to an effective cancer prevention strategy, the prospect of one day developing drugs that can safely treat or even prevent diseases of aging, including cancer, has never been more realistic.

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Chapter 6
Energy Balance and Multiple Myeloma in African Americans

Graham A. Colditz, Kari Bohlke, Su-Hsin Chang, and Kenneth Carson

Abstract Multiple myeloma (MM) is a plasma B-cell malignancy that is characterized by clonal proliferation of malignant plasma cells in the bone marrow, monoclonal (M) protein in blood or urine, and organ dysfunction. The incidence of multiple myeloma (MM) is more than twice as high among African Americans as among whites in the USA (DeSantis et al., CA Cancer J Clin 63:151–166, 2013), but the reasons for this are still not well understood (Benjamin et al., Cancer Metastasis Rev 22:87–93, 2003; Greenberg et al., Leukemia 26:609–614, 2012). Obesity—a risk factor for MM that is more prevalent in African Americans than in whites—has been hypothesized to contribute to racial disparities in this disease. This chapter reviews the evidence regarding energy balance, race, and MM.

Keywords Multiple myeloma • Monoclonal gammopathy of unknown significance (MGUS) • Smoldering multiple myeloma • M protein • Waldenström macroglobulinemia • Obesity • Vitamin D

The Burden of Multiple Myeloma

With an estimated 22,350 new diagnoses in 2013, multiple myeloma accounts for roughly 15 % of hematologic malignancies and approximately 1 % of all cancers in the USA [1]. The median age at diagnosis is 69 years [2].

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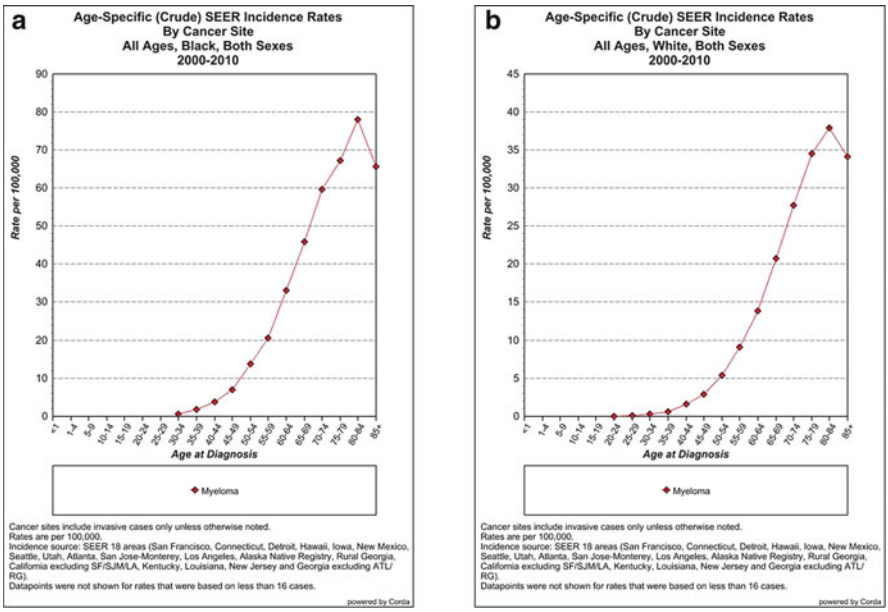

Fig. 6.1 Age-specific incidence rates of multiple myeloma for blacks (**a**) and whites (**b**), SEER 2000–2010. (Note different scales)

Well-established risk factors for MM are increasing age, male gender, African American race [3], and family history of a hematologic malignancy [4, 6]. The reasons for this excess risk remain unknown [4, 5]. In SEER data from 2006 to 2010, age-adjusted incidence of MM (per 100,000 people) was 7.1 for white men, 4.2 for white women, 14.4 for black men, and 10.2 for black women [5]. Age- and race-specific incidence rates of multiple myeloma are provided in Fig. 6.1. Similar patterns are found for mortality data, with mortality rates (per 100,000 people) of 4.0 for white men, 2.5 for white women, 7.9 for black men, and 5.4 for black women [5]. Trends in incidence and mortality over time are illustrated in Fig. 6.2. Overall, incidence rates increased between 1975 and 2010, but mortality rates have declined since the mid-1990s [5].

Survival with multiple myeloma has improved with the introduction of newer approaches to treatment [7], and racial differences in survival with multiple myeloma tend to be smaller than racial differences in incidence. In SEER 18 data from 2003 to 2009, 5-year relative survival with multiple myeloma was 44.7 % for white men, 41.2 % for white women, 41.9 % for black men, and 43.6 % for black women [5]. Improvements in relative survival over time have been larger for whites than for blacks [8].

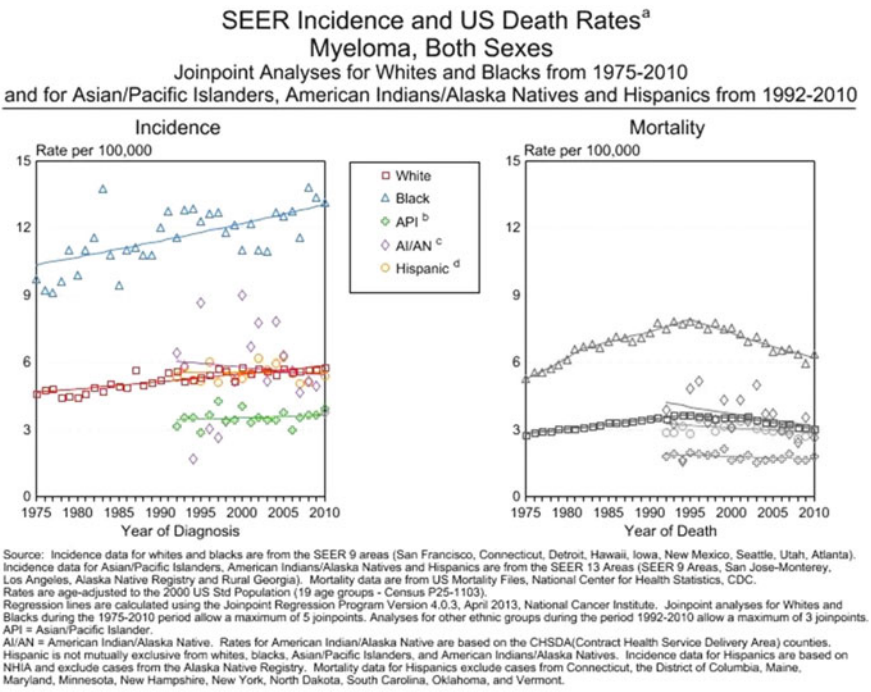

Fig. 6.2 SEER incidence and US death rates[a] myeloma, both sexes. Joinpoint analyses for Whites and Blacks from 1975 to 2010 and for Asian/Pacific Islanders, American Indians/Alaska natives, and Hispanics from 1992 to 2010

Precursors to Multiple Myeloma

Monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma are the known precursors of MM [9]. In both conditions, patients are asymptomatic [10]. MGUS—which is present in more than 3 % of whites over the age of 50 [11]—is characterized by the clonal proliferation of plasma cells in the bone marrow (<10 %) and the presence of M protein in the serum (<3 g/dL) and the absence of end-organ damage, such as hypercalcemia, renal insufficiency, anemia, and lytic bone lesions (CRAB features) that can be attributed to the plasma cell proliferative disorder [10]. CRAB features are also absent in smoldering multiple myeloma. Smoldering multiple myeloma is distinguished from MGUS by a higher percentage of clonal bone marrow cells (≥10 %) and/or higher serum levels of M protein (≥3 g/dL) [10], and has a higher rate of progression to MM [12].

MGUS progresses to MM or another related condition at a rate of roughly 1 % per year [13]. Three distinct types of MGUS have been described: non-IgM, IgM, and light chain [14]. IgM MGUS tends to progress to Waldenström macroglobulinemia rather than to multiple myeloma [14]. In the predominantly white population of Olmstead County, Minnesota, IgM MGUS accounted for 17 % of all MGUS

cases [11]. IgM MGUS accounts for a smaller proportion of MGUS among Africans and African Americans [15, 16]. Exclusion of IgM MGUS would be appropriate when considering the epidemiology of multiple myeloma precursors, but many studies conducted to date report on MGUS as a whole.

In the USA, patterns of MGUS by age, sex, and race are similar to those of multiple myeloma: the prevalence of MGUS is higher at older ages, among men, and among African Americans [17]. In a study of 1,000 black women and 996 white women with a similar prevalence of obesity and similar socioeconomic status, the prevalence of MGUS was 3.9 % among the black women and 2.1 % among the white women [18]. After further accounting for factors such as age, education, obesity, and household income, black race was associated with an 80 % increase in the likelihood of MGUS [18]. In a study of US Veterans Affairs (VA) hospital discharge diagnoses, the age-adjusted prevalence of MGUS was three times higher (95 % confidence interval (CI) 2.7–3.3) among African Americans than among whites [19]. Among those with MGUS, however, 10-year risk of progression to MM was similar in the two groups: 17 % for African Americans and 15 % for whites. This suggests that the higher risk of MM in African Americans stems from an increase in the risk of MGUS, rather than from more frequent progression of MGUS to MM. Other, earlier studies also reported a higher prevalence of MGUS among African Americans [20, 21].

In a study conducted outside of the USA, the age-adjusted prevalence of MGUS among Ghanaian men between the ages of 50 and 74 was 5.84 % [15], which the authors note is higher than the reported prevalence among white men in Olmstead County, MN [11]. The finding that both African Americans and Africans have a higher a higher prevalence of MGUS than US whites raises the possibility of race-related genetic susceptibility, though environmental factors may also play a role.

Together, these studies suggest that the higher incidence of MM among African Americans stems from the more frequent occurrence of MGUS. Prevention strategies that begin early in life—prior to the development of MGUS—are likely to be important in reducing racial disparities in multiple myeloma.

Energy Balance and Cancer

Excess body weight and the absence of regular physical activity each contribute to cancer incidence. In a 2007 report titled *Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective*, the World Cancer Research Fund and the American Institute of Cancer research concluded that there is convincing or probable evidence for a relationship between body fatness and cancers of the esophagus (adenocarcinoma), pancreas, colorectum, breast (postmenopausal), endometrium, kidney, and gallbladder [22]. A 2003 report from the Cancer Prevention Study II study estimated that overweight and obesity account for an estimated 14 % of cancer deaths in men and 20 % of cancer deaths in women in the USA [23]. There is also convincing or probable evidence that regular physical

activity reduces the risk of the colon cancer, postmenopausal breast cancer, and endometrial cancer [22].

The evidence linking energy balance and cancer incidence and mortality is most extensive for solid tumors, but a growing number of studies suggest that it is also contributes to hematologic malignancies. Meta-analyses of prospective studies have reported statistically significant, positive associations between obesity and the risk of leukemia [24], lymphoma [25], and multiple myeloma [26]. Studies of physical activity and the incidence of hematologic malignancies have produced less consistent results [27, 28].

Obesity and Multiple Myeloma

Data from several prospective studies support an association between overweight and obesity and the risk of multiple myeloma. A meta-analysis [26] included information from 15 cohort studies of multiple myeloma incidence and five cohort studies of multiple myeloma mortality. Compared with normal-weight individuals, risk of multiple myeloma was elevated among those who were overweight (relative risk (RR) = 1.12, 95 % CI 1.07–1.18) or obese (RR = 1.21, 95 % CI 1.08–1.35). Multiple myeloma mortality was also increased among those who were overweight (RR = 1.15, 95 % CI 1.04–1.27) or obese (RR = 1.54, 95 % CI 1.35–1.76) [26].

A positive association between obesity and MGUS was reported in a study of black and white women: obesity increased the risk of MGUS by 80 % (p-value = 0.04) after adjustment for race, age, education, household income, and diabetes [18].

These results suggest that overweight and obesity increase MGUS prevalence, multiple myeloma incidence, and multiple myeloma mortality. The mechanisms that link obesity with MGUS and multiple myeloma are still not well understood; several potential mechanisms have been proposed, including alterations in circulating levels of adipokines (polypeptide hormones produced by adipose tissue) [29, 30].

Physical Activity and Multiple Myeloma

In contrast to the generally consistent relationship between obesity and incidence of multiple myeloma, there is little evidence thus far that physical activity affects the incidence of multiple myeloma and other plasma cells neoplasms. The prospective VITamins And Lifestyle (VITAL) study collected information about 666 incident cases of hematologic malignancies, 80 of which involved plasma cell disorders. Regular physical activity reduced the risk of certain hematologic malignancies, particularly myeloid neoplasms, but did not reduce the risk of plasma cell disorders [27]. A combined analysis of data from the Nurses' Health Study and the Health

Professionals Follow-Up Study collected information about 215 incident cases of multiple myeloma; physical activity was not statistically significantly related to risk [31]. A lack of association between physical activity and risk of multiple myeloma was also reported in the European Prospective Investigation into Cancer and Nutrition (EPIC) study, which collected information about 165 cases [32]. Physical activity at different ages was assessed in the NIH-AARP Diet and Health Study; results at each age were null for both men and women [33]. In the Cancer Prevention Study II cohort, physical activity had a borderline-significant, inverse association with risk of multiple myeloma in women (hazard ratio for highest level of activity versus no activity: 0.52, 95 % CI 0.27–1.00), but was not associated with risk of multiple myeloma in men [34]. Time spent sitting followed a similar pattern: it increased the risk of multiple myeloma in women but not in men [34]. An inverse association with physical activity was reported in a study conducted in Japan: those who walked the least had an increased risk of multiple myeloma [35].

In summary, the evidence for an effect of physical activity on risk of multiple myeloma is far weaker than the evidence for an effect of adiposity, and likely null. Several large prospective studies have failed to find an association between physical activity and risk of multiple myeloma.

Obesity and Multiple Myeloma in African Americans

The growing evidence for an association between obesity and risk of multiple myeloma raises questions about whether this modifiable risk factor contributes to racial disparities in multiple myeloma incidence. The prevalence of obesity in the USA has reached alarming levels, and is especially high among African American women (Fig. 6.3). In 2009–2010 NHANES data, age-adjusted prevalence of obesity among women was 58.5 % among non-Hispanic blacks (95 % CI 52.4–64.3 %), 41.4 % (37.4–45.6 %) among Hispanics, and 32.2 % (95 % CI 29.2–35.3 %) among non-Hispanic whites [36]. Among men, prevalence of obesity was 38.8 % (95 % CI 33.9–43.9 %) among non-Hispanic blacks, 37.0 % (32.5–41.7 %) among all Hispanics, and 36.2 % (95 % CI 31.8–40.8 %) among non-Hispanic whites [36]. Differences by race among men are more apparent at higher levels of obesity. Grade 2 or 3 obesity (a body mass index (BMI) of $\geq$35 kg/m^2) occurs in 20 % of non-Hispanic black men, 11.9 % of Hispanic men, and 12.1 % for non-Hispanic white men [36]. The comparable numbers for women are 30.7 % for non-Hispanic black women, 18.1 % for Hispanic women, and 16.6 % for non-Hispanic white women [36].

Differences in BMI across racial and ethnic groups begin at an early age. For children between the ages of 2 and 19 years, obesity is commonly defined as being at or above the 95 % percentile of sex- and age-specific BMI [37]. In 2009–2010 NHANES data, the prevalence of obesity among children and adolescents this age range was higher among non-Hispanic blacks than among non-Hispanic whites for both girls and boys [38]. Among boys, the prevalence of obesity was 24.3 % among

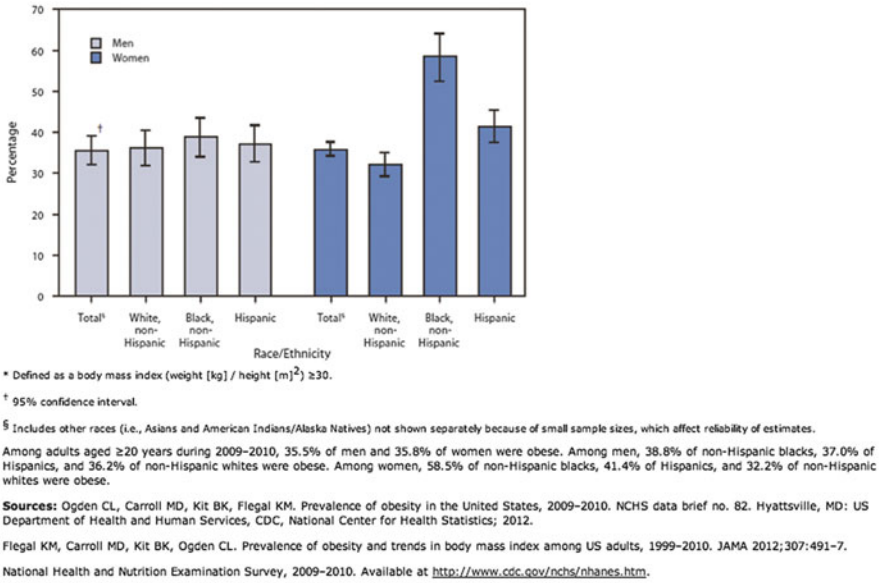

Fig. 6.3 Prevalence of obesity* among adults aged ≥20 years, by race/ethnicity and sex—National Health and Nutrition Examination Survey, USA, 2009–2010. (From http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6107a5.htm)

non-Hispanic blacks, 23.4 % among Hispanics, and 16.1 % among non-Hispanic whites. Among girls, these numbers were 24.3 % for non-Hispanic blacks, 18.9 % among Hispanics, and 11.7 % among non-Hispanic whites. A difference between non-Hispanic blacks and non-Hispanic whites was less apparent among very young children (from birth to 2 years); during these ages, high weight-for-length affects 8.7 % of non-Hispanic blacks, 14.8 % of Hispanics, and 8.4 % of non-Hispanic whites.

Several studies have provided race-specific estimates of the effect of obesity on risk of multiple myeloma. Samanic et al. evaluated the relationship between obesity and a broad range of cancer types among black and white US veterans. The effect of obesity on risk of multiple myeloma did not vary significantly by race: RR = 1.22 (95 % CI 1.05–1.40) for white men; RR = 1.26 (95 % CI 1.02–1.56) for black men [39]. An effect of obesity among both blacks and whites was also found in a case–control study by Brown et al.: odds ratio (OR) = 1.9 (95 % CI 1.2–3.1) for whites; OR = 1.5 (95 % CI 0.9–2.4) for blacks [40]. In analyses by race and gender, obesity increased the risk of multiple myeloma among white men, white women, and black women, but not black men [40]. Friedman and Herrinton conducted one of the early studies of race, obesity, and multiple myeloma; in a large managed care organization, increasing BMI was statistically significantly associated with an increased risk of multiple myeloma only among white men [41].

Though studies that stratified by both race and gender produced inconsistent results, analyses by race alone suggest that obesity increases the risk of multiple

myeloma in both African Americans and whites. Patterns of obesity, however, do not clearly explain the higher risk of multiple myeloma in African Americans. African American men have the highest risk of both multiple myeloma and MGUS, yet the overall prevalence of obesity in African American men is similar to that of white men, and much lower than the prevalence in African American women.

Other Factors That May Contribute to Higher Rates of Multiple Myeloma in African Americans

The patterns of obesity described above, coupled with an effect of race on MGUS even after adjusting for obesity [18], suggest that factors other than (or in addition to) obesity contribute to the higher rates of multiple myeloma among African Americans. The other factors remain poorly understood, but ongoing research into the biology of MGUS and multiple myeloma may provide clues. Among people with MGUS, African Americans tend to have lower levels of M protein, a lower prevalence of IgM gammopathy, and a higher frequency of abnormal serum free light chain ratios than whites [3, 16]. Genomic differences in multiple myeloma among African Americans and whites are also being evaluated [42].

Variation in cancer risk by race raises questions about a potential role of vitamin D. Serum levels of 25-hydroxyvitamin D (25(OH)D) tend to be lower in African Americans than in whites, and low 25(OH)D has been linked with an increased risk of cancer [43]. Evidence for an association between vitamin D or sun exposure and risk of multiple myeloma, however, is limited and inconsistent [44–47].

As studies continue to evaluate racial variability in multiple myeloma, it will be important to focus on the etiologically relevant time period of exposure. Characteristics or behaviors that are present prior to the development of MGUS (many years before a diagnosis of multiple myeloma) are likely to be those that drive the higher rates of multiple myeloma among African Americans.

Conclusions

Though obesity does not fully explain the racial disparities in multiple myeloma incidence, it does appear to modestly increase the risk of both MGUS and multiple myeloma, and is one of the only modifiable risk factors identified thus far for these conditions. Maintenance of a healthy body weight reduces the risk of several types of cancer regardless of race and must be a cornerstone of cancer prevention efforts [48].

Ongoing investigation into the other factors that contribute to the higher risk of multiple myeloma among African Americans may provide clues to the etiology of this disease as well as to potential new approaches to prevention and treatment.

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Chapter 7
Single Nucleotide Polymorphisms in Obesity and Inflammatory Genes in African Americans with Colorectal Cancer

Melissa Kang and Temitope O. Keku

Abstract Colorectal cancer (CRC) is one of the most commonly diagnosed cancers in the world and has one of the highest mortality rates among all cancers. In the USA, a racial disparity exists in CRC with the highest incidence and worst survival in African Americans compared to other races. This disparity persists even after taking into account the stage of CRC at diagnosis, treatment differences, or socioeconomic status. Some argue that African Americans may have more risk factors for CRC such as higher rates of obesity and insulin resistance. However, when adjusted for diet, physical inactivity, or central obesity, increased risk factors present in African Americans are not fully explained. These observations suggest that there may be genetic or biological differences between races that confer worse CRC outcomes in African Americans. Single nucleotide polymorphisms (SNPs), which occur in a race-specific manner, influence development of obesity, insulin resistance, chronic inflammation, and CRC. SNPs alter levels of circulating inflammatory cytokines and growth promoting hormone peptides while modifying response to environmental stimuli. SNPs that occur distinctly in African American populations may provide important insights into the racial disparities observed in CRC incidence and survival. This chapter provides an overview of racial disparities in CRC and the potential contribution of SNPs in obesity and inflammatory related genes.

Keywords Colorectal cancer • Single nucleotide polymorphism • SNP influence on adipokines • Insulin and inflammatory cytokines • Racial disparities in obesity • Insulin resistance • Genetic susceptibility studies • Genome-wide association studies

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Colorectal Cancer (CRC) Disparity and Racial Differences in Risk Factors

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in both men and women in the USA with an estimated 102,480 new cases of colon and 40,340 new cases of rectal cancers in 2013 (American Cancer Society (ACS), SEER data). It is also the third leading cause of cancer-related deaths in the USA and is expected to account for 50,830 deaths in 2013 (ACS, SEER data). There are many risk factors associated with sporadic CRC including increasing age, obesity [1–8], a diet high in red or processed meats [9–12], alcohol [13, 14], smoking [12, 15], a personal or family history of CRC or polyps [12, 16–18], and type 2 diabetes [19–22]. Physical activity [12, 23, 24], consumption of calcium, and higher levels of vitamin D [25–27] as well as regular use of nonsteroidal anti-inflammatory drugs (NSAIDs) have been observed to reduce risk [28–33].

The 1-, 5-, and 10-year survival rates for CRC depend on the stage at diagnosis (ACS, Cancer Statistics, 2013). When CRC is detected at an early, localized stage, the 5-year survival is 90 %, but only 39 % of CRCs are diagnosed at this stage. If the cancer has spread to distant organs, the 5-year survival decreases to 12 % (ACS, Cancer facts and figures, 2013). However, there is a significant racial variability in the incidence and mortality from CRC. African Americans are typically diagnosed at a younger age, at a more advanced stage, and have worse survival from CRC than other ethnic groups in the USA (Table 7.1). This disparity persists even after adjustments for stage, treatment, and socioeconomic status [34–39], suggesting that there may be a biological or genetic difference or predisposition depending on ethnicity. This chapter presents racial differences in the risk factors between African Americans and Caucasians that may help explain the worse outcomes observed in African American patients with CRC. The connection between obesity, insulin resistance, inflammation, and CRC is discussed in relation to the single nucleotide polymorphisms (SNPs) that influence the levels of circulating adipokines, insulin, and inflammatory cytokines. We will also demonstrate how these genetic polymorphisms can modulate susceptibility to obesity, diabetes, and CRC in a race-specific manner. Lastly, we will address some of the limitations of genetic susceptibility studies and possible future directions in this area of study.

Obesity and Insulin Resistance

Obesity is an important CRC risk factor that could contribute to racial disparities in CRC outcomes. The consumption of diets high in saturated fats and low in fruits and vegetables, as well as sedentary lifestyles, are thought to contribute significantly to the increased prevalence of obesity in Western countries [40]. Furthermore, the higher incidence of CRC in westernized nations is believed to be partly contingent upon the increased consumption of Western diets and physical

Table 7.1 Colorectal cancer incidence and mortality rates, by race/ethnicity, USA, 2005–2009 (American Cancer Society, Surveillance Research, 2013)[a]

	Incidence		Mortality	
	Men	Women	Men	Women
Caucasian	52.8	39.2	19.5	13.6
African American	65.1	48.0	29.8	19.8
Asian American/Pacific Islander	41.4	32.1	13.1	9.6
American Indian/Alaska Native[b]	50.7	41.1	18.8	14.6
Hispanic/Latino	46.9	33.3	15.3	10.2

[a]Per 100,000, age adjusted to the 2000 US standard population
[b]Data based on Contract Health Service Delivery Area counties

inactivity. Data from the 1999 to 2000 National Health and Nutrition Examination Survey (NHANES) showed that 31 % of Americans were obese, and this rate increased to 36 % between 2009 and 2010 [41, 42]. Obesity is defined by body mass index (BMI) >30 kg/m^2 and overweight by BMI 25–29.9 kg/m^2. While BMI is positively correlated with fat mass, it does not distinguish between lean mass and fat, nor does it take into account the body fat distribution (i.e., subcutaneous and central (visceral) fat). Men tend to have more visceral fat while women usually have greater amounts of subcutaneous fat. It has been suggested that subcutaneous and visceral fat deposits are metabolically distinct from each other with visceral fat secreting higher levels of cytokines and hormones [43]. Therefore, several studies have suggested using measures of central obesity as a predictor of disease (waist to hip ratio (WHR)), with suggested cutoffs for men and women: WHR > 0.90 in men or >0.85 in women or waist circumference >102 cm in men or >88 cm in women [44].

Regardless of which measure of obesity is used, studies have demonstrated that African Americans have higher rates of obesity than Caucasians [41, 42]. NHANES data from 2009 to 2010 demonstrated that among men, age-adjusted obesity prevalence was lowest in non-Hispanic Caucasians (36.2 %) and highest among African Americans (38.8 %). For women, the overall age-adjusted obesity prevalence was 35.8 % with the lowest prevalence among Caucasian women (32.2 %); the highest rate was seen among African Americans (58.5 %) [41]. Furthermore, African Americans have more difficulty losing weight than Caucasians after a weight loss surgery or randomized diet and exercise intervention [45–51].

Obesity is believed to predispose to CRC via increased secretion of hormones and cytokines, such as tumor necrosis factor-α (TNF-α), C-reactive protein (CRP), and interleukin (IL)-6, which have been implicated in chronic low grade inflammation, cellular proliferation, cell survival, and invasion (Fig. 7.1). Moreover, obesity is also a risk factor for the development of diabetes mellitus. Type 2 diabetes as well as exogenous insulin administration have been associated with increased CRC risk, which is thought to be due to the growth-promoting effects of insulin and its related growth factors such as insulin-like growth factor (IGF-1) [19–22, 52–56]. For example in animal studies, it insulin supplementation resulted in increased colonic epithelial proliferation and aberrant colonic crypt foci formation via

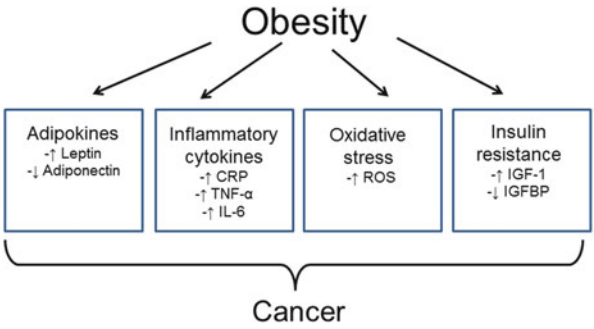

Fig. 7.1 Mechanisms underlying the relationship between obesity and cancer. Abbreviations: *CRP* C-reactive protein, *TNF* tumor necrosis factor, *IL* interleukin, *ROS* reactive oxygen species, *IGF* insulin-like growth factor, *IGFBP* insulin-like growth factor binding protein

activation of pathways such as ERK and AKT that are involved in cellular proliferation [54–56].

Existing literature suggests that African Americans are at a greater risk for insulin resistance than Caucasians. Brancati et al. found that diabetes incidence was 1.85-fold greater in African American women than in Caucasian women even after adjustments for BMI, WHR, physical activity, and dietary intake [57]. Cavicchia et al. found that the association between type 2 diabetes and colon cancer was stronger in African Americans (OR = 1.72, 95 % CI 1.21–2.46) than among Caucasians (OR = 1.24, 95 % CI 0.73–2.11) [58].

Hyperinsulinemia may modify cancer risk not only through the direct effects of insulin but also indirectly by increased production of IGF-1. In the presence of insulin, growth hormone receptor expression is increased in the liver, leading to elevated production of IGF-1. Chronic hyperinsulinemia has been associated with elevated circulating levels of IGF-1 [59]. Also, adoption of a Western diet is associated with increases in serum IGF-1 levels [60]. Extensive evidence, both in vitro and in vivo, suggests that IGF-1 promotes CRC growth, prevents apoptosis, and increases metastasis [53, 60]. IGF binding proteins (IGFBP), especially IGFBP-3, sequester and inhibit the actions of circulating IGFs [53]. Research has shown that circulating IGF levels may differ by race, where African American women had significantly higher IGF-1 levels than Caucasian women [61, 62]. Furthermore, recent studies suggest that African Americans have higher hyperinsulinemia and insulin resistance even with less visceral fat mass or similar adiposity to Caucasians [63–71]. These observations indicate that higher insulin resistance and diabetes in African Americans are not fully explained by higher rates of obesity or diet and suggest underlying biological or genetic differences as an explanation for ethnic variance in insulin resistance.

Adipokines

Adipokines are hormones secreted by fat cells. Leptin is an adipokine that is involved in food intake, energy expenditure and balance. Leptin also affects cell

proliferation, migration, and angiogenesis [72–75]. Leptin has been shown to be positively associated with obesity, insulin resistance, and CRC [76–82]. Studies have demonstrated that African Americans have higher levels of leptin independent of fat mass compared to Caucasians, although this may be partially due to leptin's positive association with insulin [83–86]. Adiponectin is another cytokine that is secreted by adipocytes. It influences energy metabolism, however, contrary to the action of leptin, adiponectin is an insulin sensitizer and exhibits anti-inflammatory and anti-atherogenic properties [87]. Thus, adiponectin has been inversely related to obesity and CRC risk [88–92]. Animal studies demonstrate that adiponectin knockout mice have significantly greater number and larger tumors and inflammation than mice with intact adiponectin [93, 94]. When mice on a high-fat diet were fed adiponectin, tumor growth was suppressed, and serum insulin levels were decreased [95]. In humans, African American children and women have lower levels of adiponectin than their Caucasian counterparts, even after accounting for adiposity [84, 86, 96, 97]. To support this, Schutte et al. found that ethnicity was a significant contributor to variances in adiponectin levels [98]. These studies on leptin and adiponectin suggest that plasma levels of these adipokines could be influenced by genetic variation and race, and as such may differentially impact CRC risk.

Inflammatory Markers and Cytokines

In addition to insulin dysregulation, visceral adipose tissue has also been shown to play a role in systemic inflammation. Obesity has been established as a chronic low-grade inflammatory state with elevated circulating levels of pro-inflammatory cytokines, such as IL-6 and TNF-α, and reduced anti-inflammatory mediators. These pro-inflammatory cytokines, produced by adipose tissue, are involved in a positive feedback loop in the liver to produce acute phase reactants such as C-Reactive Protein (CRP) that could further contribute to inflammation. All of these cytokines and resulting inflammation have been associated with tumorigenesis and CRC.

TNF-α, since its first description, has been found to have multiple functions in the areas of inflammation, apoptosis, production of other cytokines, and insulin resistance. TNF-α also has a role in tumor development [99, 100]. TNF-α has been shown to be positively associated with lymph node metastasis, CRC recurrence, or presence of colorectal adenomas, a precursor to CRC [101, 102]. Because adipocytes also produce TNF-α, obese subjects tend to have higher levels of TNF-α. Resection of visceral fat or weight loss lowers TNF-α levels in both animals and humans [103–110]. Reduction in TNF-α leads to decreased activation of JUN, a transcription factor involved in cellular proliferation and anti-apoptotic signaling [111, 112]. In rodent models, exposure to TNF-α induced insulin resistance, whereas neutralization or knockout of TNF-α increased insulin sensitivity, suggesting that TNF-α is a key player in insulin resistance [108]. In humans it

was observed that weight loss affected overweight African American and Caucasian women differently [68, 113]. Intra-abdominal adipose tissue, serum concentrations of TNF-α, CRP, IL-6, soluble TNF receptors all decreased with weight loss in Caucasian women, but only IL-6 and CRP decreased in African American women. Further, though Caucasian women had greater visceral adipose tissue and TNF-α than African American women at baseline, they had better insulin sensitivity. Olson et al. also supported race-dependent levels of TNF-α by showing that African Americans have the lowest TNF-α level compared to Caucasians or Hispanics, even after adjustment for age, gender and BMI [114]. In this study population, serum glucose and insulin levels were moderately correlated with TNF-α in Caucasians, but not in African Americans. These studies suggest that circulating TNF-α and its effects could be varied by race and genetic background.

IL-6 is a pro-inflammatory cytokine that is also produced in visceral adipose tissue. It has been observed to promote cancer proliferation and inhibit apoptosis, where an increased IL-6 expression was positively associated with increasing BMI, adenomas, and advanced stage of CRC [102, 115–120]. CRP, an acute phase reactant produced in response to factors released by macrophages and adipocytes, is a measure of inflammation. Similarly, CRP has been positively associated with CRC, and elevated CRP level has been demonstrated to be a poor prognostic factor in patients with CRC [121–124]. Supplementation with vitamin D and calcium, which are suggested to exert anti-inflammatory and protective effects from CRC via binding of free fatty and bile acids, decreased TNF-α, IL-6, and CRP in patients with adenomas [125]. Multiple studies found that African Americans had higher levels of CRP and IL-6 than Caucasians [126–128], and even after controlling for socioeconomic status, exercise, and BMI, IL-6 continued to remain higher in African Americans [128]. Similar to that in TNF-α, genetic alterations have been proposed as one of the reasons why the levels of IL-6 and CRP and associated conditions may differ between races.

In the beginning of this chapter, we mentioned that inhibitors of the cyclooxygenase (COX) enzymes, such as aspirin and other NSAIDs decrease the risk of CRC. There are two types of COX. COX-1 is expressed in most normal cells and is involved in the protection of the gastric mucosa and the regulation of platelet aggregation. COX-2, on the other hand, is expressed in inflammatory cells or cancer cells, regulates production of prostaglandins, and is involved in tumorigenesis [129]. Consistent with these findings, COX-2 expression was shown to be elevated in 55–80 % of human colon cancers and adenomas compared with normal mucosa in multiple studies [130–133]. More recently, COX-2 expression has been revealed as a poor prognostic marker in CRC [131, 134–136].

As COX-2 expression and circulating levels of above mentioned cytokines have all been linked to CRC, the study of these markers have elucidated mechanisms and pathways involved in pathogenesis of cancer. It turns out that several of the inflammation and insulin markers discussed above are genetically regulated. SNPs in genes that encode these markers can influence their production and levels in circulation. SNPs are single nucleotide sequence variations in the genome that affect transcription and translation of a gene, thus, providing a unique method of

studying how genetic mutations influence CRC risk and outcomes. In the following section, we will describe how these SNPs influence COX-2 gene expression, circulating levels of insulin-IGF markers, adipokines and inflammatory cytokines, and how they contribute to racial disparities in CRC.

Single Nucleotide Polymorphisms (SNPs)

SNPs are variations in nucleotide sequences in the DNA that occur with greater than 1 % frequency in at least one population and are inherited from generation to generation [137]. A set of associated SNP alleles in a region of a chromosome is called a haplotype. If two or more SNPs have a greater than random chance of being inherited together, they are said to be in a linkage disequilibrium. About ten million SNPs have been discovered and characterized in humans, however, only a fraction of these are known to confer a biological effect [138]. Because SNPs occur in any region of the genome, both in coding and noncoding regions, SNPs can lead to changes in amino acid sequences, which result in changes in the function or amount of encoded protein, alter enzyme stability, or cause no phenotypically visible change. Data indicate that many diseases are not directly triggered by SNPs, but are likely a result of complex interactions among multiple genes and environment. SNPs are believed to function by modifying responses to environmental exposures of health hazards or medications. For example, depending on a presence of a SNP, a patient may be a responder to a certain drug, while others are non-responders or even develop toxicities. Over the last few years with advances in technology, the field of genetic epidemiology has evolved from studying SNPs in candidate genes to genome-wide association studies (GWAS). Earlier studies evaluated candidate genes chosen for biological relevance to CRC. More recent studies have used GWAS to discover hundreds of thousands of SNPs simultaneously to assess disease associations. We will focus on some of the more well-known SNPs in insulin, diabetes, and inflammation in the next section and examine their contribution to racial disparities in CRC.

SNPs and CRC

To date, multiple CRC susceptibility alleles have been identified across chromosomes using GWAS. These loci include 8q24.21 (rs6983267), 8q23.3 (rs16892766), 10p14 (rs10795668), 11q23.1 (rs3802842), 15q13.3 (rs4779584), 18q21 (rs4939827), 14q22.2 (rs4444235), 16q22.1 (rs9929218), 19q13.1 (rs10411210), and 20p12.3 (rs961253), and range in effect sizes of odds ratio (OR) = 1.10–1.70 [139–145]. Given that there is limited information regarding how these genotypes affect phenotypes, we will focus on 8q24.21 (rs6983267), a locus that has been extensively studied. Several studies have demonstrated that

rs6983267 is associated with increased CRC risk [139–145]. Information regarding how this polymorphism affects the function of the gene as well as the relationship to the risk of CRC is being discovered in more detail. Rs6983267 has been mapped nearby to the MYC gene, which is mutated in many forms of cancer, leading to dysregulation of genes involved in cell proliferation [140]. Takatsuno et al. found that MYC gene expression was highest in cells with the GG genotype (homozygous risk allele) and lowest in cells with the TT wild type genotype [146]. Abuli et al. showed that the G risk allele was more common in advanced stages, highly differentiated tumors, and in patients with a family history of CRC in first-degree relatives [139]. Dai et al. also observed that a polymorphism at rs6983267 was significantly associated with survival for patients with stage III disease on 5-fluorouracil therapy, and there was a cumulative effect when multiple unfavorable genotypes occurred concurrently [147]. Moreover, there are racial differences in the frequencies of rs6983267 alleles. The G risk allele frequency for rs6983267 is 50 % in Europeans and 80–100 % in Africans [140]. Although most SNP studies have been performed mostly in Caucasians, this is one of the few SNPs that have been studied across ethnicities. It was found to confer risk of CRC in African Americans (OR = 1.52, 95 % confidence interval (CI) 1.11–2.07) as well as in Caucasians of European descent (OR = 1.12, 95 % CI 1.01–1.25) [148]. However, not all studies have demonstrated consistent results. For example, Kupfer et al. found a trend of association with CRC in Caucasians but not in African Americans [149]. Provided that the G risk allele occurs more frequently and has greater odds of being associated with CRC in African Americans, it is possible that this SNP could partially contribute to the racial disparity observed in CRC outcomes.

SNPs in Diabetes, IGFs, and Adipokines

Through GWAS many SNPs related to obesity, diabetes, and insulin resistance have been identified. For example, SNPs in the *fat mass and obesity-associated gene (FTO)* were discovered to associate with the risk of type 2 diabetes or obesity in Caucasians, and in particular strong associations were seen at locus rs9939609 [150–154]. Association of polymorphisms at this locus with BMI and diabetes has since been reproduced in Asian populations, as well [155–158]. However, the minor A allele at locus rs9939609, though occurring at similar frequencies in African Americans and Caucasians, was not found to be associated with obesity or diabetes in African Americans contrary to that observed in Caucasians [153, 154, 159, 160]. Rather, SNPs at other loci on the *FTO* gene were associated with elevated BMI in African Americans [153, 159], suggesting that African Americans and Caucasians have race-specific polymorphisms that could confer disease risk differentially. When assessing associations with colorectal adenomas, Nock et al. observed that having one variant allele polymorphisms on the *FTO* gene at rs9939609 or r8050136 was associated with adenomas in African Americans

[161]. However, these associations were not observed in Caucasians. Cheng et al. evaluated 19 established type 2 diabetes risk variants for their associations with CRC by race [162]. The T variant allele at rs7578597 on the *THADA* gene was protective against CRC in Caucasians, Latinos, and Japanese Americans, but not in African Americans, and this association was strongest among those without diabetes or with normal BMIs. These results further provide a possible genetic explanation for the ethnic differences in the risk of diabetes and obesity in relation to colon cancer while demonstrating the complexities involved in interpreting effects of SNPs.

SNPs play an important physiological role because allelic variation results in differential expression of peptides in plasma. Increased frequency of minor alleles at different loci of the IGF-1 gene has been observed to affect levels of growth factors, even independent of BMI [163–169]. The IGF-1 gene has a polymorphism, a microsatellite $(CA)_n$ in the promoter region, that has been shown to influence IGF-1 levels. The$(CA)_{19}$ repeat is the most common allele reported in Caucasian (62–68 %), Japanese (41 %), Indian Pakistani (56 %), and African American (38 %) populations [170]. Keku et al. observed that Caucasians with homozygous IGF-1 19/19 genotype had an increased risk of colon cancer but not African Americans [168]. Wong et al. did not observe any changes in the risk among those who carried one or two copies of the $(CA)_{19}$ allele in Singapore Chinese, but $(CA)_{21}$ homozygosity was associated with approximately half of the risk for CRC in this population [170]. Morimoto et al. detected that in a mostly Caucasian population in the USA, having an IGF-1 genotype other than the homozygous 19-repeat allele was associated with a modestly increased risk of CRC (OR = 1.3, 95 % CI 1.0–1.6) [171]. This finding was supported by Pechlivanis et al. in Germans [172]. These results provide support to the idea that SNPs differ distinctly by race and could serve to explain the racial disparities in CRC.

A number of studies have previously linked common SNPs in the leptin and leptin receptor genes such as A+ 19G (rs2167270), Gln223Arg (rs1137101), and G-2548A (rs7799039) to obesity [173–179]. Friedlander et al. evaluated SNPs in leptin and leptin receptor genes by race and observed that African Americans and Caucasians have different SNPs in leptin receptor genes (rs3828033 and rs1137101 in African Americans and rs3828033 and rs6696954 in Caucasians) that were associated with weight changes over time [180]. More recent studies evaluated the association of SNPs in these genes to the risk of CRC. Slattery et al. observed a reduction in colon cancer risk with variant AA genotype at rs2167270 in the leptin gene in a mostly Caucasian cohort and showed that vitamin D receptor and IGF-1 polymorphisms interact with leptin gene polymorphisms to modify the risk [181]. In a different Caucasian cohort, Vasku et al. observed a difference in the genotype distribution of Gln223Arg polymorphisms in the leptin receptor gene among CRC patients with low (I–II) and high stages (III–IV). Wild-type AA genotype was associated with an elevated risk to patients in III–IV stages [182] suggesting that SNPs could influence not only the risk of CRC but also the prognosis. In a Chinese cohort, Liu et al. demonstrated a different group of SNPs in the leptin receptor gene modifying CRC risk [183]. Two common polymorphisms in the adiponectin gene, T45G and G276T, have been associated with obesity and insulin resistance in European whites and Asians [184–191]. More

recently, variant SNPs at −11,391 G > A and −11,377 C > G have also been found to affect serum adiponectin levels, obesity, and insulin resistance in Caucasians [192–196]. Additionally, Woo et al. confirmed that A and G haplotypes of SNPs at −11,391 and −10,068, respectively, were associated with elevated adiponectin levels in African Americans [197]. In a Chinese population, adiponectin (*ADIPOQ*) rs1063538 variant CC genotype was associated with increased CRC risk (OR = 1.94, 95 % CI 1.48–2.54) compared with TT [198]. This CC genotype demonstrated a further increased CRC risk in those with a family history of cancer (OR = 3.18, 95 % CI 1.73–5.82) or smoking history (OR = 4.52, 95 % CI 2.78–7.34), demonstrating that SNPs can modify response to environmental agents. Keku et al. studied a SNP at rs1501299 of the adiponectin gene (*APM1*) between African Americans and Caucasians and did not find any increased risk of CRC with the variant genotype in either race [168], which could suggest that either the sample size was too small to detect a significant difference or that a SNP at this locus does not influence CRC risk. All these studies demonstrate evidence as to how various ethnicities have differential disease risk while delineating the limitations and difficulties in studying genetic variations related to CRC.

SNPs in Inflammatory Markers and CRC

As inflammatory cytokines also play a pivotal role in insulin resistance, studies have evaluated SNPs in the TNF-α gene. Multiple SNPs including −1,031 (T → C), −863 (C → A), −857 (C → A), −851 (C → T), −419 (G → C), −376 (G → A), −308 (G → A) (rs1800629), −238 (G → A), −162 (G → A), and −49 (G → A) have been reported [199]. Most extensively studied are the polymorphisms at −308 and −238. Dalziel et al. observed that those with a homozygous variant −308 AA had higher insulin resistance, systolic blood pressure and lower high density lipoprotein than those with wild type GG profile [200]. Sookoian et al. determined that those with −308 A variant alleles were at an increased risk of obesity (OR = 1.23, 95 % CI 1.05–1.45) [201]. Fontaine-Bisson et al. similarly observed an association between higher insulin resistance and the variant A allele, however, this relationship only occurred in obese individuals [202]. De Luis et al. found that on a diet lower in fats or carbohydrates, those with wild type −308 GG genotype improved in many aspects of metabolic profile including BMI, fat mass, blood pressure, insulin, and cholesterol, but those with the variant A allele only improved in BMI and fat mass without other added benefits [203]. Of note, these studies were conducted in a Caucasian population. Conclusions from these studies suggest that the variant A allele at −308 in the TNF-α gene confers susceptibility and higher risk for insulin resistance and obesity, and those with the wild-type allele at this locus may benefit more from a healthier diet. However, contrary to these findings, Rasmussen et al. did not see any associations between genetic variants in −308 and −238 with altered insulin sensitivity, BMI, WHR, fat mass, or insulin concentrations [204]. In the only study available among African

Table 7.2 Association of individual or combined inflammation related genes and colon cancer among African Americans and Caucasians (Keku et al., unpublished)

		African American		Caucasian	
		Case/control	OR (95 % CI)	Case/control	OR (95 % CI)
IL-6	GG	177/234	1.0 (Ref)	82/149	1.0 (Ref)
	GC	35/34	1.5 (0.9, 2.6)	136/231	1.1 (0.8, 1.5)
	CC	1/0	–	47/82	1.0 (0.7, 1.6)
TNF-α	GG	158/219	1.0 (Ref)	182/308	1.0 (Ref)
	AG	53/44	**1.8 (1.1, 2.8)**	79/133	1.0 (0.7, 1.4)
	AA	2/5	0.5 (0.08, 2.5)	4/21	**0.3 (0.1, 0.9)**
CRP	GG	136/175	1.0 (Ref)	116/230	1.0 (Ref)
	AG	66/81	1.0 (0.7, 1.5)	122/190	1.2 (0.9, 1.7)
	AA	11/12	1.3 (0.6, 3.1)	27/42	1.3 (0.7, 2.2)
# Var Alleles	0–1	46/62	1.0 (Ref)	9/36	1.0 (Ref)
	2–3	116/159	1.0 (0.6, 1.6)	130/200	**2.7 (1.2, 5.8)**

Cases subjects with colon cancer, *Controls* subjects without colon cancer
Values in bold demonstrate that while having a AG genotype in TNF-A locus confers increased risk to African Americans, it does not in Caucasians. Similarly, having an AA genotype demonstrate decreased risk in Caucasians, it had no effect in African Americans

women, the variant allele frequency at −308 did not differ between those with normal and obese weights [205]. However, when dietary fat intake was 30 % of the total energy intake, those with the variant A allele had reduced odds of being obese, but with increasing fat content of the diet, obesity risk increased at a faster rate. Reports on associations between CRC risk and TNF-α (at −308 or −238) demonstrate a null relationship in Caucasians and Asians [206–211]. In our work, we observed that African Americans with AG genotype at −308 had an 80 % increased risk (OR = 1.8, 95 % CI 1.1–2.8) of colon cancer compared to African Americans with wild-type GG genotype (Table 7.2). Further, increased risk was only present in those with GG (OR = 1.9, 95 % CI 1.2–2.9) or AG (OR = 3.5, 95 % CI 1.9–6.5) genotypes who had not used NSAIDs regularly compared to those with wild type GG genotype who reported taking NSAIDs regularly (Table 7.3). Similar protective effects from NSAIDs were observed for Caucasians. Our results support the previous conclusions regarding the preventative role of regular NSAID use in CRC. Further, if confirmed in larger studies and as SNP testing becomes more available, it is possible that in the future the determination of SNPS at TNF-α −308 could be useful in individualizing medical care to reduce colon cancer risk, especially among those who use NSAIDs.

SNPs on the IL-6 gene have also been evaluated for associations with obesity and insulin resistance. The majority of the studies on Caucasian populations demonstrated a positive association with increasing BMI, glucose, or insulin resistance with an increasing number of variant C allele at IL-6 −174 [212–217]. Further, this in turn influences the response to diet or exercise [212, 214, 218]. Clinical studies demonstrated that circulating IL-6 level was correlated with CRC stage, survival, or hepatic metastasis [219, 220], and that serum concentrations could be altered by SNPs in the IL-6 gene promoter region [221, 222]. However, the

Table 7.3 Joint effects of individual or combined cytokine genes and NSAIDs use on colon cancer risk among African Americans and Caucasians (Keku et al., unpublished)

		African Americans NSAID use				Caucasians NSAID use			
		Yes		No		Yes		No	
Gene		Cases/controls	OR (95 % CI)	Cases/controls	OR (95 % CI)	Cases/controls	OR (95 % CI)	Cases/controls	OR (95 % CI)
IL-6	GG	60/117	1.0 (Ref)	116/117	**1.8 (1.2, 2.8)**	30/87	1.0 (Ref)	52/62	**2.4 (1.3, 4.1)**
	GC	7/16	0.9 (0.4, 2.5)	28/18	**3.2 (1.6, 6.4)**	62/138	1.3 (0.8, 2.2)	74/93	**2.2 (1.3, 3.8)**
	CC	0/0	–	1/0	–	20/34	1.7 (0.8, 3.4)	27/48	1.6 (0.8, 3.0)
TNF-α	GG	53/110	1.0 (Ref)	104/109	**1.9 (1.2, 2.9)**	74/168	1.0 (Ref)	108/140	**1.7 (1.2, 2.5)**
	AG	14/20	1.5 (0.7, 3.2)	39/24	**3.5 (1.9, 6.5)**	37/78	1.1 (0.6, 1.7)	42/55	1.7 (1.0, 2.7)
	AA	0/3	–	2/2	1.4 (0.2, 10.7)	1/13	0.2 (0.02, 1.4)	3/8	0.8 (0.2, 3.2)
CRP	GG	41/87	1.0 (Ref)	94/88	**2.1 (1.3, 3.5)**	50/126	1.0 (Ref)	66/104	1.6 (1.0, 2.5)
	AG	21/39	1.1 (0.6, 2.1)	45/42	**2.1 (1.2, 3.8)**	52/112	1.1 (0.7, 1.8)	70/78	**2.1 (1.3, 3.4)**
	AA	5/7	1.7 (0.5, 5.8)	6/5	2.6 (0.7, 9.2)	10/21	1.2 (0.5, 2.8)	17/21	1.9 (0.9, 4.0)
# Variant alleles	0–1	14/27	1.0 (Ref)	32/35	1.5 (0.7, 3.5)	4/19	1.0 (Ref)	5/17	1.3 (0.3, 5.7)
	2–3	38/82	0.9 (0.4, 1.8)	77/77	1.8 (0.9, 3.7)	47/115	1.9 (0.6, 6.1)	83/85	**4.6 (1.5, 14.3)**

Cases subjects with colon cancer, *Controls* subjects without colon cancer

Values in bold demonstrate that while having GG or GC genotype in IL-6 locus were associated with increased risk to both African Americans and Caucasians, TNF-alph and CRP, there was a differential risk depending on ethnicity

literature examining the relationship between SNPs and CRC risk at this locus is inconclusive. Some endorse the variant C allele to be a risk for CRC [208, 223, 224] while others show that the G allele is the risk [182, 210]. A possible explanation for this discrepancy is that there is a significant interaction between NSAID use and SNPs at IL-6 −174. When individuals with the C polymorphism regularly or currently took NSAIDs, they had a reduced CRC risk, and those who were alcohol drinkers had increased risk [223, 225]. Modification of risk by NSAID use was also supported by our work (Table 7.3). Unlike TNF-α, where allelic variations are reported to occur in similar frequencies between Caucasians and African Americans, minor allele frequencies at IL-6 −174 are different depending on race. Whereas in Caucasians minor C allele is relatively common (38 %), in African Americans and Asians it is relatively rare (10 % and 3 %, respectively), which would imply that African Americans with a risk allele in IL-6 −174 as a whole would derive less benefit with medication and lifestyle interventions in reducing CRC risk [226, 227].

Circulating CRP levels are also affected by SNPs in genes coding for CRP as well as in other inflammatory genes such as in IL-6, IL-1γ, and TNF-α [228–236]. Racial differences in CRP gene polymorphisms that alter CRP levels have been best studied thus far in cardiovascular disease. Variant alleles at 1,919 A > T and 2,667 G > C were associated with higher and lower levels of CRP, respectively, in Caucasian participants, while in African Americans, the variant T allele at 790 A > T was associated with higher CRP levels [237]. Additionally, at rs3093058 having a variant T allele was associated with increased levels of CRP while having a variant A allele at rs1205 and variant G allele at rs2808630 were associated with decreased levels of CRP compared with the homozygous referent genotypes in African Americans [238]. SNPs and haplotypes in the CRP gene have been associated with obesity such that if positive for the minor allele at rs1205, as BMI increased, CRP levels in men also increased [239]. Similar results with minor alleles altering CRP levels in obese individuals were observed at rs2794521, rs1800947, and rs1130864 [240, 241]. Regarding CRC risk, Tsilidis et al. found that in Caucasians who are variant C allele carriers at the −717 T > C promoter (rs2794521) or 2,407 T > C (rs2808630), there was an approximately 50 % increased risk [221] while Asian patients with CRC were observed to have a higher percentage of homogeneous wild-type TT genotype at −757 T > C (rs3093059) than those without CRC [242]. Further, in this Asian population SNPs affected the prognosis of CRC. Homogeneous wild type TT genotype at −757 T > C was associated with a longer disease-free interval than those with TC and CC genotypes, and homogenous wild-type AA genotype at +2,147 A > G was associated with a shorter cancer-specific survival. Whether these or those SNPs at other loci in the CRP gene will influence prognosis of African American patients with CRC is yet to be determined.

As chronic inflammation is a risk factor for CRC, polymorphisms in one of the inflammatory mediators, called mannose-binding lectin 2 (*MBL2*), also have been shown to modify risks to various cancers. There are specific haplotypes that have been demonstrated to correlate with MBL serum levels [243–245]. Further,

frequencies of SNPs and haplotypes that occur in this gene also differ between Caucasians and African Americans [244, 246]. Zanetti et al. demonstrated that compared to the highly secreting haplotype (HYPA), haplotypes that produced low (LYQC) and moderate (LYPA) plasma levels of MBL had increased susceptibility to colon cancer (LYQC OR = 2.28, 95 % CI 1.20–4.30; LYPA OR = 2.6, 95 % CI 1.33–5.08), but only in African Americans and not in Caucasians [246]. Accordingly, African Americans with CRC had lower plasma MBL levels than Caucasians with CRC. As it has been observed that MBL can bind to ligands on colorectal tumor cells and inhibit tumor progression [247, 248], it is possible that genetic mutations that lead to lower plasma levels of MBL in African Americans predispose them to CRC. This represents exciting new evidence that could aid in explaining why African Americans have higher incidence of CRC.

Lastly, COX-2 gene polymorphisms in relation to CRC and adenoma risk have been evaluated. In mostly Caucasian populations having a variant C allele at −765 G > C was protective [249–251] while in Asian populations it appeared to increase the risk of CRC [252–254]. Further, the risks conferred by the SNP were dependent on the use of NSAIDs, smoking, or obesity. Siemes et al. found that carriers of the C allele who used NSAIDs in the 5 years prior to the diagnosis of CRC had survivals that were twice as long as those who were homozygous for G allele who did not use NSAIDs [250]. Xing et al. observed that smokers with homozygous wild type GG genotype had 2.68-fold increased risk of CRC compared to nonsmokers, and those who were overweight had twice the risk of CRC compared to those with normal BMIs [253]. In African Americans, the polymorphism at Val511Ala has been studied. While the SNP that changes valine to alanine at 511 is present in 4–7 % of African Americans, it is nearly absent in Caucasians [255, 256], and although not statistically significant, Ala COX-2 genotype has been shown to decrease the risk of CRC and colorectal adenomas [256, 257]. Polymorphisms at other loci in African Americans demonstrated that 6,064 T > C, 10,848 G > A, 10,935 A > G, 5,229 G > T, and 10,935 A > G may affect adenoma risk; however, these studies demonstrated contradicting risk associations regarding the SNP at 10,935 [258, 259].

Limitations of Genetic Susceptibility Studies, Future Directions, and Conclusion

Throughout this chapter, we mentioned examples of SNPs at same genetic loci resulting in conflicting associations. This showcases one of the current limitations of gene susceptibility studies using polymorphisms. Many of the association studies evaluating the relationship between SNPs and disease have been plagued by the inability to produce results that are consistent. Possible explanations for these findings could be inadequately powered studies with small sample sizes, false positivity due to execution of large number of tests, inability to determine linkage

disequilibrium, and admixture of study populations [260]. Throughout this chapter, examples of differential effects of SNPs depending on ethnicity have been presented, which suggest that a polymorphism as a disease marker from one population cannot be applied to a different group of patients. Furthermore, though statistically significant associations have been identified through GWAS, an enormous gap exists in providing biological mechanisms for how these SNPs are related to disease pathogenesis. Similarly, the majority of these genomic markers explain only a small magnitude of susceptibility risk at roughly 10 %, and with slightly higher risk for homozygotes, which points to the possibility that if higher powered GWAS could be performed, effect sizes may increase [261]. Lastly, there are limitations in these studies of identifying gene–gene or gene–environment interactions, which have had profound impacts in some cases [261].

Despite these limitations, a number of GWAS have been performed that identified and replicated genetic variants associated with CRC risk and prognosis. Programs such as the International HapMap project, the National Institute of Health's dbSNP database, and the National Human Genome Research Institute's catalog of published GWAS studies work to bring together available knowledge. Results from these studies have confirmed key pathways as well as lifestyle factors that could affect primary and secondary prevention of CRC. New findings can also lead to targeted therapies as well as identify high-risk populations that could benefit from early intervention. Future studies will reveal if currently discovered risk alleles will endure to have real clinical applications.

In conclusion, the higher incidence and worse survival in CRC observed in African Americans compared to Caucasians may be partly due to higher obesity and insulin resistance present in African Americans. While diet and exercise likely impact the incidence of these conditions, literature has shown that African Americans have a disproportionately higher insulin resistance while having lower central obesity than Caucasians. Further, currently available evidence demonstrates that levels of cytokines and peptide hormones that contribute to obesity, insulin resistance, chronic inflammation, and CRC are influenced by genetic polymorphisms that are present in a race-specific manner. These polymorphisms have been associated with altered CRC risk while modifying response to environmental agents such as NSAIDs, smoking, and obesity. Given that there are millions of SNPs, most of which have yet to be discovered and their biological significance elucidated, the extent to which SNPs or combinations of SNPs actually contribute to the worse prognosis observed in African Americans with CRC is yet to be determined. However, as GWAS and genetic analyses become more widespread and available, it becomes increasingly possible to be able to explain why African Americans or other populations (i.e., those with family history of sporadic cancer) may have increased CRC risk and understand the biological mechanisms behind disease pathogenesis. Accordingly, in the future we may be able to offer interventions and treatments tailored to specific genotypes and high-risk populations.

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Chapter 8
Ethnic Differences in Insulin Resistance as a Mediator of Cancer Disparities

Rebecca E. Hasson and Michael I. Goran

Abstract Ethnic differences in the incidence and prevalence of certain obesity-related cancers are well established. African Americans have increased risk of prostate, breast (premenopausal), and colorectal cancer and myeloma, compared to Caucasians with the lowest rates in Latinos, Asians, and Native Americans. Prior work in this area suggests that there are distinct ethnic differences in obesity-related metabolic risk factors for cancer, insulin resistance in particular, that are evident early in life, and may help explain ethnic differences in the incidence and prevalence of obesity-related cancers. The focus of this chapter is to review and discuss ethnic differences in insulin resistance and its link with other cancer-related metabolic risk factors including hyperinsulinemia, insulin-like growth factors, body fat distribution, adipose tissue biology, low-grade inflammation, non-esterified fatty acids, and oxidative stress. This chapter places a particular emphasis on ethnic differences between African Americans and Latinos for two reasons: (1) African Americans and Latinos are the two largest ethnic minority groups in the USA, and (2) these populations share a similar propensity for obesity and insulin resistance but markedly different profiles for obesity-related cancers, creating an informative comparative contrast. Although the literature is limited by an inconsistency in the terminology used for various ethnicities, in most cases we refer to Caucasian for any study using the terms Caucasian, White, or non-Hispanic White; Latino to describe people of Hispanic, Latino, or Mexican-American descent; African American to describe people of African, African American, or Black-Caribbean descent; Asian to describe people of Asian, South Asian, East Asian, and Southeast

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Asian descent or any other specific Asian ethnicity; and Native American to describe people of American Indian, Pima Indian, Aboriginal, First Nation, or Alaska Native ethnicity. We also recognize that there may be variation within these subgroups; however, comprehensive review of this literature is beyond the scope of this chapter.

Keywords Insulin • Insulin resistance • Hyperinsulinemia • Insulin-like growth factor • Non-esterified fatty acids • Oxidative stress • Psychological stress • Cortisol-induced obesity • Body fat distribution • Intramyocellular lipid • Hepatic fat • Pancreatic fat • Ectopic fat • Adipose tissue biology

The Scope of the Problem: Obesity and Cancer Disparities

According to the 2010 US Current Population Survey, there are 53 million people of Latino origin and 41 million African Americans in the USA, comprising 17 % and 13 % of the total population, respectively. Latinos are the fastest growing ethnic group in this country adding almost 13 million people to the population and increasing in size by 41 % in the last decade. Obesity is a significant problem in both African Americans and Latinos with the most recent National Health and Nutrition Examination Survey (NHANES) estimates from 2009 to 2010 suggesting higher rates of overweight and obesity in African American and Latino adults compared to Caucasians [1]. In adults, 20 years of age and older, African Americans had the highest age-adjusted rates of obesity (49.5 %), followed by Mexican Americans (40.4 %), all Latinos (39.1 %), and Caucasians (34.3 %). Of note, the prevalence of grade 2 [body mass index (BMI) of at least 35 kg/m^2] and grade 3 obesity (BMI greater than or equal to 40 kg/m^2) were highest among African Americans (26 % for grade 2, and 13.1 % for grade 3), compared to Caucasians (14.4 % for grade 2, and 5.7 % for grade 3) and Latinos (14.9 % for grade 2, and 5.4 % for grade 3). Although American Indians comprise a smaller proportion of the total US population (1.2 %), obesity is also a significant problem in this ethnic group with 39.4 % of American Indian men and women categorized as obese [2]. Among Asians, this ethnic group is 60 % less likely to be obese compared to Caucasians; however, there is substantial variation in the prevalence of overweight and obesity within this ethnic group [3]. Filipino Americans are 70 % more likely to be obese as compared to the overall Asian population. Interestingly, Southeast Asians have one of the highest prevalences of type 2 diabetes in the USA, yet the prevalence of obesity in this group is 6 % with 30–35 % of Southeast Asians classified as overweight [4]. In contrast, Chinese, Korean, and Vietnamese Americans have the lowest rates of overweight (BMI, 25 to $<$30 kg/m^2) and one in ten Korean and Vietnamese Americans are classified as underweight [3].

In 2010, pediatric obesity rates in the USA also showed a well-defined disparity by ethnicity, where 42 % of Latinos, 41 % of African Americans, and 30 % of Caucasians between the ages of 12 and 19 years were classified as overweight or obese [5]. Of note, Native American adolescents had the highest prevalence of obesity than those in all other ethnic groups combined [6]. As a result, obesity-related complications such as prediabetes and type 2 diabetes are more common in ethnic minority children and adults compared to Caucasians [7–12]. Specifically, the risk of diagnosed diabetes is 1.8 times higher among African Americans, and 1.7 times higher among Hispanics compared to Caucasians [13]. Moreover, 16.1 % of the total adult American Indian population has diagnosed diabetes [13]. A similar trend is noted in children, with African American, Latino, and Native American children reporting the highest rates of type 2 diabetes compared to other ethnicities [11, 12, 14]. The higher risk and prevalence of type 2 diabetes among these ethnic minority groups have been attributed to more severe insulin resistance and hyperinsulinemia (relative to Caucasians [8, 15–18]).

There is convincing evidence that overweight and obesity are also associated with cancers of the kidney, breast, colon, esophagus, endometrium, prostate, and colorectum, whereas studies on the relation between obesity and other forms of cancers are less consistent [19–23].

Despite a similar predisposition towards obesity, insulin resistance, and type 2 diabetes among African Americans, Latinos and Native Americans, there are marked differences in cancer incidence across different ethnic groups [24]. African Americans have increased risk of certain forms of obesity-related cancers, whereas for these same outcomes, Latinos and Native Americans appear to be somewhat "protected." In support of this hypothesis, data from the Surveillance Epidemiology and End Results (SEER) Database suggest that African American men have the highest incidence of cancer (all cancers combined) followed by Caucasians, with lower cancer rates among Latino, Native American and Asian men [25]. More specifically, African American men in the USA have the highest rates of prostate cancer worldwide. The prevalence rate is almost two times higher compared to Caucasians and Latinos and almost three times higher compared to Native Americans and Asians [25]. Breast cancer—the most common cancer among women—is highest among African Americans and Caucasian women compared to Latinas, Native Americans, and Asians. Interestingly, African American women have the highest rates of breast cancer before age 40 whereas Caucasians have the highest rates at older ages [26]. For both men and women, rates of colorectal cancer and myeloma are highest among African Americans followed by Caucasians with the lowest rates among Latinos, Native Americans, and Asians [25, 27]. Similar trends are observed for most other types of cancer, with rates among African Americans or Caucasians higher than those for other ethnic minority groups including Latinos [25]. Taken together, distinct differences in obesity-related cancer outcomes persist between African Americans, Latinos, and Native Americans despite all three

groups having an increased propensity for obesity and similar risk for type 2 diabetes. This chapter reviews ethnic differences in cancer-related metabolic risk factors, insulin resistance, and hyperinsulinemia in particular and their potential contributions to ethnic differences in obesity-related cancer outcomes.

Obesity and Cancer Risk: Potential Mechanisms

Insulin Resistance

Obesity is the strongest contributing factor to insulin resistance and hyperinsulinemia, and this is evident early in life [8, 15, 28–30]. Many studies have shown that body fatness is positively associated with circulating fasting insulin levels in both animals and humans [31]. Insulin is a critical hormone for regulating metabolism, and its concentration in circulation is carefully coordinated, varying acutely in response to glucose and meal consumption. Insulin resistance is a condition in which muscle, fat, and liver cells are less sensitive to the metabolic effect of insulin. As a result, physiologic actions of insulin are inhibited but can be compensated for by increased insulin levels in circulation (i.e., hyperinsulinemia) to clear glucose from circulation [32, 33]. In addition, elevated insulin may stimulate cellular proliferation in pancreatic beta cells and fat cells, ensuring additional insulin production and fat storage, respectively [34]. This mechanism may have substantial advantages because it provides fat cells that can hold on to ingested fat and prevent its ectopic distribution elsewhere in the body [35, 36]. Thus, obesity results in continuous exposure of body tissues to elevated background and glucose-stimulated levels of insulin.

One of the leading hypotheses explaining why "fat is bad" relates to the role of insulin resistance and hyperinsulinemia as the mediating link between obesity and cancer risk. As mentioned above, besides its metabolic effects, insulin has promitotic and anti-apoptotic effects that may be tumorigenic [23, 37, 38]. Moreover, increased insulin resistance and hyperinsulinemia have been associated with increased risk of breast, endometrial, and colon cancer [20, 39–45]. Hence, detailed studies comparing ethnic differences in insulin resistance and hyperinsulinemia have been helpful in understanding why certain subgroups of the population are at increased cancer risk.

Research has consistently demonstrated that African Americans are more insulin resistant compared to Caucasians, which is only partially explained by greater overall adiposity in this ethnic group [8, 18, 46–56]. The Insulin Resistance Atherosclerosis Study (IRAS), a large-scale multicenter epidemiological study, was the first to provide compelling evidence in support of a metabolic predisposition towards insulin resistance in African American adults [57]. Compared to

Caucasians, African Americans had significantly higher fasting and 2-h postprandial insulin concentrations, higher acute insulin responses to glucose, and greater insulin resistance [57]. These ethnic differences persisted after adjusting for differences in age, obesity, body fat distribution, self-reported physical activity, and percent calories from fat and fiber. Data from the NHANES III subsequently confirmed ethnic differences in mean fasting insulin concentrations between African American and Caucasian men and women at each BMI category [55].

Similar to African Americans, large-scale studies of obesity, insulin resistance, insulin secretion, and beta-cell response in Latino and Native American populations have consistently reported an increased insulin response to glucose [8, 50, 58–61]. Glucose-tolerant Native Americans and Latinos were found to have greater insulin resistance and fasting hyperinsulinemia compared to Caucasians [62–65]. In addition, both groups were found to have exaggerated early insulin secretory responses to both intravenous and oral glucose challenges [50, 58, 59, 66, 67]. Others have confirmed that Latino adults have greater fasting and post-challenge insulin and greater insulin resistance than Caucasians [8, 62].

Studies in children are of increased significance because they allow examination of potentially underlying biological differences across subgroups of the population to be performed in the absence of potential confounding factors such as smoking, alcohol, aging, and menopausal status. Data from the Bogalusa Heart Study were the first to report increased insulin resistance in African American compared to Caucasian children based on measures of fasting insulin [68]. Subsequently, other studies have demonstrated greater insulin resistance and greater acute insulin response to glucose in African American compared to Caucasian children [30, 69]; these differences were independent of body fat, visceral fat, dietary factors, and physical activity. A recent study, using a hyperglycemic clamp technique, supported these observations where overweight African American compared to Caucasian youth had up to a 75 % higher insulin secretion relative to their insulin sensitivity [15], an indicator of increased or up-regulated pancreatic beta-cell responsiveness.

Ethnic differences in insulin resistance have been well documented in Latino, Asian, and Native American youth, where, independent of overall adiposity, these ethnic minority groups exhibit more severe insulin resistance but an enhanced insulin secretory response when compared to Caucasian children [8, 11]. Studies comparing multiple ethnic groups confirmed greater insulin resistance during an intravenous glucose tolerance test in Native Americans compared to African Americans and Caucasians [70]. Another study reported equally greater insulin resistance assessed via hyperglycemic clamp among African Americans, Latinos, and Asians than in Caucasians [62]. In addition, Asians were the most insulin resistant followed by Latinos, African Americans, and Caucasians [62]. In prepubertal children, African American and Latino children were found to be equally more insulin resistant than Caucasian children [8]. However, in peripubertal adolescents, obese African Americans were more insulin resistant than Latinos,

independent of body composition and fat distribution [60]. Pancreatic beta-cell function and the acute insulin response to a glucose challenge were also higher in African American than in Latino adolescents, suggesting that ethnic differences in pubertal induced insulin resistance may be an important contributor to ethnic differences in insulin resistance [71]. Of interest, the compensatory responses to insulin resistance were different in African American compared to Latino children and adolescents [8]. African American children tend to compensate with a higher acute insulin response to glucose, and this effect was in part due to a reduction in hepatic insulin extraction [8]. Following the ingestion of oral glucose, lower extraction rates have also been reported in African American adults [54]. In contrast, Latino children and adolescents compensate to the same degree of insulin resistance with greater second-phase insulin secretion [8]. Both beta-cell secretion and/or insulin clearance by the liver determine peripheral insulin levels and help to maintain normal glucose levels in circulation [72]. The mechanisms by which Native American and Asian populations compensate for insulin resistance is understudied; nevertheless, increased insulin resistance and secretion as well as hyperinsulinemia are present among ethnic minority children, adolescents, and adults compared to Caucasians, and these findings have been confirmed using a variety of methodologies.

The well-documented ethnic differences in insulin resistance and secretion in children and adults have been explained in part by genetic, behavioral, and/or environmental factors. Previous research has reported a positive association between African genetic admixture and insulin resistance [73]. In contrast, recent work has demonstrated that socio-behavioral factors including physical activity and self-reported racial discrimination, but not African genetic admixture, were associated with increased cardiometabolic risk (i.e., blood pressure) among African Americans [74]. Moreover, research in the area of molecular epigenetic mechanisms of gene expression has also suggested that the genome is subject to environmental regulation [75], suggesting that ethnic differences in insulin resistance may have a gene-environmental origin. Consequently, in addition to nutrition and physical activity (which is further discussed in the next chapter), research has begun to investigate the role of the social environment, particularly psychosocial stress, and its implications for obesity and insulin resistance. The physiological stress response originates from the hypothalamic-pituitary-adrenal axis and undergoes a cascade of reactions including the release of corticotrophin-releasing hormone from the hypothalamus, causing the release of adrenocorticotrophic hormone by the adrenal pituitary, and ultimately the release of cortisol by the adrenal cortex into circulation [76]. Cortisol levels increase in response to both stressors in the laboratory [77] and naturalistic social environments [78]. Designed to increase energy availability in the short term, cortisol acutely impairs insulin secretion and increases hepatic glucose output [79]. An environment of prolonged glucocorticoid exposure (i.e., chronic stress) exerts diabetogenic effects by interfering with insulin action on several different levels [80–82], including a direct inhibition of insulin secretion from pancreatic beta cells [83], impaired insulin-mediated glucose uptake [84], and disruption of the insulin signaling cascade in skeletal muscle [85]. Under

chronic conditions, healthy lean individuals appear able to compensate for glucocorticoid-induced insulin resistance with increased beta-cell function or increased insulin release [86–88]. However, in the obese or the insulin-resistant state, those compensatory mechanisms fail to counteract glucocorticoid-induced insulin resistance, resulting in hyperglycemia [87, 88]. Hence, prolonged glucocorticoid exposure may further compromise the already lower insulin sensitivity in obese African Americans by exacerbating the progression towards insulin resistance in these populations. Previous research has demonstrated the negative association between cortisol and obesity in adults [89, 90], and a recent study showed that cortisol contributes to the reduction in insulin sensitivity over a 1-year period in overweight Latino children and adolescents [91], underlining the relevance of reducing glucocorticoid-induced insulin resistance in ethnic minority populations.

Prolonged glucocorticoid exposure also leads to weight gain and visceral fat accumulation [92–94], not only through behavioral pathways such as increased food consumption [92, 95, 96] and sedentariness [97–100] but also directly via the release of neuropeptide Y [93, 96]. Several longitudinal studies have reported a positive association between psychological stress and BMI in adults [101, 102]. Another study reported that higher levels of psychological stress over a 10-year period predicted significantly greater increases in BMI over time compared to lower levels of stress, and this relationship was significantly stronger for African American compared to Caucasian girls [103]. In Latino youth, a significant association between cortisol, total fat mass, and visceral fat accumulation has not found [91], suggesting that the mechanisms by which cortisol induced obesity and insulin resistance may differ by ethnicity.

In addition to responding to stressful events, the HPA axis also follows a strong circadian rhythm [78, 104]. Typically, cortisol levels are high upon waking; reach a peak about 30–40 min after waking; and then decline throughout the remainder of the day, reaching a nadir around midnight [104, 105]. The scientific literature examining ethnic differences in cortisol is not extensive but demonstrates divergent diurnal cortisol patterns for African Americans compared to Caucasians [106–110]. African Americans tend to have flatter diurnal cortisol slopes, with lower morning levels and higher evening levels, than Caucasians [106–110]. These findings have been replicated across studies of adolescents [107], pregnant women [110], adults [108, 111], and elderly populations [109]. Two studies examining ethnic differences in cortisol diurnal patterns in normal-weight African American, Latino, and Caucasian children and adolescents also reported flatter morning-to-evening cortisol slopes among African Americans and lower evening cortisol levels for Latinos relative to Caucasians [107, 112]. Deviations from the typical diurnal patterns have important implications for insulin resistance [113]. Specifically, flattened diurnal patterns previously reported in chronically stressed individuals are associated with insulin resistance and cancer-related metabolic risk factors (i.e., inflammation) [113]. Hence, greater exposure to psychosocial and environmental stressors (e.g., socioeconomic burden and racial discrimination) in African American populations may contribute to the increased obesity and insulin resistance, hyperinsulinemia, and subsequent cancer risk in this population.

Hyperinsulinemia and the IGF-1 Pathway

The direct effects of insulin resistance on cancer risk are unclear and likely do not solely explain the increased cancer risk among African Americans compared to Latinos and Native Americans since all three ethnic minority groups appear to be similar in degree of insulin resistance. Accordingly, the effect of insulin resistance is postulated to be mediated by the effects of chronic hyperinsulinemia on insulin-like growth factor (IGF)-1 bioactivity [23]. IGF-1 is a growth factor that is regulated by growth hormone levels [114, 115], present in circulation, and has insulin-like properties and functions [116]. The bioactivity of IGF-1 is determined by the circulating IGF-1 and IGF-binding protein (BPs) produced by the liver as well as paracrine effects of IGF-1, IGFBPs, and IGFBP proteases [23]. Insulin can also affect IGF-1 bioactivity via increasing IGF-1 secretion, IGF-1/IGFBP-3, IGFBP-3 proteolysis, and secretion of IGFBP-1 and IGFBP-2 and increased responsiveness of cells to IGF-1 and other growth factors. Numerous studies suggest that high level of IGF-1 is a risk factor for several cancers including breast, prostate, colon, and lung cancer [117–122].

IGF-1 bioactivity has been implicated in carcinogenesis as a function of its ability to stimulate the differentiation and proliferation of myoblasts as well as inhibit apoptosis [38]. Moreover, increasing evidence suggests that chronic hyperinsulinemia increases the risk of colon and endometrial cancer [20]. Thus, chronic exposure to high levels of insulin and IGF-1 is hypothesized to mediate many cancer risk factors [23], and as a result the IGF/insulin system has been suggested as a potential target for cancer therapy [37].

While obesity status is known to correlate with serum IGF-1 levels [123, 124], studies have reported an independent effect of ethnicity on IGF-1 bioactivity in children and adults, potentially explaining ethnic specific differences in cancer risk. Previous research has reported higher levels of IGF-1 and IGFBP-3 in African Americans compared to Caucasian and Latino adults, independent of adiposity [125]. Another study reported race by gender differences where African American females had higher IGF-1 levels compared to Caucasians with similar IGF-1 levels in males in both ethnic groups [126]. The lower IGF-1 levels in Latinos relative to African American have also been shown in prepubertal females [127].

It is important to note that previous studies have been inconsistent with respect to the relationships between obesity and circulating levels of IGF-1 [128]. Studies among healthy adults have reported a null association [129–131], a positive association [132], an inverse association [128, 133–135], and a nonlinear association [136, 137] between BMI and IGF-1 levels. However, data from studies examining ethnic differences in the relationship between obesity and circulating IGF-1 have shown more consistent trends and may help to explain the abovementioned inconsistencies in obesity–IGF relationships. In a multiethnic cohort study of 200,000 adults in Los Angeles and Hawaii, researchers reported a decline in plasma IGF-1 levels with increasing BMI in Latinos and Asians; this decline was attenuated in Caucasians and absent in African Americans [138]. After adjustment for age and

BMI, African Americans had the highest IGF-1 bioactivity compared to other ethnic groups. Taken together, there appears to be a progressive increase in IGF-1 levels with increasing obesity status in African Americans compared to a decline in IGF-1 with increasing obesity in other ethnic minority groups, particularly Latinos.

Ethnic differences in IGF-1 bioactivity among children are generally similar to those observed in adults. It has been shown that African American prepubertal females have higher IGF-1 levels compared to Caucasian and Latino females [125, 127]. An inverse relationship between IGF-1 and IGFBP-3 with total fat mass and body fat distribution has been reported in overweight Latino children, whereas others have demonstrated a positive association between total body fat and IGF-1 levels in both African American and Caucasian children [139, 140]. These findings were not explained by diet, physical activity, socioeconomic status, or adiposity but were related to the degree of African admixture [141], suggesting a potential genetic basis for this difference. Taken together, these results demonstrate that African American children and adults have the highest levels of IGF-1 and exhibit a positive relationship between IGF-1 and obesity, likely contributing to the increased risk of obesity-related cancers in this population.

A possible biological mechanism mediating the association between obesity and IGF-1 may be through the effect of growth hormone. Typically, obesity results in lower circulating IGFBP-1 and IGFBP-2 levels, leading to an increased negative feedback by free IGF-1 on pituitary growth hormone secretion and a decreased IGF-1 synthesis [142]. Given the positive association between obesity and IGF-1 levels in African Americans, it is possible that the growth hormone–IGF axis may be regulated differently in this population compared to other ethnic groups. Another possible mechanism may be through the effects of cortisol on IGF-1 and growth hormone levels. IGF-1 is mainly derived from the liver, which also is the sole site of splanchnic cortisol production, which suggests a close interaction between cortisol and IGF-1 [143]. Previous research has reported a negative association between cortisol and IGF-1 in obese Latino children and adolescents [80]. Hence, high cortisol and low IGF-1 may act in concert to reduce cancer risk in Latino children and adolescents. A final mechanism centers on the relationship between IGF-1, IGFBP-1, and body fat distribution. A recent study identified a modifying effect of ethnicity on the relationship between IGF-1 and subcutaneous fat as well as IGFBP-1 and hepatic fat in overweight African American and Latino adolescents, respectively [144]. IGF-1 and IGFBP-1 were inversely correlated with BMI, total fat mass, visceral fat, and hepatic fat, while IGFBP-1 was inversely correlated with subcutaneous fat. These relationships did not differ by ethnicity; however, the relationship between IGF-1 and subcutaneous fat, as well as IGFBP-1 and hepatic fat, was stronger in African Americans compared to Latinos [144]. These results suggest that the relationship between IGF-1, IGFBP-1, and body fat distribution differs among African American and Latino adolescents, which may contribute to the higher IGF-1 levels and subsequent cancer risk in African Americans. Hence, a more in-depth discussion regarding the role of body fat distribution and its association with cancer risk is given in the section below.

Body Fat Distribution

Visceral Fat

The location of body fat is important, especially with regard to how it might affect insulin resistance. Visceral fat (adipose tissue inside the abdominal cavity) in particular has been hypothesized to be one of the major factors linking increased obesity to increased insulin resistance and subsequent cancer risk mainly due to the effects of free fatty acids released from visceral fat into the hepatic portal vein with direct exposure to the liver [145]. In addition, several studies have found that insulin sensitivity is negatively associated with adipose stores in the abdominal region [146–151], particularly visceral fat, and this is consistent across age and ethnicity [152, 153], with one notable exception [154]. Increases in visceral adipose tissue in Native American adults do not explain the greater insulin resistance and hyperinsulinemia in this population when compared to equally obese Caucasians [154].

Emerging evidence however suggests that there are ethnic differences in the relationships between BMI, waist circumference, percent body fat, and visceral fat. Much research has focused on comparisons between Caucasians and Asians, with greater visceral fat in Southeast Asian women compared with their Caucasian counterparts even at the same BMI [155–158]. In addition, Latino children and adults also have greater visceral fat compared to similarly obese Caucasians [146, 159]. In contrast, several studies have reported lower amounts of visceral fat for a given waist circumference, BMI, or waist-to-hip ratio in African American compared to Caucasian women [152, 160–163]. One study confirmed similar BMIs and waist circumference measurements in middle-aged and older African American men and women compared with Caucasians and Latinos but lower visceral fat (total visceral fat and measured at the L4L5 spinal level) in African Americans. Other studies confirmed these findings and consistently reported ethnic differences in fat distribution between African Americans and Caucasians even after significant weight gain [279] and weight loss [164, 165]. Moreover, these differences are evident before puberty, both cross-sectionally and longitudinally, with a lower growth-related increase in visceral adipose tissue in African Americans compared to Caucasians [166, 167]. Taken together, these data suggest that visceral fat is associated with insulin resistance; however, the lower volumes of visceral fat previously reported in African Americans do not appear to explain the greater insulin resistance and subsequent cancer risk in this population. On the other hand, African Americans tend to have more subcutaneous fat, which may provide a better explanation for ethnic differences in cancer-related outcomes.

Subcutaneous Fat

Although some studies suggest that visceral fat plays a larger role in the development of insulin resistance [146, 147], other studies in adults suggest that subcutaneous fat has a significant impact on metabolic disease risk given its larger volume and functional characteristics, making it more susceptible to inflammation and subsequent deposition of ectopic fat [149, 168]. More specifically, subcutaneous fat has two distinct compartments, the deep and superficial depots, which differ in their contribution to metabolic disease risk [169, 170]. For example, a study in lean and obese adults found that deep subcutaneous fat and visceral fat, but not superficial subcutaneous fat, were inversely correlated with insulin sensitivity as measured by euglycemic clamp [169]. At the same time, recent studies have identified ethnic differences in the distribution of deep and superficial subcutaneous fat with Asians reporting the lowest BMI, but the largest accumulation of visceral fat and deep subcutaneous fat when compared to Caucasian, African American, and Latino adults [171–174]. In another study, higher amounts of deep subcutaneous fat were reported in Native American and Asian adults compared to Caucasians [172]. With respect to African Americans, higher levels of subcutaneous fat have been consistently reported across populations of African descent including residents in the USA, the Caribbean, South America, or Europe [175]. Taken together, these findings suggest that ethnic differences in deep and superficial subcutaneous fat could partially explain ethnic differences in insulin sensitivity and secretion. More importantly, the greater volumes of subcutaneous fat and the previously reported stronger relationship between this fat depot and IGF-1 in African Americans offer another potential explanation for the greater insulin resistance and cancer risk previously reported in this ethnic group.

Intramyocellular Lipid

More recently evidence suggests that fat deposition outside of adipose tissue (e.g., in muscle, liver, or pancreas) contributes to increased insulin resistance [176–183]. Intramyocellular lipid, for example, has been shown to be a major determinant of insulin resistance in adults [179], obese individuals [176, 178], and obese adolescents [183]. Several studies have also reported an inverse relationship between intramyocellular lipid and insulin sensitivity in inactive individuals, independent of total body fat in both animal [184] and human models [185]. Reductions in intramyocellular lipid content have also been implicated in the improvements of insulin sensitivity in response to a short-term hypocaloric diet in both normoglycemic and type 2 diabetic patients [186]. Similar improvements in insulin sensitivity have also been observed in parallel with intramyocellular lipid depletion in morbidly obese subjects after surgical treatment of obesity [187]. These findings

highlight the importance of intramyocellular lipid as a metabolically active fat depot that influences insulin resistance independent of total body fat.

Few studies have examined ethnic differences in intramyocellular lipid in adults. One study in Asian and Caucasian men reported higher intramyocellular lipid content in Asians compared to age- and BMI-matched Caucasians [178]. Interestingly, intramyocellular lipid in Asians was not related to insulin sensitivity or adiposity; this relationship was present in Caucasians [178]. Similar differences by ethnicity were reported between African Americans and Caucasians, with intramyocellular lipid content related to insulin sensitivity and adiposity in Caucasians, but not African Americans [188]. Another study in Native Americans also noted that intramyocellular lipid did not predict a reduction in peripheral or hepatic insulin sensitivity [189]. Hence, intramyocellular lipid content does not appear to explain or contribute to the increased insulin resistance in ethnic minority adults. To date, the relationship between intramyocellular lipid content and insulin sensitivity in Latino adults has not been studied.

Many more ethnic comparison studies of intramyocellular lipid content have been conducted in overweight and obese youth. One recent report demonstrated that African Americans and Latinos have more intramyocellular lipid than Caucasians, even after controlling for BMI and visceral fat [181]. Another study in African American, Latino, and Caucasian children observed an inverse relationship between intramyocellular lipid and markers of inflammation; however, the majority of these relationships were eliminated after controlling for BMI and subcutaneous and visceral fat [181], suggesting that other fat depots may be more strongly associated with low-grade inflammation and insulin resistance in ethnic minority groups. To our knowledge there are no studies examining intramyocellular lipid in Native American or Asian children. Taken together, these studies suggest that increases in intramyocellular lipid may contribute to insulin resistance in an ethnic specific manner; however, the documented correlation between intramyocellular lipid, subcutaneous, visceral, and hepatic fat makes it difficult to tease apart the exact influence of each fat depot [177, 181, 190, 191]. Hence, additional studies comparing the contribution of intramyocellular, subcutaneous, and visceral fat are warranted to better understand the relationship between body fat distribution and observed ethnic differences in insulin resistance and subsequent cancer risk in ethnic minority populations.

Hepatic Fat

Numerous studies have documented inverse associations between hepatic fat, insulin sensitivity, and pancreatic beta-cell function [171, 192–197]. In a previous study of normal-weight, overweight, and obese Caucasian adolescents, those with hepatic steatosis had lower insulin sensitivity and a twofold greater prevalence of metabolic syndrome compared to those without hepatic steatosis [196]. In another study in both Canadian Caucasian and Native American adolescents, those with

type 2 diabetes had higher hepatic fat compared to those without type 2 diabetes; moreover, hepatic fat was negatively associated with insulin sensitivity [197]. A US study that included Caucasian, African American, and Asian adolescents found that obese adolescents with nonalcoholic fatty liver disease (NAFLD) had a lower pancreatic beta-cell function compared to those who were obese and without NAFLD [193]. Others have confirmed these relationships in obese Latino adolescents where those with elevated hepatic fat (>5.5 %) had a significantly lower insulin sensitivity and higher acute insulin response to intravenous glucose compared to those with lower hepatic fat [192]. These results suggest that hepatic fat is associated with metabolic abnormalities including insulin resistance and the deleterious effects of hepatic fat on insulin resistance appear consistent across different ethnic groups [171, 194, 195, 198, 199].

When making ethnic comparisons of hepatic fat content, similar to visceral fat, both African American adolescents and adults have lower amounts of hepatic fat compared to Latinos and Caucasians [200–202]. Nevertheless, the relationship between hepatic fat and insulin resistance appears to be stronger in this ethnic group. In one study, hepatic fat, not visceral fat, was inversely associated with insulin sensitivity and the effect of high hepatic fat (>5.5 %) compared to low hepatic fat was more pronounced in African American compared to Latino children [192]. In Latinos, high hepatic fat was associated with a 24 % lower insulin sensitivity, whereas in African Americans, high hepatic fat was associated with a 49 % lower insulin sensitivity [195]. These results suggest a stronger relationship between hepatic fat and insulin resistance in African Americans. Similar studies have not been performed in children belonging to other ethnic groups. Taken together, these findings suggest that for African Americans who have greater volumes of hepatic fat, this depot may contribute to increased insulin resistance. However, for the majority of African Americans who tend to have extremely low volumes of hepatic fat, this depot is not likely to be a major contributor to the increased insulin resistance and subsequent cancer risk in this population.

Pancreatic Fat

Accumulation of fat in the pancreas has also been associated with insulin resistance and hyperinsulinemia in both normal-weight and obese/type 2 diabetic individuals; this relationship appears to be independent of total body fat [195, 199, 203]. Moreover, pancreatic fat has been used as a marker of pancreatic beta-cell dysfunction, especially in Latinos [199]. A recent study examining ethnic differences in pancreatic fat determined that when comparing Caucasian, African American, and Latino adults at similar levels of adiposity, Latinos had a twofold greater volume of pancreatic fat compared to African Americans; Latinos and Caucasians had similar levels of pancreatic fat [199].

Studies in children and adolescents are limited, and no studies to date have been conducted in Asians or Native Americans. In African American and Latino

overweight and obese adolescents and young adults [195, 198], one study reported greater hepatic and pancreatic fat volumes in those with prediabetes compared to those with normal glucose tolerance [195]. However, pancreatic fat predicted prediabetes in African Americans whereas hepatic fat predicted prediabetes in Latinos [195]. These results suggest that ethnic differences in the relationship between ectopic fat depots and metabolic disease risk are present with pancreatic fat playing a larger role in the metabolic abnormalities previously reported in African Americans. Of note, visceral, hepatic, and pancreatic fat are highly correlated; hence, future studies should aim to examine fat depots in an effort to elucidate the exact contributions of each fat depot, particularly pancreatic fat, to the increases in insulin resistance and subsequent cancer risk in African American populations.

Adipose Tissue Biology

There is increasing evidence to suggest that differences in body fat accumulation and patterning may result from fundamental differences in adipose tissue biology [145, 204]. The increase in body fat content with obesity can occur by either an increase in adipocyte cell size or number or the spillover of triglycerides to ectopic tissues [145, 204]. When adipocyte cell size increases with progressing obesity, it is an indication of the inability of adipocytes to expand in number to accommodate the extra triglyceride accumulation [204]. Increased adipocyte cell size is also related to greater insulin resistance independent of total body fat [67]. Larger adipocytes have also been shown to be associated with more lipid deposition in visceral and hepatic fat depots (but not muscle), and this may also contribute to insulin resistance [205]. Furthermore, it is now evident that adipose tissue is infiltrated with macrophages [206]. One animal study has shown that accumulation of excess body fat in response to excess caloric intake leads to increasing fat cell size and then to adipocyte death, with the excess fat deposited in the liver [207].

Despite the important role that adipose tissue biology appears to play in the link between obesity, insulin resistance, and related cancer risk, there are no studies to date examining potential ethnic differences in the metabolic risk factor. Some studies have compared adipocyte cell size in African Americans and Caucasians but have not shown any difference in subcutaneous abdominal or gluteal adipocytes from obese women [208]. There are no data in the literature comparing ethnic differences in adipose tissue biology in Latinos and the potential relationship between adipocyte cell size and spillover of triglycerides to other ectopic storage depots like liver and pancreas. It is plausible that Latinos may have larger fat cells than African Americans that are more likely to die due to greater macrophage infiltration, thus leading to the greater likelihood of ectopic fat accumulation in Latinos. On the other hand, the higher circulating IGF-1 present in African Americans may contribute to a greater likelihood for adipocyte proliferation during obesity [209], leading to less likelihood for spillover of fat into ectopic depots; the opposite scenario is present in Latinos (lower obesity-related IGF-1 profile).

Thus, differences in the obesity–IGF pathway and adipocyte differentiation/growth factor pathways may also elucidate mechanisms explaining ethnic differences in body fat accumulation, body fat patterning, and subsequent cancer risk; additional research is warranted.

Adipose Tissue Inflammation

In conjunction with the accumulation and distribution of fat throughout the body, another potential explanation for ethnic differences in insulin resistance and subsequent cancer risk involves inflammation. Studies have shown that obesity is associated with a state of chronic low-grade inflammation, which is correlated with increased insulin resistance, and impaired glucose metabolism [210–213]. Although it was once believed that adipose tissue was only involved in the storage of free fatty acids as triglycerides, researchers now recognized that this tissue also acts as a dynamic endocrine organ, contributing to the chronic low-grade inflammation seen during obesity. For instance, during excess weight gain there is a marked increase in adipose tissue inflammation, which has been shown to be associated with insulin resistance seen during obesity [214]. Obesity is characterized by elevated circulating levels of acute-phase proteins, for example leptin, tumor necrosis factor (TNF)-alpha, interleukin (IL)-6, and decreased adiponectin [215]. Although the cause and effect nature of these proteins on insulin action is not clear, it has been suggested that these inflammatory markers affect disease processes in part by causing or exacerbating insulin resistance. Epidemiologic studies have demonstrated a positive association between acute-phase proteins and insulin resistance [216]. For example, leptin serves as part of an "adipostat" mechanism, whereby increased fat mass sets in motion responses that will eventually reduce adiposity. Hence, the reduced responsiveness to leptin that accompanies obesity may play a role in causing obesity and also contribute to insulin resistance [217, 218]. Another example is TNF-alpha, which has been shown to impair insulin signaling by activating serine/threonine kinases in skeletal muscle and downregulate glucose transporter type 4 (GLUT 4) in adipose tissue [216]. Circulating levels of IL-6 increase hepatic glucose production and stimulate the release of free fatty acids; however IL-6 also appears to have anti-inflammatory actions since it decreases TNF-alpha [219]. Adiponectin is exclusively produced in adipose tissue, and in humans its production is slightly higher in subcutaneous fat than visceral fat [220]. Adiponectin levels are negatively correlated with BMI and body fat, and this protein has been shown to play a role in hepatic insulin sensitivity and whole-body metabolism [221]. Both experiments in humans [222] and in animals [223] have demonstrated that low-grade inflammation predicts the development of insulin resistance.

Recent studies have also examined low-grade inflammation from adipose tissue biopsies in young adults. Specifically, subcutaneous adipose tissue biopsies performed in Caucasian, African American, Latino, and Native American adults have shown that in addition to elevations in plasma markers of inflammation,

increases in pro-inflammatory immune cells in adipose tissue are associated with systemic and local inflammation [224–227]. In another study, subcutaneous adipose tissue inflammation was assessed by the presence of crown-like structures in obese African American and Latino young adults. Individuals with subcutaneous adipose tissue inflammation had greater levels of visceral fat, hepatic fat, TNF-alpha, and fasting insulin and glucose and a lower beta-cell function compared to those without subcutaneous inflammation [226].

Although there are no studies in children involving adipose tissue biopsies, one study in obese youth observed macrophages and lymphocytes in perivascular positions in the adipose tissue [228] while another study in children found macrophages in the subcutaneous adipose tissue of normal-weight, overweight, and obese children as young as 5 years of age [229]. Studies using plasma markers of inflammation have also found strong associations with insulin resistance in overweight and obese youth from various ethnic groups. For example, a study in boys found that those who were overweight had higher serum levels of IL-6, IL-8, interferon-γ, monocyte chemoattractant protein (MCP)-1, and C-reactive protein (CRP) compared to those of normal weight [230]. Compared to normal-weight Latino children, higher levels of CRP and IL-1beta were reported in obese Latino children [210]. Another study in African American and Latino peripubertal females demonstrated that CRP was positively related to BMI, percent body fat, fasting insulin, and acute insulin response to glucose as well as negatively correlated with insulin sensitivity [211]. One of the few recent studies including Asian children found that, after controlling for adiposity, Asians had higher levels of CRP, A1C, and insulin levels compared to Caucasian and African American children [213]. To our knowledge, there is only one study examining inflammation in Native American children. This study found elevated levels of CRP that were associated with increased adiposity, insulin resistance, worsening lipid profile, and decreased adiponectin levels [231]. Findings from these studies in children suggest that obesity is accompanied by chronic levels of low-grade inflammation starting at an early age into adulthood, possibly contributing to increased insulin resistance in these populations.

There are only sparse data on inflammatory profiles in multiethnic cohorts in the USA. These studies suggested that inflammation may be higher in African Americans [232–234], although not all studies showed this trend [235]. Specifically, CRP concentrations were higher in African Americans than in Caucasians in several large studies [232, 234, 236]. The Women's Health Study reported higher levels of CRP in African Americans than in Caucasians [232]. In contrast, NHANES data did not show this trend and instead observed higher CRP in Latina women compared with Caucasians [237]. In another study that measured visceral fat, the negative association between visceral adipose tissue and adiponectin was stronger in African Americans [237]. However, overall body fatness may still have played a role in inflammation because subcutaneous fat also had significant independent association with CRP in this ethnic group. Of note, African American women consistently exhibited greater markers of inflammation even after controlling for both L4L5 visceral and subcutaneous fat [159]. More importantly, the greater inflammation

among these African American women was present despite similar or lower self-reported rates of smoking and similar or higher self-reported rates of taking lipid-lowering medications and nonsteroidal anti-inflammatory drugs [159]. The mechanisms contributing to greater low-grade inflammation in African Americans are unclear, but possibilities include higher intrinsic activity of cytokine pathways and/or different behavioral influences (i.e., high-fat diet and physical inactivity) on inflammation.

Aside from intrinsic cytokine production pathways, lifestyle factors such as diet or exercise may play a role in the altered visceral fat/body fat–inflammatory biomarker relationship. An observational study found that diets high in glycemic load were associated with increased concentrations of inflammation and that the dose–response gradient between glycemic load and inflammation was more exaggerated in overweight women [238]. Other dietary factors that have been shown to increase low-grade inflammation include sucrose, artificial sweeteners, fats, and processed meats [239]. In contrast, fiber, fruits, and vegetables have been associated with reduced inflammation [240]. Previous research has reported eating patterns reflecting higher consumption of fat and calories and lower consumption of fruits and vegetables in African Americans [241], which may contribute to the greater inflammation in this ethnic group. Moreover, African American women in particular have been shown to have lower rates of physical activity participation compared to Caucasians [242–245], which may independently contribute to inflammation. Hence, studies examining whether ethnic differences in exercise or dietary patterns account for the altered visceral fat–inflammation relationships among African Americans are warranted to better understand the increased cancer risk in this population.

Non-esterified Fatty Acids

Studies in obese adults have documented a relationship between adipose tissue insulin resistance and non-esterified fatty acids (NEFA) [246]. Given that increased hepatic fat, intramyocellular lipid [247, 248], and inflamed adipose tissue [249] are associated with increased whole-body insulin resistance, it is possible that NEFA play a mediating role in the link between ethnic differences in ectopic fat, inflammation, and insulin resistance. However, most of the research in this area has been conducted in children. Studies in overweight and obese youth have observed elevations in fasting NEFA and NEFA levels after an oral glucose or intravenous lipid challenge. Longitudinal data has confirmed an inverse relationship between fasting NEFA and insulin secretion following a 30-min oral glucose challenge in children with normal glucose tolerance [250]. Other researchers have shown that when compared to normoglycemic Latino children, those with prediabetes had higher fasting NEFA that were also inversely related to insulin secretion [195].

The earliest work in this field with regard to ethnicity first showed that after an intravenous lipid infusion, elevations in NEFA were associated with increased

insulin resistance in African American and Caucasian adolescents [251]. Of note, ethnicity did not modify the relationship between NEFA and insulin resistance despite lower insulin sensitivity in African Americans compared to Caucasians [251]. Another study reported ethnic differences in NEFA during an intravenous glucose tolerance test [181, 252]. Independent of insulin secretion, African American women and girls had lower NEFA than Caucasian women and girls [181, 252]. To our knowledge, there are no studies examining these relationships in Asian or NA children, warranting their inclusion in future studies. Hence, NEFA contributes to insulin resistance and ethnicity does not appear to modify this relationship. However, African Americans tend to have lower NEFA suggesting that this mechanism does not explain the increased insulin resistance and subsequent cancer risk in this population.

Oxidative Stress

The potential role of oxidative stress in carcinogenesis is rapidly evolving, which may also link obesity and insulin resistance to increased cancer risk. Oxidative stress occurs when there is excessive production of reactive oxygen species (ROS) or insufficient in vivo antioxidant defense mechanisms [253]. This results in damage to DNA as well as lipid peroxidation, protein modification, membrane disruption, and mitochondrial damage [218, 254]. Data support the notion that increased formation of ROS may play an important role in carcinogenesis as well as atherosclerosis, diabetes, and neurodegenerative diseases [255]. Although ROS-induced lipid peroxides are usually described as harmful to cellular systems, they are also critical mediators of apoptosis [256] and have been shown to inhibit cancer growth in a number of experimental studies [257]. More specifically, factors that increase lipid peroxidation could also increase cancer and other degenerative diseases in people with innate or acquired high levels of ROS. However, factors that increase lipid peroxidation can increase apoptosis of precancerous and cancerous cells and thus protect against cancer, particularly in people with a low innate baseline level of ROS [256]. Thus, antioxidants may protect against certain cancers if background levels of ROS are higher in "at-risk" populations, but not if background ROS levels are lower because this may place a greater importance on the suppression of oxidation-induced apoptosis [256].

The relationship between obesity, insulin resistance, and oxidative stress has not been widely explored, but some supporting evidence suggests a link. Obese adults have elevated levels of lipid peroxidation that is reversible with weight reduction [255]. Metabolic conditions associated with insulin resistance are associated with elevated lipid peroxidation, including hypertension [255], impaired glucose tolerance [258, 259], and type 2 diabetes [258, 260–268]. In addition, increased oxidized low-density lipoprotein or susceptibility to oxidation has been reported in patients with type 2 diabetes [261, 262, 265, 268, 269]. Small dense low-density lipoprotein particles, which are also a component of the metabolic syndrome, are more

susceptible than larger ones to oxidative modification [270, 271]. Finally, lipid peroxidation and oxidative stress, induced by elevations in glucose and possibly free fatty acid levels, may play a key role in causing insulin resistance by their ability to activate stress-sensitive signaling pathways [272].

Relatively few studies have compared lipid peroxidation and oxidative stress in different ethnic groups. In adults with type 2 diabetes, increased levels of lipid peroxidation were found in African Caribbeans compared to Caucasians [273]. Previous work showed greater lipid peroxidation in Latinos compared to Caucasians with [274] and without type 2 diabetes [275]. In another study, lipid peroxidation was higher in African Americans than in Caucasians during hyperlipidemia induced by lipid infusion [276]. Of note, recent data from the multiethnic IRAS cohort reported lower urinary F2-isoprostane levels, a marker of lipid peroxidation, among African American compared with Caucasians and Latinos [277, 278]. When stratified by BMI, ethnic differences in F2-isoprostance levels were not observed among participants with normal BMI but appeared among overweight participants and increased among obese participants [278]. Hence, additional studies comparing the markers of oxidative stress are warranted to better understand its potential contributions to ethnic differences in cancer risk.

Summary and Conclusions

Obesity is a predisposing risk factor for certain forms of cancer, and the link between obesity and cancer appears to be particularly complex. Obesity is associated with increased insulin resistance, and hyperinsulinemia may play a critical role in influencing cancer risk. It is notable that obesity-related cancer risk differs dramatically by ethnicity. African Americans appear particularly prone to obesity-related cancers including prostate, breast, and colorectal and myeloma, whereas Latinos appear relatively protected. Based on previous literature, it is plausible that ethnic differences in the insulin response to obesity may contribute to ethnic differences in obesity-related cancer profiles. Obese Latinos seem more prone to an ectopic fat pattern (increased visceral, hepatic, and pancreatic fat), and this might be driven by greater fat cell size, greater likelihood of adipocyte macrophage infiltration and cell death, and decreased capacity for fat cells to differentiate, possibly due to a lower obesity-related IGF-1 profile. On the other hand, obese African Americans seem more prone to some forms of obesity (subcutaneous fat pattern) and insulin-related cancers compared to Latinos and have less likelihood of ectopic fat. These differences could be driven by the much higher obesity-related hyperinsulinemia (especially in response to glucose) and IGF-1 profile in African Americans. This is important because it suggests that reducing levels of insulin in obesity in this population as a strategy to prevent obesity-related cancers may have the unwanted side effect of reducing fat cell proliferation and promotion of hepatic fat, and other ectopic fat deposition, unless it is combined with behavioral interventions to influence energy balance (reduce energy intake and

increase physical activity) and subsequent weight status. Additional factors that contribute to increased insulin resistance and cancer risk in African Americans include chronic glucocorticoid exposure, chronic inflammation, and possibly greater oxidative stress. Hence, additional therapies that reduce multiple cancer-related metabolic risk factors in African American children and adults are warranted.

In summary, the causes and consequences of obesity and insulin resistance differ by ethnicity of people and much more work is needed to establish the specific mechanisms linking obesity and insulin to various cancer outcomes. These mechanistic issues are fundamental to understanding the basic pathophysiology of why increased body fat and hyperinsulinemia are related to cancer outcomes in some ethnic groups but not others and will ultimately have widespread implications for the application of more individualized prevention and treatment approaches to reduce the disparity in obesity-related cancers.

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Chapter 9
Role of Ethnic Differences in Mediators of Energy Balance

Sarah S. Cohen and Loren Lipworth

Abstract The rapid increase in the prevalence of obesity in the USA in the past 30 years has many health implications. Obesity is strongly associated with incidence and mortality of several common cancers including post-menopausal breast cancer, renal cell cancer, colorectal cancer, prostate cancer, and endometrial cancer. Obesity patterns in the USA vary substantially by race, particularly for women, with black women having a higher prevalence of obesity than white women. Moreover, black men and women experience higher incidence and mortality for many common cancers and cardiovascular disease.

Keywords Racial differences—insulin IGF-1 • Racial differences—adiponectin • Racial differences—leptin • Racial differences—sex steroid hormones • Racial differences—inflammation

Definition and Measurement of Obesity

Obesity defined at the most basic level is an excess accumulation of body fat [1]. This excess results from a multifactorial process involving an imbalance in energy consumption and expenditure, resulting in enlarged fat cells (also known as adipose cells) as well as an increase in the number of adipose cells [2]. The major sites for adipose tissue storage are both within the abdominal cavity (abdominal or visceral fat) and just under the skin (subcutaneous fat). Visceral fat tends to

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accumulate with age and is more strongly associated with metabolic disorders and cardiovascular disease [3].

There is little agreement on the best way to measure obesity accurately in either clinical settings or in large-scale research studies. In epidemiologic studies, obesity is most often measured by BMI because the component measures (height and weight) are easily obtained via self-report from study participants or from inexpensive and easy-to-use tools [1, 4]. BMI is calculated as the weight in kilograms divided by the square of height in meters. Standard categories of BMI have been put forth by the World Health Organization and include underweight (BMI $<$18.5 kg/m^2), healthy weight (BMI 18.5–24.9 kg/m^2), overweight (BMI 25.0–29.9 kg/m^2), obesity class I (BMI 30.0–34.9 kg/m^2), obesity class II (BMI 35.0–39.9 kg/m^2) and obesity class III or extreme obesity (BMI $\geq$40.0 kg/m^2) [5]. BMI has excellent validity as a measure of absolute fat mass adjusted for height [4], and the widely used, standardized cut-points established for BMI categories allow for ease of comparison across studies [5, 6]. However, because BMI includes body weight (which is made up of both lean body mass and fat tissue), it is a less valid measure for percent body fat than other measures that account for differences in the proportion of each type of body tissue [4].

Other measures to assess body composition include densitometry (underwater weighing) as well as newer techniques such as dual energy X-ray absorptiometry (DEXA), bioelectrical impedance analysis (BIA), and computed tomography (CT)/magnetic resonance imaging (MRI). Densitometry requires that an individual be submerged in water. By measuring the ratio of body weight measured in air and body weight measured under water, an estimate of the proportion of fat in the total body mass can be calculated [4]. DEXA uses an X-ray with low- and high-energy peaks to distinguish fat mass, fat-free mass, and bone mineral mass in the whole body or by specific region (such as in the abdomen) [4]. DEXA is not able to distinguish visceral fat from subcutaneous fat [7]. BIA involves sending a weak electrical current through the body and measuring its impedance by muscle tissue; because muscle is composed mainly of water and fat tissue contains virtually no water, the impedance values can be used to estimate percentage body fat [4]. CT and MRI are considered to be the most accurate methods for assessing body composition including the quantification of visceral versus subcutaneous fat [7]. However, these three measures all require expensive equipment, specialized technicians, and can be time-consuming to perform on a large number of individuals, and thus are not widely used in epidemiologic research.

Distribution of body fat, not just the total amount, has also been shown to be related to health risks. While fat distribution can be measured using imaging tools such as DEXA and CT/MRI, waist circumference and waist-to-hip ratio (WHR) are also used to measure differences in fat tissue distribution and have been used frequently in epidemiologic studies because the required measurements are inexpensive and quick to obtain. One limitation of these measures is that many factors can affect the measurement of waist and hip circumferences including the degree of training of the individual making the measure, the time of day, and timing of the most recent meal [4].

Another level of complication arises when obesity is measured in individuals of different racial or ethnic backgrounds. Many studies have concluded that commonly used measures of obesity have different meanings for whites and blacks, likely due to differences in fat distribution. Several studies report that for a similar waist circumference and BMI, blacks have less visceral fat than whites [3, 8]. Hip circumferences of blacks have been found to be smaller than those in whites, resulting in an increased WHR for a given amount of central fat deposition [1]. The relationship between BMI and percent fat measured by DEXA has also been shown to differ by race with black women having lower body fatness than white women at the same BMI [9]. In contrast, Gallagher and colleagues found that BMI reflected the same level of fatness in black and white adults with BMI $\leq$35 kg/m^2 after age and sex adjustment [10]. Differences also exist between blacks and whites with respect to fat-free body mass with blacks generally having more bone mineral density and body protein than whites [11].

Racial Differences in Obesity Prevalence

Based on measured height and weight data from the National Health and Nutrition Examination Surveys (NHANES), the prevalence of obesity among American adults began increasing rapidly in the late 1970s and early 1980s [12] and started leveling off only in the most recent decade. The prevalence of obesity (BMI $\geq$30 kg/m^2) among all women in NHANES from 1988 to 1994 was 25.4 %, increased dramatically to 33.4 % in the NHANES data from 1999 to 2000 [13], then showed only a relatively small increase to 35.5 % in the 2007–2008 NHANES [12], and mostly recently was estimated at 36.1 % in the 2011–2012 NHANES [14]. For men, the prevalences of obesity were 20.2 %, 27.5 %, 32.2 %, and 33.5 % for 1988–1994, 1999–2000, 2007–2008, and 2011–2012, respectively [14, 15].

In addition to the rapid rate of increase in the obesity prevalence overall in the past 30 years, there is strong variation in the prevalence of obesity by race. NHANES data from 2011 to 2012 show that 32.8 % of white women were obese compared to 56.6 % of black women [14]; the difference for males is smaller with 32.4 % of white males being obese compared to 37.1 % of black males [14]. Differential increases in the prevalence of extreme obesity (BMI $\geq$40 kg/m^2) by race were even more pronounced with the prevalence increasing from 3.4 to 6.4 % among white women and from 7.9 to 14.2 % among black women between the NHANES surveys covering 1998–1994 and 2007–2008 [12, 13].

Environmental and Behavioral Determinants of Obesity

It is likely that genetic factors contribute to the ability of humans to store excess fat when food is abundant and to lose fat when food is scarce [15]. However, the recent increase in obesity in the USA, as well as in other populations around the globe, is unlikely to be explained solely by genetics because it has happened over such a short period of time. Thus, individual-level behavioral and environmental factors are also thought to be strong contributors to obesity, including physical activity levels, energy and nutrient intake, reproductive patterns, and socioeconomic status [16–19]. Population-level characteristics related to changes in occupations and infrastructure (such as changing modes of transportation) are also likely important influences on the development of obesity but are not reviewed here.

Physical Activity

The modern environment does not require nor encourage physical activity for most adults [20]. The Centers for Disease Control and the American College of Sports Medicine recommend that adults engage in at least 150 min per week of moderate-intensity physical activity [21] but data from the Behavioral Risk Factor Surveillance System (BRFSS) finds that more than half of US adults do not meet physical activity recommendations based on activity patterns in three domains (household work, transportation, and discretionary/leisure time) [21, 22]. Physical activity patterns by race have been extensively examined but there is inconsistency in the literature. Many studies have found blacks are less physically active than whites [23–25], in some cases, beginning as early as adolescence [26]. However, other studies have found no evidence for differences in physical activity levels across racial groups. Using data from the Health and Retirement Study, He and Baker found that leisure-time physical activity did not differ between blacks and whites after adjustment for education and health status [27]. Similarly, Marshall and colleagues found that within strata of social class (including education, income, employment status, and marital status), there were few differences in the prevalence of physical inactivity between white and black women [28].

Energy and Nutrient Intake

Energy intake that exceeds the energy needs of the body has been shown in controlled studies to cause weight gain in the form of stored fat [29]. However, the role of particular dietary factors as determinants of obesity is much less clear. Several methodological problems have been identified in studies of diet and obesity including short time periods of measurement, correlations between dietary factors

and other determinants of obesity such as physical activity, and the validity and reliability of the tools used to measure dietary intakes [29]. Despite these limitations, ecologic, observational, and intervention studies have identified links between obesity and the consumption of fats, high-fructose corn syrup, fast food, and snack foods [30–33]. Recently, Drewnowski set forth a single explanation for these findings, namely that the consumption of low-cost foods which contain refined grains, added sugars, and added fats, explain the many links observed between weight gain and individual foods on a population level [34]. This hypothesis is consistent with the increased risk of overweight and obesity among black women who are disproportionately of lower socioeconomic status (SES) than white women.

Reproductive Factors

There may also be important racial differences in reproductive factors that affect the prevalence of obesity. While the role of parity in the development of obesity remains somewhat uncertain [35, 36], several studies have indicated that increasing parity is associated with an increase, albeit modest, in the risk of obesity [37–41]. In the few studies with sizable numbers of black women, it has been observed that black women may be more susceptible to weight gain following pregnancy than white women [42, 43]. For example, black women were found to retain more weight post-partum than white women at similar levels of gestational weight gain [42]. A recent analysis that stratified women by metropolitan status found that the effect of increased parity was significant only in black women living in metropolitan areas but not black women living in non-metropolitan areas [44]. A cross-sectional study using data from the Southern Community Cohort Study found a modest increase in the odds of obesity among both white and black women having five or more births compared to nulliparous women [45]. In addition, black women have more children on average than white women [46] and some studies have indicated that high levels of parity are most strongly associated with obesity [38, 39, 47]. Further, differences in the prevalence and length of breastfeeding exist with black women being less likely to breastfeed compared to white women [48, 49]. Some studies have reported that breastfeeding is associated with a small decrease in weight retention post-partum [50, 51] which in combination with a lower prevalence of breastfeeding among blacks could contribute to the disparity in the prevalence of obesity.

Socioeconomic Status

Underlying many of the observed associations between environmental and behavioral characteristics and obesity is the issue of SES. In a descriptive review of the literature regarding obesity and SES, McLaren reported that in resource-rich

countries, such as the USA, lower SES was associated with larger body size among women in nearly two-thirds of the reviewed studies [52]. Racial differences in BMI have been found to be only partially explained by measures of SES such as education and income [53–56]. Wang and Beydoun [54] hypothesize that a major reason for this finding is that factors such as body image, lifestyle, social structure, and physical environment are responsible for much of the racial difference in body size and that these constructs are not adequately accounted for by adjustment for standard SES measures such as education and income.

Associations Between Obesity and Cancer

Obesity is one of the few modifiable risk factors for many cancer sites. The higher prevalence of overweight and obesity among blacks and observed disparities in cancer incidence and mortality for several common sites underscores the importance of studies of obesity in relation to cancer in diverse populations. For instance, the age-adjusted mortality rate for breast cancer in the USA in 2010 was 21.3 per 100,000 women among whites and 30.2 per 100,000 women among blacks [57]. Similarly for colorectal cancer, the age-adjusted mortality rate among whites (males and females) in 2010 was 18.1 per 100,000 compared to 27.5 per 100,000 among blacks [57, 58]. For prostate cancer, the racial disparity is very pronounced with the 2010 age-adjusted mortality rate being 20.1 per 100,000 for white males and 48.2 for black males [58].

All Cancers

Obesity is associated with incidence and mortality for several of the most common cancer sites [59–62]. In the Cancer Prevention Study II (CPS II), including 495,477 women followed for 16 years, the relative risk for all cancer mortality was 1.62 (1.40–1.87) comparing women with a BMI of $\geq$40 kg/m^2 to women with a BMI between 18.5 and 24.9 kg/m^2 [62]. Among the women in the CPS II, obesity was found to be associated with cancer of the esophagus, colon and rectum, liver, gallbladder, pancreas, kidney, breast, uterus, cervix, and ovaries with relative risks (RR) ranging from 1.46 (95 % confidence interval (CI) 0.94–2.24) for colorectal cancer to 6.25 (95 % CI 3.75–10.42) for the uterus [62]. The 2002 report on Cancer Prevention, Weight Control, and Physical Activity from the International Agency for Research on Cancer (IARC) concludes that, based on a comprehensive evaluation of the literature, there is sufficient evidence for a cancer-preventive effect of avoidance of weight gain for colon, post-menopausal breast cancer, endometrial cancer, kidney, and esophageal cancers [63]. This chapter will focus primarily on breast and kidney cancer in illustrating the role of ethnic differences in mediators of energy balance.

Breast Cancer

For breast cancer, existing epidemiologic studies indicate a complex relationship with obesity, which has generally been shown to be associated with increased risk among postmenopausal women but somewhat reduced risk among premenopausal women [64, 65]. For premenopausal women, in a meta-analysis, Ursin and colleagues found reductions in the RR for breast cancer in four cohort studies (RR for 8 kg/m^2 reduction in BMI = 0.70, 95 % CI = 0.54–0.91) and 19 case-control studies (RR for 8 kg/m^2 reduction in BMI = 0.88, 95 % CI = 0.76–1.02) although the individual study estimates were quite heterogeneous [66]. In the Pooling Project of Diet and Cancer, a pooled analysis of seven large prospective studies, the RR for premenopausal breast cancer among women with a BMI $\geq$33 kg/m^2 was 0.58 (95 % CI = 0.34–1.00) compared to women with a BMI $<$21 kg/m^2. A similar reduction in the RR was seen for women with a BMI between 31 and 33 but not for women with a BMI below 31 [67].

However, results are not entirely consistent for premenopausal women, and emerging evidence over the past several years suggests that obesity may in fact be associated with increased risk for breast cancer among premenopausal women [64, 68]. In particular, results have been noted to vary across studies by hormone receptor status or intrinsic subtype of breast cancer, and for triple negative breast cancer (TNBC) or basal-like breast cancers, an increased risk for breast cancer associated with obesity has been observed among premenopausal women in virtually all studies [68–72]. A recent review and meta-analysis focused on TNBC demonstrated, after stratification by menopausal status, a significant positive association between obesity and TNBC which was restricted to premenopausal women (odds ratio (OR) 1.43; 95 % CI 1.23–1.65 for those with BMI $\geq$30 versus $<$30), suggesting distinct molecular mechanisms involved in the onset of different subtypes of breast cancer during a woman's reproductive years.

The incidence of breast cancer is lower among black than white women greater than 40 years of age, but higher among black women at younger ages [73]. Despite a somewhat lower overall lifetime risk of breast cancer, black women are more likely to be diagnosed with aggressive and late-stage breast cancer, with lower survival rates, and breast cancers diagnosed among black women are more likely to have negative hormone receptor status. In fact, in every age group, white women have the highest rates of estrogen receptor-positive (ER+) breast cancer and black women have the highest rates of ER- breast cancer [73]. Despite the differential distribution of breast cancer subtypes among black compared to white women, and the higher prevalence of obesity among black women, limited and inconsistent information exists on the obesity-breast cancer association for premenopausal black women. Several studies among black premenopausal women [58, 74–79], but not all [58, 80], have indicated increased breast cancer risk associated with increased BMI, the standard index for assessing obesity, or with higher waist circumference or WHR, measures of central adiposity that are more prevalent among blacks than whites. In the Carolina Breast Cancer Study, a large case-control study of black and

white women, BMI was inversely associated with breast cancer among white, but not black, premenopausal women [75], and an increased risk for basal-like tumors was associated with increased WHR among black and white pre- or postmenopausal women [69]. Few other studies have presented results for black women by hormone receptor status; in the Women's Circle of Health Study, elevated BMI, as well as waist circumference and WHR, were nonsignificantly positively associated with both ER+/PR+ and ER−/PR− breast cancer in black premenopausal women [74], while in the Multiethnic San Francisco Bay Area Breast Cancer Study, BMI was inversely associated only with ER+/PR + tumors but not with ER−/PR− tumors [81].

In contrast, among postmenopausal women, increased body size is positively associated with breast cancer risk [82, 83]. In the Pooling Project of Diet and Cancer, the RR for breast cancer among postmenopausal women with a BMI greater than 28 kg/m^2 was 1.26 (95 % CI = 1.09–1.46) compared to women with a BMI <21 kg/m^2, and a stronger positive association with obesity was seen among women who had never used hormone replacement therapy (HRT) [67]. In the Women's Health Initiative cohort, evidence of effect measure modification by HRT was also seen with obesity found to be a risk factor for breast cancer among nonusers of HRT but not among women who had ever used HRT [84]. Positive associations between adult weight gain and breast cancer risk as well as central adiposity and breast cancer risk have been consistently reported as well [82, 83]. While the positive association between obesity and postmenopausal breast cancer has been consistently observed among white women, the few studies of among black women have had more variable results; a 2011 review found only 8 studies conducted among black women, and the results were mixed with some studies showing a positive association with obesity and postmenopausal breast cancer and others being null [85]. In the Multiethnic Cohort Study, the hazard ratios (HR) for postmenopausal breast cancer for each five unit increase in BMI were very similar between white and black women (HR = 1.06 [95 % CI 1.00–1.14] and 1.08 [95 % CI 1.01–1.16], respectively)[86].

Renal Cell Carcinoma

An estimated 63,920 new cases of kidney cancer are expected in the USA in 2014, making it the sixth and eighth most commonly diagnosed primary cancer among men and women, respectively [87]. Approximately 85 % of kidney cancers are renal parenchyma (renal cell carcinoma, RCC) cancers, while the remainder are mainly urothelial cancers of the renal pelvis. Incidence rates for RCC have been steadily increasing over several decades; between 2001 and 2005, while the rate for all cancers combined dropped 1.8 % among men and 0.5 % among women in the USA, kidney cancer incidence rose 1.7 % and 2.2 % per year for men and women, respectively [88]. The most salient feature of these incidence trends has been the more rapid increase among blacks than whites [89, 90], leading to a pronounced

shift in excess from among whites to among blacks beginning in the mid-1980s. Kidney cancer is now the 4th and 6th most common cancer among black men and women, respectively [91]. RCC is comprised of several histologic subtypes with distinct genetic and clinical features, the most common of which are clear cell, accounting for approximately 70 % of cases, papillary (10–15 %) and chromophobe (5 %); however, the proportional distribution of papillary RCC appears to be substantially higher among blacks than whites [92].

RCC is one of the malignancies most consistently and strongly associated with BMI among both men and women, regardless of study design or population [90, 93–95]. A recent quantitative summary analysis of the epidemiologic evidence reported RRs for RCC of 1.24 (95 % CI 1.15–1.34) among men and 1.34 (95 % CI 1.25–1.43) among women per 5 kg/m^2 increase in BMI [96]. Despite the higher and more rapidly increasing incidence of RCC among blacks, virtually no information exists on the obesity-RCC association specifically for blacks [97]. Limited evidence suggests that the association between obesity and RCC may differ by histologic subtype, with stronger associations observed for clear cell and chromophobe than papillary RCC among men [98], but this finding requires confirmation in larger studies.

Biological Mechanisms Linking Obesity to Cancer

Although mechanisms are not entirely clear, it is in general believed that obesity acts primarily by inducing insulin signaling and resistance, inflammation, and increased estrogen biosynthesis and signaling to increase the risk of cancer [99–101] (Fig. 9.1). The relative contribution of these mechanisms and their mediators to the complex association between obesity and cancer is likely to differ between blacks and whites, which may contribute to racial differences in risk and/or subtype distribution of cancer.

Insulin Resistance and IGF1 Pathway

The effects of obesity on cancer may be mediated by its effects on increased levels of insulin and related growth factors, in particular increased bioavailable concentrations of insulin-like growth factor 1 (IGF1) [102]. Over 90 % of IGF1 circulates bound to insulin-like growth factor-binding protein 3 (IGFBP3) [103], with less than 1 % of IGF circulating unbound [104]. IGF1 has important mitogenic, cell proliferative, and anti-apoptotic effects [102]. Insulin and IGFs induce signaling by binding to insulin receptor (IR) and IGF1 receptor (IGF-1R) and their hybrid receptors widely expressed on normal and neoplastic cells. These receptors may also play a role in the association between obesity and cancer [105, 106].

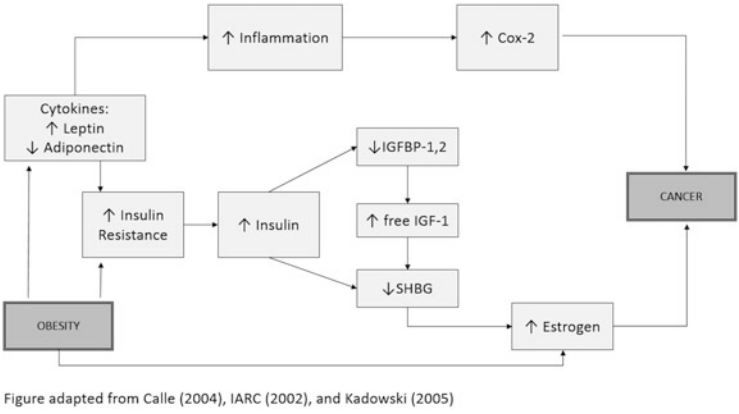

Fig. 9.1 Select obesity-mediated pathways leading to cancer. *IGF* insulin-like growth hormone, *IGFBP* insulin-like growth hormone binding protein, *SHBG* sex hormone-binding globulin. Figure adapted from [59], [63], and [165]

A recent study in a multiracial population demonstrated that black women had higher mean IGF1 and lower IGFBP3 levels than white women. IGF1 levels declined with rising BMI at age 21 among whites only, which led to increased racial differences in IGF1 among women who were obese in early adulthood [107]. Levels of insulin, IGF1 and IGFBP3 (and their ratio), and C-peptide, a surrogate of insulin secretion, have been linked to an increased risk of breast cancer in some, but not all, epidemiologic studies [108–117]. In a recent pooled analysis of 17 prospective studies, IGF1 was strongly positively associated with breast cancer risk the relative risk for women in the highest versus the lowest quintile of the distribution of IGF1 was 1.28 (95 % CI 1.14–1.44), with no significant difference according to menopausal status [116]. Although the association of both IGF1 and IGFBP3 appeared to be confined to ER+ tumors, the evidence is not entirely consistent, and whether IGF1 or IGF-binding protein 3 (IGFBP3) increase risk for breast cancer differentially for blacks and whites or for certain breast cancer subtypes, such as triple-negative breast cancer, is largely unknown [118, 119].

For RCC, in vitro studies have shown increased expression of insulin and IGF1 receptors in human RCC tissue, and IGF1 stimulates growth in human RCC cell lines [120–125]. An immunohistochemistry analysis of tissue from 180 RCC patients suggested differential IGF1 expression across RCC histologies, with stronger expression in clear cell tumors [125]. Some, but not all, in vitro studies have shown increased expression of insulin and IGF1 receptors in human RCC tissue, and IGF1 stimulates growth in human RCC cell lines [120–125]. An immunohistochemistry analysis of tissue from 180 RCC patients suggested differential IGF1 expression across RCC histologies, with stronger expression in clear cell tumors [125]. The only prospective analysis to date to investigate pre-diagnostic circulating levels of IGF1 in relation to RCC risk is a relatively small case-control study, nested in the Alpha-Tocopheral, Beta-Carotene (ATBC) Cancer Prevention Study

cohort of Finnish male smokers; in this study, IGF1 was inversely associated with RCC risk [126, 127]. These results appear to contradict the observations from some experimental studies described above, in which IGF was demonstrated to stimulate renal carcinogenesis, but require confirmation.

Sex Hormones

The association between circulating sex steroid hormones and breast cancer risk among postmenopausal women has been studied extensively, with results consistently showing strong positive associations with estradiol (E2) and estrone (E1), and an inverse association with sex hormone-binding globulin (SHBG), which binds to estrogen to reduce its bioavailability [128–130]. SHBG also may act directly on breast cancer cells to inhibit E2-induced cell proliferation [131]. High BMI is consistently associated with higher levels of estrogens and lower levels of SHBG in postmenopausal women [132]. Among obese postmenopausal women, this reflects the higher rate of conversion of androgenic precursors to E2 through increased peripheral aromatase enzyme activity in adipose tissue.

Differences in endogenous steroid hormone levels between postmenopausal black and white women in the USA have been demonstrated in a small number of studies [133–135]. In a cross-sectional analysis including 240 black and 91 white postmenopausal women within the Multiethnic Cohort Study [135], black women had 20 % higher age-adjusted mean levels of E1 and total and bioavailable E2 compared with whites, but also the highest levels of SHBG, even after adjustment for BMI. However, few studies of postmenopausal breast cancer in relation to levels of steroid hormones have included black women [108, 136], and to our knowledge no study to date has evaluated these associations separately among black women. In a case-cohort analysis of incident postmenopausal breast cancer within the Women's Health Initiative Observational study, which included 56 black cases, E2 was associated with a significantly increased risk of breast cancer among women not using HRT [108].

Data among premenopausal women are more limited, primarily due to large variations in endogenous levels of estrogen throughout the menstrual cycle [137], but generally support a similar role for increased E2 and decreased sex hormone-binding globulin (SHBG) in the development of breast cancer among young women. SHBG binds to estrogen to reduce its bioavailability but may also act directly on breast cancer cells to inhibit E2-induced cell proliferation [131]. In a recent pooled analysis of data from seven prospective studies, including 767 cases of breast cancer, circulating concentrations of E2, calculated free E2 (a measure of bioavailable E2), and E1, as well as testosterone and androstenedione, were significantly positively associated with risk for breast cancer in premenopausal women, after adjustment for known breast cancer risk factors [138], with ORs ranging from 1.08 to 1.30 for a doubling in sex hormone concentrations. Sex hormones were more strongly associated with risk of ER+ breast cancer than ER− breast cancer,

but the number of women with ER− disease was small. SHBG was not associated with breast cancer risk. Virtually all of the women included in the pooled analysis were of European ethnicity. There have been few studies of premenopausal breast cancer in relation to levels of steroid hormones among black women [108, 136], even though differences in endogenous steroid hormone levels between black and white women in the USA have been demonstrated [133, 139–141], including higher E2 levels throughout the menstrual cycle.

Obese premenopausal women have also been shown to have elevated levels of non-protein-bound and total estrogens and decreased levels of SHBG [142, 143]. Among controls in the pooled analysis described above, compared to normal weight women, those with a high BMI ($\geq$30 kg/m^2) had lower mean concentrations of E2 but higher concentrations of free E2 due to a strong inverse association of SHBG with BMI [138]. E1 was also positively associated with BMI, perhaps reflecting the higher rate of conversion of androgenic precursors through increased peripheral aromatase enzyme activity in adipose tissue, similar to what is observed among postmenopausal women. The few studies of sex hormone levels among premenopausal black women demonstrated a similar hormonal profile associated with obesity or increased WHR, with higher level of free E2 and a lower level of SHBG among obese compared to non-obese women in multivariate analyses [142, 144].

Inflammation

Most cancers develop in a background of chronic inflammation, and a tumor can be considered a chronic inflammatory state. It has been well documented that many types of cancer, including breast cancer, are heavily infiltrated by inflammatory cells. These cells express a large variety of cytokines and growth factors, some of which are known to function as regulators of tumor growth, metastasis, and angiogenesis. Adipose tissues produce not only estrogens, but also cytokines, including several major pro-inflammatory cytokines. A positive energy balance increases adipose tissue mass, but also induces hypoxia and cell necrosis in the fat depot. In response, there is a dramatic infiltration of pro-inflammatory macrophages. Similarly, there may be an increase in neutrophils and natural killer cells in adipose during the course of obesity. Obesity, and its consequent unbalanced inflammatory response, leads to uncontrolled chronic inflammation. Remarkably little is known about racial differences in inflammatory response in relation to breast cancer risk.

Many cytokines regulating immune system function and an inflammatory response, including tumor necrosis factor-α (TNFα), transforming growth factor β (TGFβ) and interleukins (IL), such as IL-6 and IL-1β, circulate at concentrations positively correlated with BMI, in total leading to a chronic pro-inflammatory state. IL-8 is an important pro-inflammatory CXC chemokine [145], and studies have demonstrated overexpression of IL-8 in tumor cells, as well as enrichment of

normal breast tissue of obese women for markers of macrophage infiltration (CD68) and for genes associated with IL-8, IL-6 and other inflammation, or macrophage-associated pathways [146]. As a downstream biomarker, CRP provides functional integration of overall upstream cytokine activation and exerts several important pro-inflammatory effects. BMI, waist circumference, and WHR are significantly associated with higher serum CRP levels [147–149], while weight loss is associated with lower CRP levels [150, 151]. Ethnic differences in CRP between Eastern and Western populations have been shown to disappear after controlling for BMI and other metabolic factors [147]. However, population-based data to systematically assess the association of CRP with cancer risk are limited. In a large prospective study of blacks and whites in the southeastern USA, both the prevalence of elevated CRP and the magnitude of its association with BMI were markedly greater among blacks than whites, with the OR (95 % CI) for elevated CRP comparing obese with healthy-weight black women reaching 22.8 (7.1–73.8), compared with 4.6 (1.7–12.7) among white women [152].

Adipokines (Adiponectin and Leptin)

Associations between obesity and cancer may reflect levels of adiponectin, whose secretion from adipose tissue is down-regulated among obese individuals [153], and leptin, which is positively correlated with BMI. Leptin, which is positively correlated with obesity, may promote local or distant immunocyte differentiation, in addition to a proliferative signaling effect on cancer cells [154] and acts as a growth-promoting factor for cancer via the PI3K/Akt pathway [155]. Leptin also is thought to down-regulate the apoptotic response of tumor cells through as yet undetermined mechanisms [155]. In contrast, loss of adiponectin leads to an inflammatory response mediated via NF-κB activation [156]. Adiponectin exerts anti-cancer effects, including anti-angiogenesis and anti-proliferation via activation of its two known receptors, ADIPOR1 and ADIPOR2 [157–159], and may block effects of IGF1-stimulated PI3K/AKT signaling and cell proliferation [105, 160]. Since insulin exerts positive feedback on leptin gene expression and can suppress adiponectin secretion, these cytokines also may exert indirect effects on cancer through insulin-related mechanisms.

Adiponectin

Adiponectin is produced exclusively in adipose tissue and is found in a high concentration in the blood, accounting for approximately 0.01–0.05 % of total serum protein [161, 162]. Adiponectin levels appear to be relatively stable within individuals who do not undergo drastic changes in body weight. Circadian variation has been shown to be low overall with adiponectin levels varying less than 20 %

throughout the day, and slightly more variation is seen in females than in males [163]. Most evidence seems to indicate that adiponectin levels remain unchanged in relation to meal ingestion [163].

Two adiponectin receptors have been identified to date, AdipoR1 and AdipoR2 (6, 120). These receptors are found in the cell membrane and are located throughout the body in liver, muscle, and adipose tissue although AdipoR1 is found predominantly in muscle cells while AdipoR2 is primarily found in the liver [164]. The binding of adiponectin to these receptors mediates the activation of AMP kinase which leads to expression of peroxisome proliferators-activated receptor-alpha (PPAR-α) [165]. This activity is believed to increase gene expression of enzymes related to fatty acid oxidation and glucose uptake [161, 165]. This process is thought to be one of the main mechanisms linking adiponectin and insulin sensitivity. Additionally, increased obesity is thought to either directly decrease expression levels of adiponectin receptors or reduce the post-receptor signaling which may also contribute to insulin resistance [161].

Racial Differences in Adiponectin Levels

Racial differences in adiponectin levels have been examined in a relatively small number of studies most of which had low sample sizes; however, reports have been generally consistent that adiponectin levels are lower in blacks compared to whites and the differences emerge relatively early in life [166, 167]. Two small studies of children and early adolescents both reported that adiponectin levels were lower in blacks compared to whites in both genders [166] and among boys after matching on BMI percentile [167]. Two additional studies of middle-age adults reported lower adiponectin levels in American blacks ($N = 212$) [168] and in African blacks ($N = 27$) [169] compared to whites. Two larger cohorts of young (age 23–45) and middle-aged (age 48–58) adults also reported lower adiponectin levels in black participants compared to white participants [170, 171]. In a large study of older adults (age 70–79), adiponectin levels were found to be lower in blacks ($N = 1{,}044$) compared to whites ($N = 1{,}429$) [172]. Hulver and colleagues [173] reported mean adiponectin levels in strata of race and obesity status. They found that mean adiponectin levels were similar in obese white women, obese black women, and non-obese black women but higher in non-obese white women [173]. In a study of white and black South Africans, adiponectin levels were lower in normal weight blacks compared to whites but no differences were seen for overweight and obese women [174]. Both of these studies to examine adiponectin levels over categories of body size were limited by their small overall sample size ($N = 85$ and $N = 217$, respectively). Wassel Fyr and colleagues measured the percentage of European ancestry using 35 ancestry informative markers in a sample of 1,241 older adults (age 70–79) who self-reported as black. In models adjusted for adiposity, fasting glucose levels, insulin levels, blood pressure, and lipids, increasing adiponectin levels were found to increase as the percentage of European ancestry increased

[175]. This pattern is consistent with the previous reports described above that found lower adiponectin levels among blacks compared to whites using self-report.

Adiponectin Levels and Obesity

Serum adiponectin levels are negatively correlated with BMI and WHR [161, 162] which reflect overall adiposity and fat distribution, respectively. This is somewhat paradoxical given that most cytokines (such as leptin) increase directly in relation to body fat. It has been hypothesized that feedback loops exist between obesity, adiponectin expression, and regulation of the adiponectin receptors, resulting in the observed inverse association between obesity phenotypes and adiponectin levels in the blood [165, 176].

Most evidence to date regarding the obesity–adiponectin relationship has been observed in white or Japanese populations [177–180]. Despite the known differences in the prevalence of obesity and risk for obesity-related disease, a relatively low number of studies have examined the relationship between adiponectin and obesity in blacks and many have had very small sample sizes. In a study of adolescents including 40 white and 46 black participants, Degawa-Yamauchi et al. observed that adiponectin was negatively correlated with both BMI and percentiles of BMI [167]. In another small study, Hulver et al. found that adiponectin was negatively correlated with BMI only among whites ($N = 48$) but not blacks ($N = 37$) [173] while, in contrast, Araneta et al. found that adiponectin was negatively associated with increasing tertiles of BMI, waist circumference, and WHR in both blacks ($N = 212$) and whites ($N = 143$) [168]. Comparing black and white South Africans, adiponectin levels were found to be negatively correlated with BMI in each race group in univariate analysis although not in the final multivariate model [174]. In a genetically homogeneous sample of 431 individuals from 7 families living on the Caribbean island of Tobago, adiponectin was also found to be negatively correlated with BMI [181].

Reports from larger studies with sizeable black participant populations remain scant; among 522 black participants in the Insulin Resistance Atherosclerosis (IRAS) Family Study, visceral adipose tissue measured by CT was strongly negatively correlated with adiponectin levels [182]. In the Atherosclerosis Risk in Communities Study (ARIC), mean adiponectin levels were found to decrease over categories of BMI in 630 black and 523 white participants age 48–58. Further, the adjusted mean adiponectin values were lower for black women than for white women in each BMI category [171]. Waist circumference was found to be negatively associated with adiponectin levels in the CARDIA study of 1,615 white and 1,360 black young adults (age 23–45) [170]. Among 996 black and 996 white women age 40–79 enrolled in the Southern Community Cohort Study, which includes black and white participants from similar geographic and socioeconomic situations, black women had significantly lower adiponectin levels than white women even after adjustment for BMI. Both race groups demonstrated a strong

inverse association between adiponectin and BMI although the trend was monotonic in white women but leveled off for black women with severe obesity [183].

Leptin

Leptin was first discovered in 1994 [184], and like adiponectin, is a protein produced and secreted by adipose tissue. The leptin protein is translated as a 167 amino acid polypeptide including a signal peptide consisting of a cleaved strand of the first 21 amino acids [185]. Leptin plays a critical role in regulating energy intake, energy expenditure, and overall adiposity [183]. Leptin secretion shows clear circadian variation with basal levels observed between 08:00 and 12:00, then rising progressively to a peak between 24:00 and 04:00 and finally receding steadily to a low point again by 12:00 [186].

Rodent models with leptin deficiency (homozygous for a mutant *ob* gene) have morbid obesity, and enough evidence has accumulated to implicate leptin as having a critical role in behavior, metabolism, and endocrinology [187]. Two general types of mutation affect the *ob* gene and alter the structure of protein that is produced. The first is a nonsense mutation that produces a stop codon prematurely in the nucleotide sequence, resulting in a shortened and nonfunctional protein. The other mutation affects the promoter region, resulting in no transcription and thus no protein is produced at all [185].

Leptin Levels and Obesity

Several studies including individuals of different ethnic backgrounds have shown that leptin levels are universally positively associated with BMI. This positive leptin-BMI association was demonstrated in all subpopulations within a relatively large study of European, Chinese, South Asian, and Aboriginal Canadians [188]. In the Multi-ethnic Study of Atherosclerosis (MESA), leptin levels were positively associated with BMI in white, Chinese, black, and Hispanic individuals although the magnitude of association varied with blacks having the weakest association compared to the other groups [186]. In the Southern Community Cohort Study, adjusted leptin levels also increased as body size increased in both black and white women. In contrast to the MESA results, however, leptin levels were similar for both race groups at BMI $<$18.5 and 18.5–24.9 but were higher in overweight and obese black women compared to white women at the same BMI [189].

Racial Differences in Leptin Levels

Initial studies examining leptin levels across race groups generally utilized convenience samples, and conflicting results have been reported, with some studies

finding no difference in leptin levels according to race [12, 59] and at least one finding lower levels in black women compared to white women [190]. Larger population-based studies, however, have consistently found leptin levels to be higher in black women than in white women. In the Multiethnic Cohort Study, mean leptin levels were 27.9 ng/ml among 73 black women versus 21.4 ng/ml among 71 white women [191]. The Health, Aging, and Body Composition Study ($n = 718$ black and 840 white women aged 70–79 years) also reported higher leptin levels among the black women (geometric mean 20.2 ng/ml) versus white women (13.9 ng/ml) [1] as did the ARIC study ($n = 305$ blacks and $n = 388$ whites) with median leptin levels of 20.3 ng/ml in black versus 9.8 ng/ml in white participants [2]. In the third National Health and Nutrition Examination Survey ($n = 957$ black women and $n = 1{,}441$ white women), mean leptin levels were found to be 16.4 ng/ml among the black women and 12.2 ng/ml among the white women [3]. Also, within the Southern Community Cohort Study, mean adjusted leptin levels were again higher in black women ($n = 829$) than white women ($n = 915$), 22.7 vs. 18.8 ng/ml [4].

Differences in leptin levels between black and white women may reflect actual physiological or genetic differences in the production of leptin in adipose tissue between race groups. But a methodological consideration is that incomplete adjustment for fat distribution could be responsible for the consistently observed higher leptin levels in black women compared with white women in large population-based studies. It has been established that black women have an overall higher proportion of subcutaneous fat than white women [5, 6], and leptin secretion is known to be higher in subcutaneous fat than in visceral fat [7, 8]. Thus, incomplete adjustment for fat distribution could bias estimates of differences of leptin levels between blacks and whites. However, at least two studies have adjusted for fat distribution, either percentage fat and visceral fat [1] or skinfold thicknesses and waist and hip circumferences [3], and both still found that black women had modestly higher leptin levels than white women.

Adiponectin and Leptin Levels and Cancer

In vitro studies have examined the effects of adiponectin on epithelial breast tissue and on breast cancer cell lines. MCF-7 breast cancer cells were found to express functional adiponectin receptors in several in vitro studies [192–195]. Conflicting evidence exists as to whether breast cancer cell proliferation is inhibited by adiponectin with some groups finding evidence for this activity in vitro [192, 195, 196] while others have been unable to replicate this finding [193, 194]. Additionally, several tumor cell lines have been shown to express the adiponectin receptors AdipoR1 and AdipoR2 indicating that adiponectin could act directly on cancer cells through signaling of its receptors [197].

To date, at least seven studies in human populations have examined associations between adiponectin and breast cancer risk. Five relatively small case-control

studies conducted in women residing in Japan, Greece, and Taiwan found a reduced risk of breast cancer at the highest levels of adiponectin compared to the lowest levels [198–202]. In two studies [198, 201], the results were consistent between pre- and post-menopausal women while two others found an association only among post-menopausal women [200, 202]. The Japanese study also found that lower adiponectin levels were associated with larger tumors and higher grade tumors but these results have yet to be replicated [201]. A fifth case-control study, conducted in Korea, found no association between tertiles of adiponectin and breast cancer risk (OR = 0.92, 95 % CI = 0.46–1.81) [203]. The Nurses' Health Study used pre-diagnosis blood samples for a prospective case-control study including 1,477 cases and 2,196 controls [204]. These authors found that breast cancer risk was reduced when comparing the highest quartile of adiponectin to the lowest among post-menopausal women (OR = 0.73, 95 % CI = 0.55–0.98) but not among pre-menopausal women [204]. However, a recent meta-analysis reported an inverse association between circulating adiponectin and breast cancer risk among premenopausal women [205]. With the exception of the Nurses' Health Study, the remaining case-control studies to have examined adiponectin levels in relation to breast cancer used blood samples collected post-diagnosis. Without a clear understanding of the determinants of adiponectin levels, the measurement of adiponectin in blood samples in women after a cancer diagnosis has been made has serious implications for potential bias and is an important limitation. Notably, none of these studies included any appreciable numbers of women of African descent.

For leptin, a positive association has been reported with breast cancer, albeit markedly less consistently than the association with adiponectin [206]. Among women with breast cancer, blood levels of leptin are reported to increase concomitantly with E2 levels, and it is hypothesized that the role of leptin may be specific to postmenopausal ER+ breast cancer among overweight women [207].

Several case-control studies have demonstrated associations between levels of adiponectin or leptin and risk of RCC, or between adiponectin (inverse) or leptin (positive) levels and markers of tumor aggressiveness [208–215]. However, reverse causation cannot be ruled out in these studies which were based on post-diagnostic blood samples. The only prospective analyses to date to investigate pre-diagnostic circulating levels of adipokines in relation to RCC risk reported an inverse association between adiponectin and RCC risk among Finnish male smokers [126, 127].

Crosstalk

While each of the pathways of insulin resistance, estrogen biosynthesis/signaling, and inflammation/adipokines may play an independent role in the association between obesity and breast cancer development [99], there is evidence for crosstalk between the insulin/IGF1 and ER signaling pathways [101, 216, 217]. Chronic hyperinsulinemia is associated with increased ovarian estrogen production and

reduced secretion of SHBG [218, 219], leading to increased estrogen bioavailability. Moreover, estrogen induces expression of IGF1 and IGF-1R in ER+ breast cancer cells [220, 221], resulting in enhanced activation of signaling pathways downstream insulin and IGF1 receptors [106]. Despite this crosstalk, not all studies of circulating IGF1 levels have evaluated associations according to tumor ER status or controlled for endogenous sex hormone levels [108, 116]. A better understanding of the joint effects of hormones is needed in order to assess the independent associations of IGF1 and estrogen with breast cancer risk. Similarly, increased TNFα expression in adipose tissue blocks insulin signaling, thereby inducing insulin resistance [222], and also regulates IL-6 synthesis and aromatase expression, thus stimulating estrogen production [223]. Serum concentrations and adipose tissue expression of IL-6 also are positively associated with insulin resistance [224, 225], and expression of IL-8 is regulated in part by steroid hormones [145]. Moreover, estrogens can suppress secretion of adiponectin by adipocytes [226], and studies of postmenopausal women show strong associations between adiponectin and SHBG (positive) or free E2 (inverse) [108, 227–229].

Conclusion

Several types of cancer are strongly and consistently associated with obesity. There are complex biologic mechanisms underlying these associations, and it is possible that racial differences in the contribution of these biological mechanisms and their mediators play an important role in observed racial differences in cancer incidence and mortality patterns. In particular, accumulating evidence demonstrates racial differences in biomarkers related to obesity, lending support to the hypothesis that these biomarkers act differently in their association with obesity and risk of breast cancer between racial groups. The examination of racial differences in metabolic biomarkers of obesity is important, because although BMI is the standard index for assessing general obesity in epidemiologic studies, it is not a biologic trait and thus does not capture body fat distribution or distinguish between adipose tissue, fat-free mass, and skeletal muscle mass [3, 8, 230], which vary widely across multiethnic populations for a given BMI value [231] and are crucial for characterizing the "multifaceted" obese phenotype and its physiological and pathological risks [232].

Identification of mechanisms through which obesity increases risk for cancer will contribute to delineation of persons at high (and low) risk, specific to race, and pave the way for developing clinically useful cancer prediction biomarkers. This may provide novel targets for development of mechanism-based prevention or treatment approaches in obese patients with cancer, including strategies for cancer prevention linked to insulin resistance or inflammation pathways (e.g., via agents that block the IGF-1 receptor to decrease IGF signaling, or nonsteroidal anti-inflammatory drugs (NSAID), to disrupt the inflammatory process and thereby reduce risk of cancer).

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Chapter 10
Community-Based Strategies to Alter Energy Balance in Underserved Breast Cancer Survivors

Melinda Stolley

Abstract Breast cancer survival rates are significantly lower for African-American women compared to white women. Additionally, African-American women with breast cancer are more likely than other women to die from comorbid conditions including diabetes and hypertension. Such disparities are not easily explained and likely involve complex issues related to social injustices. However, obesity and behavioral factors may be additional contributors. Seventy-eight percent of African-American women are overweight or obese, and data suggest that many do not engage in regular physical activity and tend to have diets high in fat and low in vegetables and whole grains. The combined effects of obesity, unhealthy diet, and inactivity may contribute to the disparity in breast cancer survival between African-American and white women and may be the easiest modifiable factors to address in the near term. Although several weight loss interventions have reported beneficial results for breast cancer survivors, the inclusion of AA women has been extremely limited. This chapter presents a review of health behaviors among African-American breast cancer survivors, followed by a discussion of qualitative work exploring the beliefs, attitudes, barriers, and facilitators related to health behaviors and weight loss. A summary of interventions to date is provided as well as an in-depth look at one particular community-based intervention, Moving Forward.

Keywords Breast cancer • African-American women • Moving Forward • Weight loss • Health behaviors • Economically stressed neighborhoods • Weight loss barriers and facilitators • Exercise barriers and facilities • Community-based interventions • Socio-ecological model • Social cognitive therapy • Self-efficacy

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Breast cancer is the second leading cause of cancer death among African-American women [1]. Despite lower incidence, breast cancer mortality rates for Black women are higher than those for women of other races even after controlling for age, SES, tumor stage and histology, hormone receptor status, and menopausal status [2–4]. Additionally, African-American women with breast cancer are more likely to die from comorbid conditions including diabetes and hypertension [5, 6]. Energy balance contributes to breast cancer progression as well as the development and exacerbation of many comorbid conditions [7–12]. This association remains after adjusting for stage at diagnosis, nodal status, treatment type, and menopausal status prior to diagnosis [9, 13–15]. Obesity is thought to promote tumor progression by three primary mechanisms: (1) producing higher concentrations of estrogen and testosterone [3, 16, 17], contributing to (2) insulin resistance leading to increased levels of insulin-like growth factor-I (IGF-1) and insulin-like growth factor-binding protein-3 (IGFBP-3) [11, 18, 19], and (3) chronic inflammation [20]. Obesity is also related to increased risk for all-cause and cardiovascular mortality among women with breast cancer [8, 12]. Seventy-eight percent of African-American women are overweight or obese [21]. Given the associations between obesity, BC prognosis, and all-cause mortality, the prevalence of high body mass index (BMI) could be a significant factor in the lower survival rates in AA women [8, 22].

Although weight loss or prevention of further weight gain is important to many breast cancer patients [9, 23–25], it is often an elusive goal. Studies of white women show that rather than lose weight, most gain weight over the course of chemotherapy treatments [26–29]. This weight gain is related to time since diagnosis, postmenopausal status, adjuvant chemotherapy, current energy intake, and physical activity [26–30]. Little is known about posttreatment weight gain in Black women. However, the Women's Healthy Eating and Living Study Group (WHELS) (91 % white, 9 % African-American) showed that posttreatment weight gain was positively related to African-American ethnicity [30]. Moreover, average weight gain was significantly greater in African-American (13 lb) compared to white participants (6 lb) [30]. These results are concerning given the likelihood that many Black women are overweight or obese at the time of diagnosis [31].

Changing behaviors that contribute to obesity could benefit breast cancer survivors [9, 32, 33]. In particular, efforts to eat a higher quality, lower calorie diet and increase physical activity may help to reduce the risk for breast cancer recurrence [9, 34, 35], secondary cancers [36], and comorbid conditions [37] as well as improve quality of life [38–41]. Anecdotal evidence supports that being diagnosed with cancer can promote self-initiated changes in health behaviors [42–44]. For example, in a study of 126 breast cancer patients nearly 60 % made dietary changes, 30 % began a new physical activity, and 64 % took new dietary supplements since their diagnosis [45]. In another study of 250 breast cancer patients, 41 % reported dietary changes, with decreases in meat and increases in fruit/vegetable intake being the most frequently identified changes [46]. Participation in behavioral interventions may also promote healthful behavior changes among breast cancer survivors [47–52]. The Women's Intervention Nutrition Study (WINS) [48] reported decreases in dietary fat, while the WHELS reported decreases in

dietary fat as well as increases in fruits and vegetables [49]. Other interventions that addressed sedentary lifestyles report increased physical activity [47, 50–58]. These results are encouraging, but efforts thus far have primarily targeted white women.

In this chapter, we focus on efforts to address weight loss and health behavior change among African-American breast cancer survivors. We begin with a discussion of health behaviors in survivors and qualitative work conducted to understand more about the beliefs, attitudes, barriers, and facilitators related to health behaviors and weight loss. We proceed to provide a review of community-based efforts including a description of the "Moving Forward" program followed by recommendations for future directions.

Health Behaviors, Weight, and Breast Cancer

Few studies have examined the diet and physical activity patterns of African-American breast cancer survivors. Those that have show high caloric and low fruit and vegetable consumption and low levels of physical activity [59–62]. In an analysis of dietary intake at baseline among minority women participating in the WHELS trial, Paxton and colleagues reported that African-Americans ($N = 118$) consumed significantly more calories from fat and less fruit than Asians or whites [62]. Dennis-Parker and colleagues examined compliance with national nutrition recommendations in 31 overweight African-American breast cancer survivors enrolled in a weight loss program. Although the majority of survivors were consuming the recommended daily servings of fruits and vegetables, they exceeded recommendations for energy intake from fat, saturated fat, and added sugars. Additionally, most did not meet the recommendations for whole grains and fiber intake [60]. Both studies reflect the dietary behaviors of women enrolled in intervention trials and thus are not generalizable to the general survivor population. Population-based studies are needed.

Low physical activity levels have been reported in two studies. The first analyzed baseline data of minority women participating in the WHELS trial. African-American women were less likely than other women to meet the guidelines for physical activity. Additionally, health-related quality of life was positively associated with physical activity [62]. The second study surveyed 468 African-American breast cancer survivors and reported similar results. The majority of women did not exercise regularly, and median television viewing was over 5 h daily [61].

Qualitative studies provide further insight into African-American survivors' thoughts and experiences regarding health behaviors, weight, and breast cancer [63–65]. Data support anecdotal evidence that many African-American women make behavioral changes following their diagnosis [63, 64]. For some, this stems from their beliefs that their eating and exercise behaviors contributed to their cancer.

> I'm becoming more conscious. I just know that all the fat I used to eat in Haagen Dazs probably contributed to my cancer. I just have to forget about all of that sweet stuff. It's not going to help me in the long run. So I am trying to give it up. Now I try to eat sherbet and keep up with my exercise—jazzercise 4 days a week. I know I should do more though.

Additional reasons for changing behavior include wanting to improve overall health, to feel better physically and emotionally, and to lose weight. Increasing fruit and vegetable intake, decreasing meat intake, choosing lower fat foods, and increasing physical activity are the most commonly adopted behaviors [63, 64]. The focus of dietary changes may differ by socioeconomic status. In one study, survivors with more education and higher incomes spoke of increasing food items that they had heard might reduce cancer risk [44]. Such foods included green tea, flaxseeds, foods with omega-3 fatty acids, soy, and whole grains.

> You might want to grind the flax seeds and sprinkle them on your yogurt. The dieticians that I've spoken to suggested that the seeds themselves rather than the oil are what help you.

Survivors with lower incomes were more focused on getting rid of specific "bad foods" including high-salt foods, fried foods, or sugar.

> I know that your immune system will fight whatever problems are in your body and what we have to do is to watch what we eat, what will make our immune system weaker, the chocolates, sweets, no raw sugar at all. I found that out. It depresses your immune system for like three hours.

In terms of exercise, qualitative data suggest that many African-American breast cancer survivors are aware of the multiple health benefits of regular physical activity. Those with a history of exercising also report on their improved quality of life. However, many report difficulty with initiating and/or maintaining a regular exercise program [63].

> I know that exercise is very important. I exercised a lot for weeks before my surgery (mastectomy) because I had to get my blood pressure down so I had to get the weight off. I did that and I kept doing that even when I was going through radiation. But now, the regular physical exercise that we all know we need to have, I don't do that. I am having trouble getting going again. I know that it is important to do to maintain good health especially if being a survivor of an illness.

Despite their efforts to make behavioral changes following their diagnosis, survivors relate feeling that they are not doing enough. For many, this frustration is related to the challenge of losing weight. Weight gain is common after breast cancer and serves as an important source of concern and distress [63–65].

> Now I find that I don't eat a lot, but the least little thing I am just picking up weight. And I thought, is it just me or is this something we all of us survivors go through you know this weight gain thing? And that sort of bothers me because I am not used to the extra weight I have gained, and it makes me feel so sluggish. It's miserable with this weight.

In addition to feeling "weighed down," survivors report being concerned about their appearance, not being able to fit into their clothes, needing to afford to buy new wardrobes, and, for some, about how the weight impacts their risk for a recurrence or comorbid conditions [63, 64]. Overall, the weight gain impacts

quality of life leaving women feeling frustrated and helpless. Their helplessness may be due in part to not expecting the weight gain but also due to believing that the weight is a result of their hormone treatments.

> I've gained 25 pounds on hormone treatments. I mean 25 pounds. And my eating habits really haven't changed that much, I'm just tired of feeling tired all the time. I don't want to do anything. I work and come home. I'm too tired to go out with friends.

At the same time, survivors recognize that personal behaviors influence weight status and that making lifestyle changes will impact their weight as well as their overall health.

> ... The only thing I want to say about hormone treatment is the jury with me is still out. Once I started exercising and working weight watchers I've lost 26 pounds and I'm still on the hormone treatment. So for me, I know now it was my high caloric intake and lack of exercise. Simple.

> I was on the hormone treatment for five years, I completed it and I gained the weight maybe the first couple of years I was on it. Then I was ok. When I started to exercise that I found out that no matter what you eat you've gotta have some kind of exercise to balance out what you eat.

As evidenced by their efforts to make behavioral changes after their cancer diagnosis, African-American breast cancer survivors are interested and motivated to adopt healthier eating and exercise patterns and lose weight. However, urban African-American women face multiple barriers in their quest to practice healthy lifestyles. For example, a higher percentage of African-Americans in the general population live in economically stressed neighborhoods where access to fresh fruits and vegetables may be limited or cost prohibitive [66, 67]. Alternatively, cheaper high-fat foods are easily accessible. In addition, opportunities for physical activity in disadvantaged communities are frequently limited by a lack of safe open spaces, sidewalks in disrepair, gang violence, poor lighting, and insufficient police [68]. Focus group data with African-American breast cancer survivors highlight other important barriers as well as facilitators. Barriers include pain, family, mood, and confusion [63, 64]. Facilitators include faith and spirituality, family and friend support, desire to reduce overall health risks, and risk of recurrence (Table 10.1).

Pain is mentioned in several qualitative studies with African-American breast cancer survivors [63–65]. Restricted range of motion as a result of surgery, joint and bone pain due to hormone treatments, and/or arthritis are common and interfere with physical activity.

> I just started really exercising because at first I didn't feel like doing it. And I was in a lot of pain too. So what I do now I just walk around the plaza about three miles you know, as much as I can. When I get tired I just stop. But you know my bones hurt. My body hurts and there's only so much you can do with your arms and I don't force myself to do anything that might hurt me.

Negative emotions such as anxiety, depression, and sadness are identified both as instigators for unhealthy eating and inhibitors of exercise. This may be particularly true for women who are retired or live alone. Additionally, for some women, the breast cancer experience is still quite upsetting.

Table 10.1 Barriers and facilitators to healthy lifestyle changes

Barriers	Facilitators
Access (easy access to cheap high-fat foods; difficult access to fresh fruits and vegetables and safe places to exercise	Faith and spirituality
Pain due to surgery, hormone treatments, arthritis	Family support
Negative emotions (anxiety, depression, sadness)	Friend support
Family food preferences	Group participation in exercise
Confusion about which dietary and physical activity recommendations to follow	Desire to reduce the risk of breast cancer recurrence and comorbid health condition risk

> I have fish and I steam my vegetables . . . but when I am not feeling so well about things, especially before my doctor's appointments, I grab a bag of Lays. It's like a comfort. I recognize that my eating habits tend to change with my emotions.

An additional barrier is confusion. Survivors relate feeling bombarded with information about the "right" way to eat to lose weight and/or stave off a cancer recurrence. Specific topics about which many have questions are organics, soy, supplements, dietary fat, and timing of meals. "When I got diagnosed, I was told by a dietician here to stay away from soy." While another survivor offers, "I work with a lot of Asian women who say you have to put soy in your diet and eat a lot of tofu." Survivors also express confusion about the best way to lose weight and what types of exercises are most helpful in terms of weight loss and reducing health risk.

Family is another significant barrier that is also a facilitator. As a barrier, family members' food preferences make it difficult to avoid eating high-fat and sweet foods. Also challenging is accommodating the traditional value of preparing preferred foods as an expression of love for friends and family. "I have grandkids and they really like fried food, so I cook it for them and then I eat it with them." The pervasive linking of food and family within African-American culture is illustrated in this comment, "Any celebration is a food celebration. Think of soul food, think of my family. Come over Sunday, FOOD." As a facilitator, survivors acknowledge that making good choices is easier when other family members and friends are making the same good choices. "It's easier for me to eat right because my husband eats right. He is not a junk food fanatic, he eats soy, vegetables, fruits and fish and he looks like a million." Providing motivation and company for exercise is an important enabler. "At first I didn't like it. I mean they were, "C'mon, c'mon." And I was, "No, no." But once I started keeping pace, I enjoyed it, I really did."

In keeping with the importance of the support of friends and family, African-American survivors make special note of the value of group participation when attempting to initiate or maintain lifestyle changes. This is particularly true for exercise.

> I think group activities are a help to me. When I can be a part of a group and be accountable or responsible to being there, it's a big motivation to me to have somebody other than myself. If I miss my group and they say where were you last week? That kind of thing helps you keep it going. It's very helpful to me in keeping the commitment to the exercise program.

Other facilitators such as faith and spirituality and the desire to reduce overall health risks and risk of recurrence also support efforts to change behaviors and lose weight. Historically, the African-American culture has relied on faith and spirituality to cope with difficult and painful experiences [69–71]. Breast cancer survivors relate that their faith enabled them to get through their breast cancer treatments and will now help them to lose the weight to improve their health.

> I took myself to the Lord and He lost my desires. Everything through Christ. I changed my life, I changed my desires. The Lord still has some more dealings with me, but I'll get there, we'll get there.

Concerns about comorbid health conditions such as diabetes and hypertension, along with worry about recurrence, are often the strongest motivator for initiating behavior change.

> For the first time my sugar level rose . . . so that was something that shocked me even more than the cancer. I have friends that are on dialysis and I don't want to go that route. So . . . now, I walk and I eat small meals.

These health concerns are equally important during slips or lapses.

> I think it's the realization that there are consequences and there is no avoiding that thought when I peer into the ice cream section at the grocery store . . .. I can't even enjoy it the way I used to because it's looming over me that I might be doing something to bring it back. And maybe this is what brought it the first time. There is no way for me to know.

Weight loss intervention efforts that acknowledge and address barriers while supporting facilitators are needed. Further, African-American breast cancer survivors want programs that provide holistic information on how to make realistic changes that can be incorporated into their lives [57]. They are not interested in diet or exercise patterns that are not sustainable. Survivors also want to know more about "psychological" strategies, such as mindful eating, controlling their environments (stimulus control), and relapse prevention.

Weight Loss Interventions for Breast Cancer Survivors

Several weight loss interventions have reported beneficial results for breast cancer survivors, including weight loss [54, 55, 57, 58, 72]; prevention of weight gain [47]; improved body composition and lipids [53, 55]; decreases in sex hormones [53]; decreases in dietary fat intake [47]; increases in fruit, vegetable, and/or fiber intake [47]; increased physical activity [47, 57]; and improved psychological status [47]. Until recently, the inclusion of African-American women was limited and no intervention had targeted African-American women [72–75].

Considering the high rates of breast cancer mortality, comorbidities, and obesity among African-American breast cancer survivors, weight loss is an important goal for women in this group. However, due to a complex interaction of behavioral, cultural, and societal factors, data suggest that African-American women are less

likely to participate in traditional weight loss programs, more apt to drop out, and lose less weight than white women [76, 77]. To meet the needs of African-American breast cancer survivors, weight loss programs must consider and address the personal (e.g., preferred tastes, body image, hair concerns), interpersonal (social support, roles, and responsibilities), and environmental factors (access to and availability of food and physical activity resources) that influence their behaviors [63, 64, 78–80]. In recent years, several studies have examined the feasibility and efficacy of weight loss interventions for African-American breast cancer survivors [57, 72–74].

One such program examined the effects of an 8-week walking intervention based on tenets of the Health Belief Model [73]. Groups met weekly at a community location to discuss the benefits of and barriers to exercise, the relationship of exercise to health and cancer risk, and self-monitoring/problem solving related to motivation. Twenty-two of 24 African-American breast cancer survivors completed the program, and 95 % reported satisfaction with the number of sessions. Significant improvements were noted for steps per day (+3,506), body weight (−2.0 lb), percent body fat (−3.4), diastolic and systolic blood pressure, and exercise attitude. Seventeen participants completed a 3-month follow-up. The increase in steps per day was maintained; however weight and percent body fat had increased, but not significantly [73].

A second intervention trial explored the effects of the commercial *Curves* program on the weight of 42 survivors, 9 of whom were African-American [74]. *Curves* is a commercial exercise facility that offers a comprehensive weight loss program. The 6-month weight loss program included a 30-min exercise circuit and a high-vegetable/low-fat/calorie-restricted diet. Weekly dietary counseling was provided, but sessions took place at a university hospital, as opposed to the community-based *Curves*. Women in the treatment arm lost an average of 3.3 % (± 3.5 %) of their body weight, compared to 1.8 % (±2.9 %) of the waitlist control group. At a 6-month follow-up, the treatment group had regained some of their weight, such that there were no longer group differences. Participants noted that weight loss maintenance was challenging due to the costs associated with maintaining their membership at *Curves*.

Djuric and colleagues examined a spirituality-based weight loss maintenance intervention following a standard weight loss program [72]. Thirty-one obese African-American breast cancer survivors participated. The weight loss program included dietitian-led counseling by telephone, weight watchers coupons, and the recommendation that participants exercise at least 30 min most days each week. At the end of 6 months, 24 participants were randomized to either a dietitian-led maintenance program or one that included weekly spirituality counseling. The goal of the spirituality counseling was to address barriers to weight loss maintenance: (1) dealing with a crisis, (2) setting priorities, (3) coping with emotions that might lead to relapse, and (4) developing accountability for adhering to healthy diet and exercise patterns. Twenty-three women completed the program. Results were modest; 2.5 % and 2.6 kg weight loss was reported for the standard weight loss program. There was a slight regain at the 18-month follow-up, and no differences were noted between the two maintenance groups [72].

These studies are important in that they establish the feasibility and efficacy of weight loss interventions for African-American breast cancer survivors and address the needs of an underserved group. However, further work is needed to develop comprehensive programs that address diet and physical activity patterns as well as cognitive-behavioral strategies related to lifestyle changes. Basing the program within a community setting will promote sustainability. Attention to the psychosocial needs of breast cancer survivors is also important. For many African-American women, breast cancer is a topic not easily shared and thus incorporating support within the context of a weight loss program facilitates discussion. Finally, a significant limitation of the research to date is the lack of any data on the biological impact of weight loss for African-American breast cancer survivors. Weight loss trials with white breast cancer survivors support the positive impact of weight loss on intermediate markers of breast cancer including sex hormones (estrogen, estradiol, testosterone, sex hormone-binding globulin), chronic inflammation (C-reactive protein [CRP], interleukin-6 [IL-6], and TNF-α), and hyperinsulinemia (leptin, IGF-1, IGFBP3). These data, along with those for body composition (percent body fat vs. lean mass), are particularly important for African-American survivors given the historically low levels of weight loss observed in interventions. Furthermore, results from a prospective study of 278 overweight/obese postmenopausal women (38 %/105 African-American) not affected by breast cancer within the Weight Loss Maintenance Trial showed that African-American women exhibited higher levels of estrogen and testosterone concentrations, independent of adiposity [81]. Gathering body composition and biological data will enhance our understanding of how weight loss, even small amounts, impacts breast cancer recurrence risk and overall health risk among African-American women.

Moving Forward: A Community-Based Weight Loss Intervention

To address the limitations of intervention efforts to date, researchers in collaboration with African-American breast cancer survivors developed "Moving Forward," a weight loss program and intervention trial for African-American breast cancer survivors [57]. Preliminarily, focus groups informed the development of the intervention, after which an advisory board of African-American survivors reviewed and adapted the program. Twenty-three African-American survivors participated in a pilot study. Attendance and satisfaction data supported the acceptability and feasibility of the program with the majority of the women attending at least 75 % of the 52 classes and 87 % completing the 6-month program. Post-intervention differences were significant for weight (−5.57 lb), BMI (−1.0 kg/m^2), dietary fat intake (−23.6 g), vegetable consumption (+1.6 svgs/day), vigorous physical activity (+23.6 min/day), and social support. Although a nonsignificant increase of 20-min moderate physical activity was observed post-intervention, the combination

of vigorous and moderate physical activity (>40 min/day) represented an important shift in behavior. Quality of life, as measured by the FACT-B and ES, was high at baseline, and thus no significant change was noted post-intervention.

Based on feedback from the pilot study, the investigators and advisory board once again reviewed and adapted the intervention. Primary changes included adding more information and activities related to how lifestyle and weight status impact breast cancer recurrence and comorbidity risk; integrating more practical advice related to grocery shopping and meal planning; and basing the program within the community at a location with affordable exercise facilities. Following we provide a description of the *Moving Forward* program and a description of the methods for the intervention trial.

Program Structure

Moving Forward is a 6-month program that meets twice weekly. The program is conducted in partnership with a city park district. The program is conducted in city park district facilities where participants enjoy reduced-fee or free memberships, ongoing access to classes and fitness rooms, and the opportunity to maintain contact with program participants once the program concludes. The content of the intervention is designed to provide participants with the tools they need to make independent changes in important health behaviors. Table 10.2 provides a list of weekly curriculum topics. The first meeting each week includes a 60-min class that addresses *knowledge* (e.g., relationship between obesity and breast cancer; food label reading; portions; available healthy living community resources), *attitudes* (e.g., pros and cons of weight loss; understanding the roles that food plays in one's life; the concept of fail to plan, plan to fail), and *cognitive behavioral strategies* including self-monitoring of weight, food, and physical activity; realistic goal setting; stimulus control; problem solving; mindfulness; cognitive restructuring; and relapse prevention. Pilot data showed that many women entered the program with low levels of knowledge about healthy eating and exercise. Thus, the first weeks are devoted to teaching core concepts (e.g., concept of calories in/out; food label reading; measuring heart rate). Other class activities include weekly weigh-in; completing a food and activity self-monitoring record for the current day; increasing awareness of portions by weighing and measuring foods according to one's typical portions and then according to recommended portions; creating stimulus control plans for home, car, and work; identifying barriers to healthy eating and/or exercise and problem solving within small groups; going on a field trip to a local grocery store to practice reading food labels; creating an eating out management plan; and identifying high-risk situations and brainstorming ways to manage them. The first weekly meeting also includes a support "icebreaker" (share the funniest moment of your breast cancer journey; what has been the most frustrating; etc.) and a 60-min exercise class taught by a certified cancer exercise trainer.

Table 10.2 Moving Forward—weekly curriculum topics

Week 1	Introduction to program
Week 2	Self-monitoring and goal setting
Week 3	Using self-monitoring tools to make better choices
Week 4	Energy requirements
Week 5	Reading food labels and monitoring heart rate
Week 6	Measuring portions
Week 7	Breakfast and water—two key tools to losing weight
Week 8	Healthy grocery shopping
Week 9	Meal planning
Week 10	Holiday eating (moved according to when holiday falls)
Week 11	Stimulus control
Week 12	Mindful eating
Week 13	Eating away from home—restaurant and party strategies
Week 14	Program review—where were you, where are you now
Week 15	Building movement into your daily life
Week 16	Barriers to healthy eating and exercise
Week 17	Problem solving
Week 18	The power of habit
Week 19	Strategies to increase fruits and vegetables
Week 20	Where you were, where you are, and where you plan to go
Week 21	Relapse prevention I—what is a lapse vs. relapse
Week 22	Relapse prevention II—identifying high-risk situations
Week 23	Relapse prevention III—maintaining a physically active lifestyle
Week 24	Relapse prevention IV—motivation to maintain changes
Week 25	Transitioning from Moving Forward to being on your own
Week 26	Graduation

The second meeting each week is a stand-alone 60-min exercise class taught by a certified cancer exercise trainer. The exercise classes incorporate a variety of activities, including traditional aerobics, line dancing, African dance, salsa, yoga, Pilates, and strength and flexibility training. Class time is also spent learning to use the park district fitness facility equipment to ensure that women feel comfortable and competent on the equipment, thus promoting enhanced self-efficacy and mastery of new skills. Many participants enter the program at very low levels of fitness; therefore, physical activity levels are increased gradually with special attention to concerns such as lymphedema and balance. Increased physical activity outside of class is encouraged by suggesting enrollment in additional exercise classes, providing safe outdoor walking routes, and alerting women to activity resources online and on Fit TV or other television channels that provide regular fitness and exercise programs.

Participants often need further support and reinforcement of lifestyle changes outside of class as well as timely information related to healthy eating and exercise resources. To do this, Moving Forward uses text messaging, a strategy successfully used in previous weight loss interventions with low-income African-American women [82, 83]. All participants receive three text messages each week. Messages

are 200 characters in length and are written to be brief, clear, and motivational. The intent is to reinforce concepts covered in class while also supporting self-efficacy, social support, and perceived access.

Intervention Goals

The overall goal of Moving Forward is to make independent changes in health behaviors to promote a healthy weight. The weight loss goal is 7 % of baseline body weight (1–2 lb/week) consistent with the recommendations of an expert panel at NIH [84]. Dietary goals aimed at producing weight loss, decreasing BC recurrence risk, and improving overall health include (1) a decrease in daily caloric intake (based on weight in pounds × 12 kcal/day with 500–750 cal subtracted to create an energy deficit); (2) a decrease in dietary fat consumption to 20 % of total calories; (3) an increase in fruit and vegetable consumption to seven daily servings; and (4) an increase in fiber to 25 g/day. For exercise, participants will gradually increase their activity to a minimum of 180 min/week at 55–65 % maximal heart rate.

Theoretical Framework

The Moving Forward intervention integrates concepts from social cognitive theory (SCT) [85] and the socio-ecological model (SEM) [86, 87] to promote independent behavior change. SCT suggests that behavior can be explained by the dynamic interaction between behavior, personal factors (e.g., self-efficacy), and the environment (e.g., social support). Self-efficacy is a person's confidence in performing a particular behavior and overcoming barriers to that behavior. A number of studies have supported the mediating role of self-efficacy in making independent health behavior changes [88–92]. The intervention also incorporates tenets of the SEM [86, 87], a model that goes beyond individual-level variables and emphasizes that support from the larger social context is needed for long-term behavior change [93]. Accordingly, SEM posits that weight status, diet, and physical activity are influenced by individual (e.g., beliefs, taste preferences), interpersonal (e.g., social support, traditions, and role expectations), and community factors (e.g., access to resources that support health promotion) [94]. Interventions hoping to promote long-term behavior change must address these three levels of influence [95, 96]. Moving Forward accomplishes this by addressing (1) *individual* factors—acknowledging heavier body image ideals and the importance of hairstyles; (2) *interpersonal*—the importance of food in the African-American culture and finding ways to integrate this value with healthful eating; providing low-fat versions of culturally traditional "soul food" recipes; acknowledging and addressing family roles and family resistance/support to change; providing information on integrating healthful lifestyle practices for the family; facilitating social support for

making changes in diet, physical activity, and weight; and understanding the important role of religion and worship in the women's lives and how it affects their health perspectives; and (3) *community*—incorporating a sustainable link to a community physical activity resource that can address barriers to regular physical activity (i.e., safety, weather, access); problem solving around cost and availability of healthy food; and introducing participants to unfamiliar community resources. Interestingly, a positive sense of community (e.g., social bonds between individuals and between individuals and their community) is associated with self-efficacy for physical activity among African-American women [97].

Based on these theoretical models, the content and structure of Moving Forward were developed to address mediators of long-term behavior change by enhancing self-efficacy, increasing social support, and addressing perceived access to healthy eating and exercise resources. Self-efficacy is enhanced by (1) teaching participants the information and cognitive behavioral skills necessary to make healthy changes; (2) modeling the process of structuring behavior change into incremental steps that participants can realistically achieve; (3) providing opportunities for repeated practice and mastery of skills and behaviors that support weight loss; (4) having participants share testimonials of their achievements; and (5) fostering social support.

Increased social support is facilitated by (1) creating a cohesive community of African-American breast cancer survivors who are working toward a common goal; (2) providing opportunities to tell stories related to their breast cancer and weight loss experiences; (3) sharing potluck dinners in honor of holidays and significant events with group participants and their family members; (4) participating regularly as a group (with family members) in local breast cancer events such as walks; (5) creating a "Moving Forward" Facebook page that will continue to be maintained and updated once the program is completed; (6) providing contact information (with permission) to enable participants to text or call each other; (7) exercise buddies; (8) CPD sites devoting a section of their bulletin boards to address BC information; and (9) sending motivating text messages.

Perceived access to environmental resources is improved by (1) showing participants strategies for learning about healthy eating and exercise resources in their home and work communities via computer searches and media ads; (2) providing participants with a list and description of local healthy eating and exercise resources; (3) problem solving around access issues to healthy eating and exercise resources; (4) creating individual and group plans to overcome barriers to resources (including identifying safe, reliable transportation); (5) increasing familiarity with resources by doing class visits or having community resource staff come to class; (6) Park district postings on local resources, store specials; and (7) text messages to announce/remind participants about sales/events at local sites.

Intervention Trial Methodology: Details of the Moving Forward Trial Are Provided Below

Study Design

We are conducting a randomized study with 240 African-American diagnosed with stage I, II, or III breast cancer. Study aims include evaluating the effects of a guided weight loss program (Moving Forward) on the BMI, body composition, and waist: hip circumference of overweight/obese African-American breast cancer survivors. Diet and physical activity patterns, intermediate markers of breast cancer recurrence (i.e., estradiol, estrone, testosterone, leptin, C-peptide, IGF-1, IGFBP-3, SHBG, and CRP), fatigue, and quality of life will also be examined. The study will be based in six predominantly African-American communities in Chicago, and the intervention will be conducted at Park district facilities. Forty African-American breast cancer survivors will be recruited from each community area (20 guided, 20 self-guided). Figure 10.1 provides an overview of the study design, and Fig. 10.2 provides an overview of the conceptual framework for the study.

Procedure

Women who respond to recruitment efforts will complete a brief telephone interview to verify eligibility. Once eligibility is established, all participants are asked to complete a 75-min pre-intervention interview plus a blood draw, blood pressure measurement, and height and weight measurements. Subsequently, participants are randomly assigned to one of the two 6-month interventions: (1) Moving Forward guided weight loss intervention (MF) or (2) Moving Forward self-guided weight loss intervention (SG) that includes a program binder with all information, activities, and supplies, but no participation in classes or exercise sessions. Following the intervention and at a 6-month follow-up, participants from both groups complete a 75-min post-intervention interview plus a blood draw, blood pressure measurement, and weight measurement.

Recruitment

Recruitment centers around a number of community and institutional partners including breast cancer support organizations, hospital cancer registries, local churches, community leaders such as aldermen, block clubs, and community centers. Thus far, the most effective mode has been direct contact with survivors through support groups or hospital registries. An equally effective strategy is

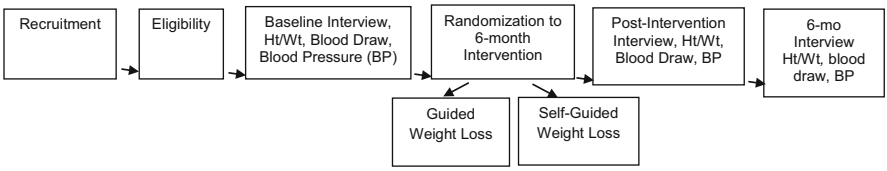

Fig. 10.1 Study design

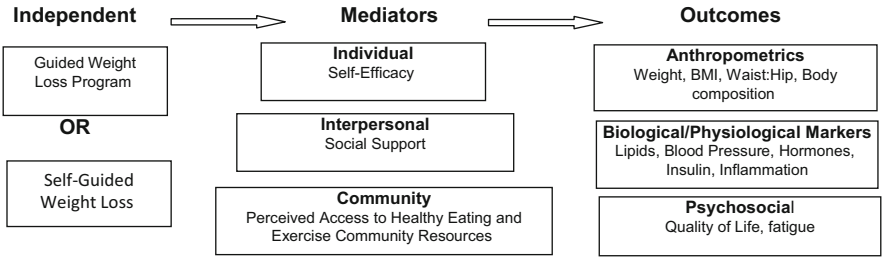

Fig. 10.2 Study conceptual framework

hosting educational events about breast cancer at community venues such as police stations, churches, and community centers. Community leaders and stakeholders are invited, and lunch is served. Presentations address breast cancer screening (presented by a radiologist from a community hospital), diagnosis, what happens during treatment, life after treatment, and, finally, a brief review on Moving Forward and survivorship.

Eligibility

Inclusion Criteria

Inclusion criteria include the following: (1) self-identification as Black or AA (including individuals who are biracial but identify themselves as Black or AA); (2) female; (3) stage I, II, and III invasive breast carcinoma; (4) treatment (surgery, chemotherapy, and/or radiation) completed at least 6 months *prior to* recruitment (ongoing treatment with tamoxifen or aromatase inhibitors is acceptable); (5) age 18 or above at the time of diagnosis; (6) BMI at least 25 kg/m^2—chosen because this includes only those participants who are overweight and would not be harmed by a 7 % weight loss; (7) physically able to participate in a moderate physical activity program as assessed by a screening questionnaire and PCP approval; (8) agreeable to random assignment and data collection including blood draw; and (9) able to attend twice-weekly classes for 6 months.

Exclusion Criteria

Exclusion criteria include the following: (1) plans to move from the community during the study; (2) medical condition limiting adherence as assessed by PCP; (3) history of significant mental illness; (4) currently pregnant, less than 3 months postpartum, or pregnancy anticipated during the study; (5) current/planned use of an FDA-approved or over-the-counter weight loss medication; or (6) participation in another structured weight loss program.

Measures

Demographics

Demographic data will include name, address, date of birth, marital status, number of children, education, occupational status, annual income, and insurance status.

Breast Cancer Data

Diagnosis and treatment history are collected from the treating oncologist.

Comorbid Condition Rating Scale

The Modified Cumulative Illness Rating Scale [98, 99] classifies comorbidities by 14 organ systems that may be affected and rates them according to severity from 0 to 4. This measure can generate four ratings including total score, number of categories endorsed, severity index (total score/number of categories endorsed), and number of categories at level 3.

Self-Efficacy for Eating and Exercise Behaviors [100]

This measure consists of 12 items that assess exercise self-efficacy (e.g., beliefs about one's ability to exercise five times a week despite barriers) and 20 items that assess healthy eating self-efficacy (e.g., eating low-fat foods and healthy portions despite high-fat temptations).

Social Support for Eating and Exercise [101]

This questionnaire asks respondents to rate on a five-point scale (1 = none, 5 = very often) the frequency that friends and family have done or said certain things related to the respondents' efforts to change dietary or exercise habits. The social support for eating survey includes ten items and two subscales (i.e., encouragement and discouragement) each for friends and family.

Perceived Access to Healthy Eating and Exercise

Respondents rate their level of agreement to statements related to access to physical activity resources and five items related to healthy eating resources. There are also five items asking about the availability of activity-related facilities that require a yes/no response. These questionnaires were used in two studies with urban minority populations [102, 103].

Body Mass Index

Height (baseline only) is assessed using a portable stadiometer. Weight will be assessed using a Seca company digital scale with participants wearing light clothes and no shoes. BMI is calculated as weight (kg)/height $(m)^2$.

Waist-to-Hip Ratio

Waist-to-hip ratio (WHR) is measured with participants standing without outer garments and with empty pockets. Waist is measured at the level midway between the lower rib margin and the iliac crest, with the participant breathing out gently. Hip is recorded as the maximum circumference over the buttocks.

Diet: Brief Block 98 Food Frequency Measure

While there is no gold standard for dietary assessment and all dietary assessments are prone to underreporting [104], a combination of 24-h recalls and a food frequency questionnaire (FFQ) may be sufficient to address the concern of underreporting. However, this method is costly, burdensome for participants, and not necessary for determining mean consumption of dietary components for a group of participants. Our goal is to determine group means for consumption of energy, fruits and vegetables, fat, and fiber. A semiquantitative FFQ is the most appropriate tool in this case [105–107]. The Block 2005 Food Frequency Questionnaire [108] estimates the usual intake of a wide array of nutrients and food groups. Reliability

and validity have been established for the measure in a wide range of age, gender, income, and ethnic groups [109, 110].

Physical Activity (Self-Report and Objective)

The Modified Activity Questionnaire (MAQ) [111] assesses self-reported leisure and occupational activity, television viewing, and inactivity due to disability. For leisure activity, respondents review a list of 29 popular activities (e.g., walking, gardening) and select those that they performed on at least ten occasions in the last year. Respondents then provide information on average frequency and duration for each activity. For occupational activity, respondents provide information on common activities performed at work and transportation to/from work. The MAQ has been used in many large studies with diverse samples, including cancer survivors [112], and has well-established reliability and validity [111].

Accelerometer

The limitations of self-reported physical activity are well established [113]. Therefore, the ActiGraph GT1M activity monitor is used to obtain an objective measure of physical activity. The ActiGraph is a small, lightweight accelerometer designed to detect normal body motion. Participants are asked to wear the ActiGraph during waking hours for 7 days. Only days on which the participant wore the accelerometers for at least 10 h are included; participants with fewer than four valid days are excluded. Thresholds suggested by Troiano and colleagues will be used to calculate the amount of time spent in moderate and vigorous physical activity [114].

Biological/Physiological Markers of BC Progression

Markers for three proposed mechanisms by which obesity may contribute to BC progression are being measured. These include levels of sex hormones (markers: estradiol, estrogen, sex hormone-binding globulin, testosterone), hyperinsulinemia (markers: leptin, IGF-I, IGBP3, C-peptide), and chronic inflammation (markers: IL-6, CRP) [115].

Biological/Physiological Markers of Comorbidities

A fasting blood sample is also drawn (at the same time as sample above) for lipid profile analysis (HDL, LDL, triglycerides) as a marker of dyslipidemia and HbA1c as a marker of diabetes. Diastolic and systolic blood pressure are also measured using a standard protocol.

Psychosocial (Quality of Life and Fatigue)

The SF-36-item short-form health survey [116] assesses eight health concepts: (1) limitation in physical activities due to health problems, (2) limitations in social activities due to physical or emotional problems, (3) limitations in usual role activities due to physical health problems, (4) bodily pain, (5) general mental health (psychological distress and well-being), (6) limitations in usual role activities because of emotional problems, (7) vitality (energy and fatigue), and (8) general health perceptions. This instrument has been widely used with diverse healthy and clinical populations and has good reliability and validity [117–119]. Specific scales within the Functional Assessment of Cancer Therapy series are also administered: the FACT-B (assesses effects of breast cancer treatment), the FACT-ES (assesses the side effects and putative benefits of hormonal treatments for breast cancer), and FACT-F (assesses cancer-related fatigue) [120, 121].

In sum, the Moving Forward intervention trial seeks to address the limitations of the literature to date by examining the impact of a community-based weight loss intervention on physical, biological, and psychosocial outcomes.

Conclusions

African-American women with breast cancer are more likely to die from breast cancer and comorbid conditions than women with breast cancer of other races. The combined effects of obesity, diet, and physical inactivity may contribute to this disparity. Developing interventions that address these risk factors in African-American women is an important public health goal. Although such interventions have been shown to be feasible and effective with white women [47, 54–56, 58], limited efforts have been initiated for African-American women [72]. Four interventions have established the feasibility and efficacy of weight loss program for African-American women. Results reinforce the importance of offering comprehensive, community-based programs that can be sustained once the evaluation is completed. Further efforts to address the needs of African-American survivors are warranted, as are data that provide insight into the biological and physiological impact of energy balance interventions.

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Chapter 11
The Role of Policy in Reducing Inflammation

Deborah J. Bowen and Stacey Zawacki

Abstract Obesity continues to be a major public health problem affecting approximately 33 % of adults and approximately 20 % of children in the USA (Centers for Disease Control and Prevention (CDC). http://www.cdc.gov/obesity/. Accessed on 31 Oct 2013). The obesity prevalence within minority subgroups of the population is significantly higher (CDC. http://www.cdc.gov/obesity/. Accessed on 31 Oct 2013); differences in dietary and physical activity behaviors likely underpin these disparities (Larson and Story, Ann Behav Med 38:S56–S73, 2009; Story et al., Annu Rev Public Health 29:253–272, 2008). Inflammation occurs because of some combination of genetics and behavior and is often linked with obesity. To address this problem, focused prevention efforts among adults and children is a key strategy (Committee on Prevention of Obesity in Children and Youth, Food and Nutrition Board. Washington, DC: The National Academies Press, 2004; Larson and Story, Ann Behav Med 38:S56–S73, 2009; Story et al., Annu Rev Public Health 29:253–272, 2008). Yet, solely relying on individual-level strategies to change inflammation, obesity, and associated behaviors is not sufficient; creating supportive environments for behavior change is also needed (Affenito et al., J Obes 2012:150732, 2012; Hafekost et al., BMC Med 11:41, 2013; Kahn et al., Am J Prev Med 22 (4 Suppl):73–107, 2002; Larson and Story, Ann Behav Med 38:S56–S73, 2009; Story et al., Annu Rev Public Health 29:253–272, 2008; Mitchell et al., Psychiatr Clin North Am 34(4):717–732, 2011).

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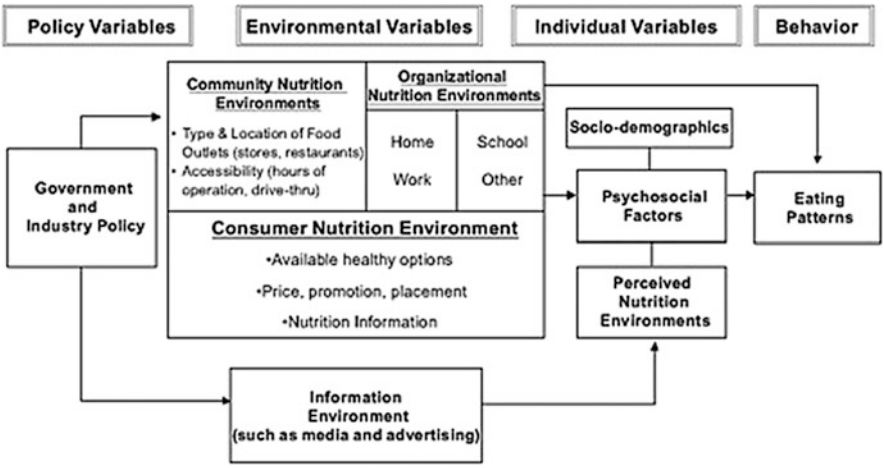

Fig. 11.1 Elements of the nutrition environment (reprinted with permission from American Journal of Health Promotion)

Keywords Inflammatory environment • Obesogenic environment • Nutrition environment • Community effects • Organizational effects • Government effects • Consumer effects • Special Supplemental Nutrition Assistance Program (SNAP) • Soda tax • Menu labeling • Food availability and purchase policy

Why Use Environmental Strategies to Reduce Inflammation

The adjective "obesogenic" has been used to describe environments that promote obesity either through increased energy intake or decreased energy expenditure [119]. For the purpose of this review, we will focus our attention on environments that affect energy intake (i.e., nutrition environments). A socio-ecological framework tailored to characterize nutrition environments [53, 115, 32, 2, 31] has guided much of the research to date. Suggested conceptualization of the nutrition environment centers on individual perceptions of food and activity options in the neighborhood and radiates outwardly to other higher order domains including consumer level (i.e., neighborhood food and activity marketing), community level (i.e., food and activity outlets in the neighborhood), organizational level (i.e., inflammatory opportunity in systems, institutions, or workplaces), informational level (i.e., media and advertising), and policy level (i.e., behaviors affected by governmental decisions) [53] (Fig. 11.1).

Evidence suggests that obesogenic and potentially inflammatory environments are spatially patterned such that they co-occur in areas with larger proportions of low-income and minority populations [115, 78, 126, 66] and may thus contribute to socioeconomic and racial disparities in obesity [115, 78]. Evaluating this potential mechanism has begun by assessing observational associations between mainly availability, accessibility, and affordability dimensions of inflammation, and

associated behaviors within domains of the nutrition environment and behavioral indices of high-energy intake seem reasonable [30, 28, 29, 55, 49, 22, 110, 78, 115].

While earlier reviews noted many positive associations between the environment and intake or activity [115, 78], subsequent reviews have concluded that the evidence supporting a causal relationship is moderate to mixed—likely due to conceptual differences and a lack of standardization of measures used to assess the nutrition environment [36, 90, 115, 30, 55, 49, 22, 110]. More in-depth description of measures used to describe the qualities of the environment and methodological considerations are presented elsewhere [55, 74, 32, 84]. In addition to standardizing measures of the environment, research recommendations include conducting studies that (1) employ more rigorous study design, (2) employ a multidimensional approach to characterizing the environment, (3) evaluate a broader array of obesogenic behaviors, (4) address the co-occurrence of obesogenic nutrition and physical activity environments, and (5) measure inflammation as an outcome [30, 23, 55, 49, 22, 110].

Government and Industry Policy Environment

Description

Governmental policy has been used to shape the accessibility of food within organizations, communities, and retailers. Likely the most far-reaching policy is the federal Farm Bill which oversees the largest of the 15 federal nutrition assistance programs—the Special Supplemental Nutrition Assistance Program (SNAP), formerly known as the Food Stamp Program (FSP) [115, 81]. SNAP has significant influence on the accessibility of food overall for low-income Americans [115]; an average of 47 million persons participated in SNAP in 2012 which roughly translates to about 1 in 7 Americans [123]. Eligibility in the program is determined by having a household income $\leq$130 % of the federal poverty level and $<$\$2,000 in countable assets [81]. By participating in SNAP, income-eligible adults are provided vouchers to purchase foods from program-approved retailers; the current average monthly benefit provided by the program is \$133 per person [123].

Other policies implemented at regional and local levels which affect the food environment include food and beverage taxes, menu labeling, commercial zoning policies, as well as licensing and permitting requirements for food outlets [73].

Supporting Evidence

Participation in SNAP has been associated with stocking a wider variety of fruits and vegetables among small retailers as well as increased purchasing of fruits and vegetables among residents in low-income communities [86]. Despite its emphasis on promoting the availability of nutritious foods among low-income Americans,

SNAP has been criticized because benefits can be used to purchase unhealthy food (e.g., baked goods, sweet and salty snacks, and sugar-sweetened beverages) [81]. Studies have identified that SNAP participants do not adhere to the 2005 dietary guidelines for Americans [81, 10]. For example, using NHANES data between 1999 and 2008, SNAP participants reported eating 39 % fewer whole grains, 56 % more potatoes, 46 % more red meat, and 61 % more sugar-sweetened beverages (women only) compared to non-SNAP participants [81]. Similarly, sugar-sweetened beverage purchases were found to account for a greater proportion of all beverage purchases made by SNAP households compared to non-SNAP-eligible households [9, 19]. A recent Institute of Medicine (IOM)/National Research Council (NRC) committee was tasked to ascertain whether the adequacy of the SNAP allotment could be evaluated and concluded that additional factors, *including those related to the nutrition environment*, would need to be considered in the evaluative process [68, 56].

Broader level food and beverage taxes and subsidies have also been proposed to facilitate healthy eating [6, 104, 51, 121, 78, 115], thereby potentially reducing inflammation. Studies have looked at price elasticity, a dimensionless construct representing the percent change in sales resulting from a 1 % price manipulation, to determine the price sensitivity of specific food items among consumers [104, 51]. Fruits and vegetables and fast food tended to have smaller absolute price elasticity values meaning that consumers were generally unwilling to pay higher prices for these items [104]. In a recent review of price elasticity studies, Powell and colleagues found that, in general, higher fast-food prices and lower fruit and vegetable prices were associated with lower body weight outcomes for both children and adults [104]. This consumer purchasing behavior has been suggested to be true for soda as well [8], although perhaps to a lesser degree [104]. It has been estimated that a penny per ounce soda tax could reduce per capita caloric intake by 50 cal, translating to about 3.8 lb/year for adults, if individuals do not substitute another caloric beverage and could also generate significant tax revenue [7, 100]. Among a population-based survey, one-third of respondents indicated that they would cut back on their consumption of sugar-sweetened beverages in response to an added 20 % tax [108].

Menu labeling has also been a proposed strategy to facilitate healthy food choice among consumers. Food away from home now accounts for about one-third of total calories consumed in the USA [71]. Yet, the content of the food provided within restaurant venues is of concern; a review of Web-based nutrition information found that only 4 % of main entrees at major chain restaurants fell within one-third of the recommended daily intake using USDA guidelines for dietary intake of energy, sodium, fat, and saturated fat [133]. While the energy content and diet quality of fast-food meals have not appreciably changed over the past decade, sodium content of meals has increased significantly [14, 64, 112]. Making decisions for healthful eating is difficult in restaurant environments that do not provide point-of-purchase nutritional information and promote energy-dense foods and large portion sizes [115, 78].

Zoning and business permitting or licensure requirements are additional ways cities may impact the nutrition environment, although it is less studied in the public health literature [11]. These policies have traditionally fallen under the purview of urban planning, and use of these strategies to achieve public health objectives is emerging [117, 11]. Cities have begun exploring ways to facilitate a healthy nutrition environment by limiting the number of fast-food restaurants, increasing healthy foods sold within corner stores, and support and space for farmer's markets and community gardens through amending zoning, permitting, and licensure requirements [117, 11]. Impacts of food access within neighborhoods on dietary intake of residents are discussed in further detail in subsequent sections (i.e., "Community Nutrition Environment" and "Consumer Nutrition Environment").

Intervention Results

In 2009, changes, including the offering of additional fresh fruits and vegetables, whole grains, brown rice, soy products, and 2 % milk (instead of whole milk), were made to the SNAP food package to facilitate the meeting of 2005 USDA dietary guidelines among SNAP participants [65]. As a result of this policy change, availability of certified foods increased among samples of supermarket, grocery, corner, and convenience stores [134, 65, 63, 10, 12]. While studies have found that purchasing of whole grains and brown rice increased among SNAP participants after the SNAP benefit change [9, 131, 101], one study found that increased purchasing of whole grains by SNAP participants was not significantly correlated with the actual intake [101]. Additional evaluation of the changes to the SNAP allotment and individual purchasing and consumption of certified foods among SNAP participants is needed. Continued evaluation of the adequacy of the SNAP allotment over time will be informative.

Excluding or limiting sugar-sweetened beverages or providing subsidies for healthy food purchases within SNAP has also been proposed to encourage healthy eating among low-income populations. More studies among SNAP participants across the country are needed to test these relationships among "real" people as well as explore the roles of environmental variables which may differ regionally and locally. Further evaluation of changes to agriculture-led food policies in the USA is needed [37]. Two earlier reviews of menu labeling intervention findings have noted a lack of consistent associations between menu labeling and foods purchased or [118, 61]. However, given the recent federal mandate for menu labeling as a part of the Affordable Care Act in 2010, continued review of this literature is needed as more evidence is published. Ten additional studies have been published since the last published review in 2011 [59, 133, 96, 38, 76, 94, 25, 120, 124]. Again, findings are mixed, although differences could be explained by the study design employed (i.e., experimental versus quasi-experimental). Findings from two studies employing a stronger experimental design were more positive [59, 94]. Typical "treatment" groups included (1) menu label including caloric information only, (2) menu label including a picture cue such as a traffic light in addition to caloric

information, and (3) no menu label. Studies also used a quasi-experimental design (i.e., a natural experiment) to evaluate either pre- and post-consumption patterns [96, 38, 76, 120, 124] or changes to restaurant foods offered [133, 96, 25] in response to enacted menu labeling policies.

Overall, findings from these studies do not provide evidence supporting menu labeling as an effective strategy to change purchasing patterns [38]. Analysis by subgroups does provide additional information. One study found that calories purchased decreased among patrons of coffee shops compared to patrons of restaurants [76], while another study found that calories purchased decreased among those who used the menu label in their food purchasing decision compared to those who saw and did not use or did not see the menu label [124]. Restaurants may be responsive to modifying menus in response to consumer demand for more information. Some studies have found that healthy menu options increased after menu labeling enactment [96, 25], although none noted a difference in the overall menu caloric content [133, 96, 25]. Beyond labeling, implementation of nutritional standards for restaurants has also been proposed [35].

Simulation studies on the price elasticity of soda have demonstrated minimal impact on weight-related outcomes [104]. A study using a quasi-experiment design to model changes in taxes on soda within states in relation to population levels of body mass index and obesity over time found evidence of a small positive effect [44] but no data on inflammation or other biological changes. No studies were found that evaluated the effect of a "fat tax" on outcomes within the USA, although evaluation of this strategy has begun in Europe [97] and Great Britain [85]. More studies that evaluate the impact of implemented taxes on actual dietary intake are needed.

Evaluation of interventions employing more local public policy including zoning, permitting, and licensure on obesity-related or dietary outcomes is needed. South Los Angeles implemented a ban on incoming fast-food outlets, which did not appear to change obesity rates at the census tract level [117], but associations with dietary outcomes have yet to be assessed. Also, the Pennsylvania Fresh Food Financing Initiative is a flagship statewide financing program to increase supermarket development in underserved areas [48] which has yet to be evaluated with respect to dietary outcomes. Similar policy development in other regions and cities is emerging [122, 67], and evaluation of these programs will be informative.

Implementation Issues

Acceptability of changes to the SNAP benefit allotment appears high among participants with some notable exceptions [17]. The substitution of whole milk with 2 % milk was not endorsed by Hispanic women, and soy products were not endorsed by the majority of participants [17]. Targeted provision of health information may increase the acceptability of these foods among select populations. Process information is also needed to ensure that changes to the SNAP benefit allotment maximize dimensions of healthy food access and translate to the actual

intake. Interestingly, in a cost-effectiveness simulation study on SNAP nutritional changes and chronic disease outcomes, it was noted that banning foods from SNAP allotments may be less desirable as SNAP participants could opt to purchase these items with disposable income, resulting in increased food insecurity; subsidizing healthy foods was found not to affect food security [13]. Instituting a subsidy for healthy foods, therefore, has become a more popular recommendation for revamping SNAP allotments [106], although studies with respect to dietary outcomes are needed. Evaluations of the 2009 change in foods subsidized by SNAP also appear to support this conclusion.

The differences in association between menu labeling and purchasing by subgroup may provide additional process information for this research. Specifically, this strategy as implemented appears to be more effective for more individuals who are more educated or familiar with nutrition labeling in general [111]. Process information in minority and low-income samples indicates, however, that menu labeling implementation can have high fidelity in these communities [80] and that caloric information is salient to purchasing decisions [98]. This nutritional information, however, does not necessarily translate to decreases in consumption [39] which may be related to how and what nutrition information is provided. For example, difficulties in calculating calories per serving arise when ranges of calories are presented for a menu item that comes in multiple flavors or when calories are presented for a menu item that contains multiple servings [35].

The soda tax has not been effective in altering weight-related outcomes, and this may be because the amount of the tax has been too small [34, 104]. Based on price elasticity data, a tax which raises the price of soda by an estimated 10–20 % is needed to significantly impact consumption [104, 34, 8]. Simulation studies and the quasi-experimental study using the 4 % average state soda tax found small effects on obesity [104, 44] which may also provide evidence to raise soda taxes. Barriers to a more rigorous implementation of soda taxes include opposition from the beverage industry as well as established state sales tax exemptions for food and beverages [34, 104]. An excise tax (i.e., a tax on the manufacturer) may be more attractive to manufacturers than a sales tax and is administratively easier for governing bodies to implement and enforce [103]. An excise tax may also be more effective in altering consumer purchasing as it would raise the shelf price of the product which may be a more salient point for purchasing decisions as opposed to during checkout [103, 34]. However, consumers do not appear to support implementation of soda taxes overall, although greater support has been demonstrated among groups of younger age and higher socioeconomic status [108].

Future Directions

Studies are needed to evaluate how changes in the SNAP benefit allotment affect purchasing or dietary intake of participants across the country. Identifying additional strategies to enhance menu-labeling practices is needed as nutrition

information alone has not been found to change dietary behavior overall [91, 95]. This may be partly attributed to a lack of understanding of portion sizes, especially in venues outside of the home [43]. Larger portion sizes have been associated with eating meals away from home as well as obesity [40]. In concert with providing more healthy options and nutrition information, limiting portion sizes within restaurants may also be a useful strategy to promote healthy food environments. Further evaluation of menu labeling at the population level is also warranted given the federal enactment of this strategy as a part of the Affordable Care Act [102, 109, 133]. Finally, the need to raise soda taxes may be suggested given that currently enacted tax levels among 28 selected states were not found to be sufficient to impact population-level dietary behaviors or weight-related outcomes.

Organizational Nutritional Environment

Description

This environment is a fertile one for intervention, since strategies can make use of existing structures and of the policies and programs that can be offered within them to influence healthy eating and activity. Also, inflammatory markers could be measured with relative ease in an organizational setting. Therefore, these organizations have great potential for inflammation-related policy. Structures discussed here are workplaces, health care systems, and religious organizations.

Supporting Evidence

Worksites provide access to almost three-quarters of the adult population [24], which makes them ideal settings to implement strategies for changing eating behaviors. A variety of foods and many meals are available and eaten at workplaces, making access to healthy foods at work important, but observational studies of workplace nutrition environments in relation to healthy eating behaviors appear not to have been conducted. Workplaces serve both as existing channels of communication and as social support networks, both important to adult behavior changes from a theoretical perspective. Finally, many opportunities exist in workplaces for environmental and policy change to foster healthy dietary practices. The costs of unhealthy eating are born by employers as well as employees, providing motivation for both groups to push for change [27].

Intervention Results

In contrast to the lack of observational studies of workplaces, intervention studies are plentiful. Workplaces are perhaps one of the most studied of the organizational

areas of intervention. There have been Cochrane reviews and other systematic reviews of workplace interventions to improve eating behaviors in adult populations [129]. The Community Guide to Preventive Services Task Force recommends multicomponent interventions that include nutrition and physical activity (including strategies such as providing nutrition education or dietary prescription, physical activity prescription or group activity, and behavioral skill development and training) to control overweight and obesity among adults in worksite settings [5]. In addition, Cochrane reviews [129] found consistent changes as a result of workplace interventions, although most of the focus of workplace interventions has been on physical activity as an outcome. Many workplace interventions in workplaces have included multiple components (materials, classes, access changes in food supplies, and changes in social norms) and have also focused on physical activity to reduce obesity, making it difficult to specify which components are more prominent [5]. Incentive programs at workplaces, providing rewards for healthy eating, physical activity, and/or weight loss, have shown to be of generally positive benefit, although these were not typically used in conjunction with more programmatic or policy interventions.

Health clinics and hospitals are special cases of workplaces, but any policy changes have the potential to reach beyond employees to the patients whom they serve. They have been the subject of multiple intervention projects and reviews. Other organizations, such as public housing developments, look promising [15, 16].

Religious organizations have been used as a setting for policy and programmatic change, both multidenominational settings [21] and primarily Black churches [4] and Hispanic churches. In general these studies have found that a multicomponent intervention that includes policy change, promotional materials, religious organizational involvement, and community health workers has resulted in improvements in eating behaviors. The sustainability and reach of these interventions were tested in follow-up studies, with positive outcomes in organizational changes, indicating high potential for dissemination to occur [3, 60].

Implementation Issues

The field of organizational nutrition environment change is mature enough that there are multiple efficacy studies that target organizations for change and there is a growing literature on dissemination of these types of interventions to change population health. A recent task force on worksite health promotion intervention discussed issues of dissemination and implementation research and recommended several strategies [113]. Issues discussed in this review include the mechanisms by which workplace interventions work, the diversity of workplaces and the individual and unique responses to intervention, and the contributions of individual and environmental multicomponent interventions to changes in workplace behaviors [114]. We are learning about the extent of reach and sustainability of these long-term studies that attempt to put into place policy and programs in organizations that

are expected to lead to health promotion changes, such as reductions in obesity, in very large numbers of working adults.

Future Directions

One understudied direction is in research to change opportunity for healthy eating in places that encourage or engage people in inflammation-reducing activities, like healthy eating or activity. Organizations have a remarkable ability to control the offerings that occur in their presence, as exemplified by the use of tobacco sales policies in workplaces and other organizations. A similar set of strategies could be enacted for food or activity availability, increasing the access that individuals have to healthy options. Indeed, policy that improves the availability of healthy foods in workplaces and other organizations and structures seem like a key element of future interventions.

Another area that is also understudied in the literature is the use of multiple strategies or combinations of strategies in multiple channels and organizations. This means that dissemination of policies and programs that have changed small groups now needs to happen at the larger population level. For example, organizational statewide policies that encourage healthy eating need to be evaluated and tested. Again, using tobacco control as a model might provide a blueprint for action in this setting.

The new technologies used in our future national health care system might be an area of focus for healthy eating. This is an area of innovation, as our changing health care system and inclusion of more patient-centered care might open doors for the testing of new interventions that rely on following participants with screening and assistance no matter where they receive care and no matter what care they receive. Engaging these technologies in support of healthy eating might be a novel approach with potential for high yield.

Resolving the gulf between health promotion and worker health and safety might be another area of consideration. There have been a few projects, notably those of Sorenson and Barbeau [113], that have integrated these two areas of workplace health activity, and this might be a promising area for future focus.

Community Nutrition Environment (Neighborhood Level)

Description

The community environment domain has been defined as the distribution of neighborhood outlets including supercenters, supermarkets, grocery stores, convenience stores, and restaurants (both full and quick service), gyms, sports facilities, and activity opportunities [53, 54, 115, 80]. Two methods have mainly been used to quantify the community environment. The most highly used approach involves

enumerating the number of food outlets within a specified area such as a census tract or a predefined circular buffer using geographic information systems (GIS), while a second approach involves on-the-ground audits of stores in a neighborhood [30, 110, 86]. Most studies enumerate food sources around the home, but more studies are now assessing food sources in reference to other places such as workplaces and schools. Typically, studies have used GIS technology to quantify density and proximity measures of walkability or food outlets within defined geographical units [30, 88]. Linking extant geospatial data to individual-level observational data is attractive to many investigators as this approach is less time and resource intensive than field enumeration of neighborhood outlets.

Supporting Evidence

Reviews of studies of the community environment have noted moderate-to-mixed findings with respect to many dietary outcomes with fruit and vegetable intake being the most studied. Again, this discrepancy is likely attributable to a lack of standardization in measures, especially those derived from GIS methods, used to quantify the environment. Evaluation of studies by assessment method found that findings were the least consistent if derived from GIS methods, while findings using store audits of the community nutrition environment were only slightly more consistent [30]. For example, several studies have found that people who lived closer to supermarkets have higher diet quality whereas people who lived closer to fast food or convenience stores have poorer diet quality [30, 78] or other measure of dietary behavior [30]. That this relationship holds independent of socioeconomic status may be important [82, 89, 92]. On the other hand, not all studies have confirmed these relationships [83, 130, 132]. In one study in California, neighborhood density of fast food, but not grocery, outlets was related to dietary intake among a large sample of adults [62]. In a large national study, no relation was found between fast food outlets in neighborhoods and fast food consumption among young adults [107].

Inconsistent findings could be due to differences in variables used to operationalize the environment either due to a lack of "ground truthing" or validity testing of GIS variables within studies or differences in data sources and units of measure used across studies [20, 30, 26]. Lack of consistency among findings could also arise from variation in area sizes used to define the boundaries of the nutrition environment or specific characteristics of the populations under study [30]. In fact, a study among a diverse group of young adults suggested that commonly used GIS boundary sizes in many studies were too small and did not sufficiently represent the food environment for this group [79]. That is, respondents may also access outlets beyond study-defined boundaries of the neighborhood environment [32]. In addition, evaluation of the community food environment (number or proximity of stores in an area) without *concurrently* accounting for what happens within the food store may contribute to some level of misclassification, possibly biasing toward the null, as many supermarkets also contain unhealthy options [125]. Other accessibility

dimensions are likely necessary, yet are only just beginning to be incorporated in GIS-based studies [70].

Intervention Results

Several intervention studies have undertaken environmental strategies to increase the number of food outlets offering fresh produce in neighborhoods [33, 46, 93]. Successful interventions include introduction of additional farmer's market days and of community gardens [105, 42, 46, 87]. The Veggie Project was a multicomponent intervention which brought farmer's markets to four Boys' and Girls' Club sites situated within low-income, minority, urban communities in Nashville, Tennessee [46]. The intervention included a discount voucher program to offset the cost of healthy foods for participating families and was associated with a significant increase in purchase of fruits and vegetables, as evaluated by a before–after quasi-experimental design [46].

Three separate ongoing community-level obesity prevention initiatives to change the community environment in California used community-based participatory approaches to identify ways of providing additional healthy outlets into the neighborhood [33]. Selected strategies varied by community and examples included establishing an organic farmer's market, delivering boxes of fruits and vegetables to low-income neighborhood residents, setting up a low-cost fruit and vegetable stand at an elementary school, and transforming a convenience store into a produce outlet [33]. These efforts also proposed to incorporate national low-income voucher programs (e.g., Women, Infants, and Children) to address the economic barriers of people in those communities [33]. Evaluation of these efforts has yet to be completed.

Implementation Issues

Due to the novelty of this intervention research, the main barrier to the implementation of environmental and policy interventions by public health practitioners is a lack of evidence-based model strategies and demonstrated protocols about how to create change in communities [47]. The structural changes to the neighborhood required to implement these environmental approaches can be difficult to achieve in the short term, let alone ensure sustainability, within the timing of grant funding cycles [47]. Other barriers to success include failure to identify intervention partners with all of the expertise needed—interventions may engage community stakeholders who have limited experience with advocating for or implementing structural- or policy-level changes [47]. For example, Morland found an overall lack of business expertise among key personnel [93] when creating a community-based cooperative (co-op) market. Nonetheless, reviewing this type of formative research may be invaluable for the planning and execution of similar strategies. Changelab Solutions (formerly Public Health Law & Policy) provides an online

collection of reports which address these issues, although evaluation of these recommendations is needed (http://changelabsolutions.org/. Accessed October 10, 2013). Lessons learned from smoking cessation policy and business change implementation over the last decade may also prove informative, given the possible consideration of unhealthy eating choices as an addictive behavior [75].

Future Directions

Interventions within more rigorous study designs that include a nonintervention control group and that target the community nutrition environment still need to be implemented and evaluated. To more directly attribute behavior change to the structural changes effected, designs should be set up to allow parsing out these effects from other individual-level intervention elements. Using a randomized controlled design, comparison of multiple arms (e.g., environmental change alone, environmental change plus other intervention elements, and control) would be ideal to ascertain whether modifications to the nutrition environment are effective in increasing healthy dietary behaviors. Given that the cost of this study design may not be affordable, another approach could be to estimate the role of the environment as an effect modifier of traditional individual-level intervention approaches on the corresponding outcomes [57]. Evaluation of the impact of environmental strategies on intermediate outcomes such as psychosocial correlates of healthy eating (e.g., social support and self-efficacy) may also provide valuable insights.

Finally, long-term evaluation of any of these strategies is entirely lacking to date, since those studies that are of interventions focused on environmental or policy-level changes to the community environment are still in progress or have only short-term or only behavioral outcomes. Threats to including long-term outcomes include the high mobility of low-income populations. These groups are more likely to be the focus of these interventions but may be difficult to follow for a long term [87].

Consumer Nutrition Environment (Retail Level)

Description

This domain of the nutrition environment includes measures of food availability *within* neighborhood food outlets. Strategies to influence product stocking, pricing, and display are used to affect what is available and promoted to the consumer within a store or a restaurant. Policies to change these are needed as well as evaluation of these policies and evaluation of the link between the policies and inflammation.

Supporting Evidence

The number of studies exploring the consumer environment continues to increase, especially among urban populations [55]. These studies have typically used some version of a store audit and have found more consistent relationships with behaviors than measures of the environment at the community level [30, 55, 88]. Caspi and colleagues noted that 8 of 15 studies using store audit methods found at least one positive association between various measures of neighborhood healthy food access and dietary behavior [30]. In general, greater availability of healthy food/fruit and vegetables in the neighborhood may be associated with higher diet quality/fruit and vegetable consumption among urban neighborhood residents [55]. For example, living near a store that stocked at least five varieties of dark-green or orange vegetables was associated with higher fruit and vegetable consumption [69] while greater store shelf space devoted to fruits and vegetables was associated with greater increases in fruit and vegetable consumption at 1-year follow-up [28]. Lower availability of healthy foods within the nearest store has also been associated with lower diet quality [45]. These findings, however, were not replicated in a study in rural communities in North Carolina [57].

In addition to potentially increased study power by characterizing healthy foods available in the neighborhood environment, additional domains of availability including affordability can also be more elaborately assessed. The pricing of foods offered within stores may also play a significant role in consumer demand [8, 104], yet findings vary by methods used to measure price [41]. Contrary to price elasticity studies, reviewed studies measuring food price via store audit methods in relation to dietary behavior or studies of price changes on purchasing behavior have been null [30] or mixed [41].

Intervention Results

Some intervention studies have been designed to test whether modifying components of the consumer nutrition environment (e.g., availability, price, and acceptability of healthy food) within the retail environment of existing food outlets is associated with increasing healthy dietary choices. Consumer-level strategies share a common goal of increasing the accessibility of healthy food in neighborhood stores and may work through influencing the behaviors of store retailers as well as of consumers.

Targeting store retailers is important as they decide what products to stock, how to display them, and how much variety to offer [51]. Strategies to change retailer food stocking and display practices include offering incentives to provide more healthy foods and produce [33, 50, 102], improving mechanisms and offering incentives for purchasing food from local farms [102], monitoring or purchasing refrigeration units for the storage of perishable produce items [50], placement of healthy foods within the store [1, 33, 50, 51], as well as point-of-purchase

promotion of healthy foods and produce [1, 50]. Implementation of these strategies may also require operation within higher policy-level domains.

Similar approaches to increase the availability of healthy foods have also been used within restaurant settings including nutrition training for chefs on how to prepare dishes lower in fat, changing catering policies to require healthy food choices, and point-of-purchase promotion and information such as table tents and menu-labeling policies [52, 76]. Some success has been demonstrated for interventions among small grocery retailers using a combination of product placement and promotion strategies with reported small increases in sales of fruits and vegetables among specific customers [1, 50].

Other environmental level strategies focus on making healthy foods attractive to consumers in store environments. The most popular strategy evidenced in the literature was the implementation of price discounts for healthy food [46, 50, 99, 116, 127], while a few studies also attempted in-store sampling and cooking demonstrations of healthy food items [1, 50]. Although there currently is no evaluation data available for in-store taste demonstration strategies, the use of price discounts has been consistently associated with changing food purchasing in several studies [46, 99, 116, 127]. Larger increases in sales of fruits and vegetables were demonstrated among participants given price discounts within the previously described Veggie Project [46]. A similar increase in healthy food sales was noted at 6 and 12 months post-intervention among those assigned to receiving price discounts in randomized controlled trials [18, 99, 128]. A combination of discount plus nutrition education strategies resulted in an even greater increase in fruit and vegetable purchases, and the number of participants who consumed recommended amounts of fruits and vegetables increased from 42 % at baseline to over 61 % for both discount groups [127]. In an observation study in South Africa, participation in healthy food discount programs was associated with reported consumption of more fruits and vegetables and wholegrain foods as well as decreased consumption of "fast" and fried foods and foods high in sugar or salt [6]. These findings were replicated using grocery receipt scanner data to measure food purchasing [116].

Implementation Issues

Fidelity of intervention strategies targeting small store owners may be a concern that could limit the potential impact to customer food choice via these approaches [1]. Reviews of small store interventions have noted differences in intervention fidelity [50, 1], although these differences could be due to location of small stores studied (i.e., the US versus the UK implementation). Although most small store owners in the UK were supportive of intervention goals to improve health among members of the neighborhood, the inability to compete with larger supermarket pricing of fruits and vegetables was a common barrier to maintaining produce availability [1]. Similar to community-level strategies used in the USA, a lack of business expertise and clear definition of roles and responsibilities was also cited as a significant barrier by store owners for implementing healthy food stocking

strategies [1]. Barriers to stocking healthy foods identified by the US small store retailers included a lack of consumer demand, refrigerator or freezer space, and profitability [12] in addition to neighborhood crime [77].

With respect to pricing interventions, the effects of these programs have been demonstrated in mostly white populations, but effects may vary by ethnic group [18]. In a randomized controlled trial in New Zealand, for example, increases in healthy food purchasing tied to the price discount intervention were seen in European and Asian, but not Maori, groups [18]. Selection or cultural adaptation of strategies to address group food preferences may be warranted.

Future Directions

Continued study is needed to determine whether increased availability of healthy foods in retail stores impacts shopping and dietary behaviors of neighborhood customers [51]. Facilitating low-pricing or promoting alternative strategies for small store owners as well as recruiting intervention workers who have both health promotion and retail experience may be helpful. Evaluation of programs using retailer incentives to promote healthy food availability may provide evidence of a solution to address pricing barriers faced by small stores. Exploration of the impact of placement and promotion of healthy foods is also needed as well as further development of tools to assess these components [51]. These may be more attractive alternative strategies for small store owners who are not able to provide discounted pricing on healthy foods. In addition, interventions evaluating price discounting among at-risk groups may be warranted given the noted differences in response in groups differing by indicators of socioeconomic status [18] and to ensure that efforts do not contribute to greater disparities in healthy dietary behaviors. Ensuring that price discounts include culturally appropriate foods is a must.

Conclusions and Future Directions

We have identified recent evidence concerning effective strategies for changing the environment through policy to reduce inflammation. These include instituting a tax on sodas, using worksite environments to support healthful changes in the obesogenic environment, increasing the numbers of farmers' market days, and discount pricing of healthy foods within stores, but we found the results not always to be consistent. Research into the efficacy and effectiveness of intervention modalities incorporating environmental strategies is falling behind associational research. To drive these efforts forward, successful models and demonstrated protocols for community-level change are needed. Incorporation of a nonintervention control group in study designs is ideal for assessing effects directly attributable to changes in the environment. Yet, not everything can be evaluated in the context of a randomized controlled trial. Taking advantage of natural experiments may be one

key way to evaluate environmental strategies and be efficient in the use of resources for research. Evaluations of community environment as an effect modifier of other interventions on obesity risk may hold promise. For example, considering the home or the workplace environment when delivering an individually based intervention might help explain findings that vary by a higher group level or might identify future research opportunities.

More studies incorporating both objective and perceived measures of the environment are also needed to further understand relationships with behaviors. Also desperately needed is the use of inflammatory markers as outcomes, alongside obesity and behaviors. Policy changes are clearly needed and so is evaluation of such policies. Given the lack of success demonstrated by informational strategies alone (e.g., menu labeling), perhaps we should take advantage of lessons learned from smoking cessation policy to invoke desired behavioral change. There is now a rigorously conducted set of studies that supports the use of tobacco control policies of many types implemented concurrently to help smokers quit and to prevent youngsters from beginning to smoke. Using this evidence and applying it to eating behavior change may yield novel and more effective approaches to using the information and policy environment to effect dietary behavior change. For example, behavioral change as a result of currently enacted soda taxes has not been demonstrated. Increasing the tax further, as was done for tobacco products, for sugar-sweetened beverages may be called for. To be commensurate with taxes placed on cigarettes, for example, soda tax would need to be an added 58 % which would translate to a population-level shift in BMI of 0.6 kg/m^2.

Policy and evaluation of policy to control marketing and promotion of sales of food and activity opportunity is a key element of the promotion of healthy behaviors. Given the outlay of money for advertising, these efficacious messaging systems do change people's behaviors and need to be considered and curtailed to reduce future increases in inflammation. These types of policies are underevaluated and often misunderstood, as in the case of the recent law to limit sales of large soda containers in New York City [135]. This law is currently under review by a higher court, but this attempt to limit soda manufacturers from selling oversized soda containers in New York City brought on a campaign by the beverage distributors to label the law as anti-freedom and misguided in its attempts to control soda sales [95]. Evaluating the effects of these types of policies on both individual behavior and on the behaviors of food companies will be enlightening.

Counteradvertising such as is being done with tobacco might be an additional answer. Counteradvertising to provide truthful messages to the public about tobacco products has been shown to be efficacious in changing individual smoking behavior. How it will affect healthy behaviors is currently unknown. In addition, how to engage counteradvertising without increasing stigma for overweight people is also unknown and should be the focus of research.

A larger focus on the use of multiple organizational units (worksites, hospitals, schools, communities) within natural policy units such as cities, counties, or states is a promising direction. The use of theory to guide these interventions is often quite poor, and the role of theory in this area of research is not well established. Some

interventions might be more powerful or more reaching and sustainable with the use of theory. This area needs research attention.

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Chapter 12
Cancer Prevention Through Policy Interventions That Alter Childhood Disparities in Energy Balance

Debra Haire-Joshu

Abstract Dramatic increases in obesity and cancer risk are more pronounced across various socially disadvantaged populations (Dixon et al., Adv Nutr 3(1): 73–82, 2012). These disparities have their beginnings in early childhood with devastating effects that track into adulthood. The purpose of this chapter is to describe the (1) prevalence of obesity disparities in youth, (2) social determinants and dimensions of obesity disparities, (3) influences on stages of obesity development, and (4) role and types of policies designed to prevent obesity disparities in young children. The need to behaviorally disrupt the intergenerational cycle of obesity that begins in early life is discussed. How socioeconomic, sociocultural, living and working conditions, and life course exposures influence this cycle is addressed. The role of evidence-based policies, and their impact across target environments where children spend time, is presented.

Keywords Obesity prevention • Early childhood • Social determinants • Target environments • Evidence-based policy

Introduction

Almost 69 % of adults and 32 % of children are overweight and obese, the result of energy imbalance between calorie intake and expenditure [1, 2]. Obesity is associated with increased risk of several cancer types including colon, breast, endometrium, liver, kidney, esophagus, gastric, pancreatic, gallbladder, and leukemia and can lead to poorer treatment and increased cancer-related mortality [3–5]. In 2007 about 34,000 new cases of cancer in men (4 %) and 50,500 in women (7 %) were due to obesity [6]. Cancer attributed to obesity was as high as 40 % for

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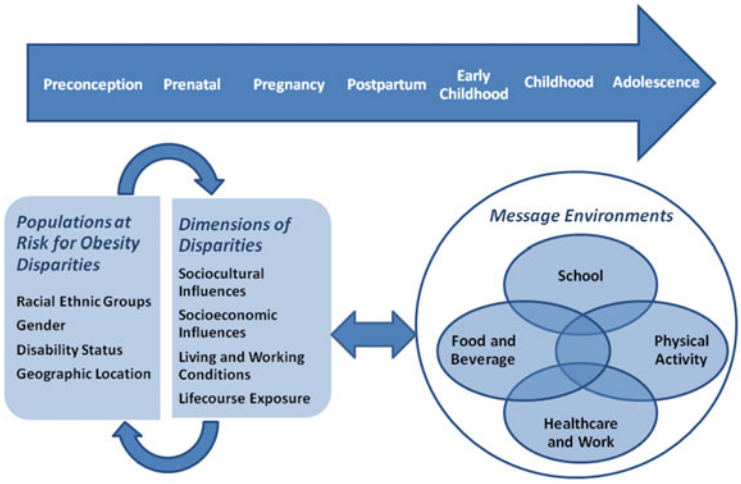

Fig. 12.1 An organizational model for addressing disparities and policy interventions to prevent obesity. Adopted from Institute of Medicine. *Evaluating Obesity Prevention Efforts: A Plan for Measuring Progress*. Washington, DC: The National Academies Press, 2013

endometrial cancer and esophageal adenocarcinoma [6]. The link between obesity and cancer underscores the importance of maintaining a healthy body weight throughout life as one of the most important ways to protect against cancer. This is in addition to other sequelae associated with obesity including metabolic syndrome, diabetes, cardiovascular disease, hypertension, and other chronic diseases [7].

Dramatic increases in obesity and cancer risk have been more pronounced across various racial ethnic groups and socially disadvantaged populations [8]. These disparities have their beginnings in early childhood with devastating effects that track into adulthood. Additionally, the onset of the obesity epidemic in the 1980s has yielded a generation of adult mothers who now parent at-risk children [9].

Eating and physical activity behaviors, learned and reinforced by parents and families, directly impact energy balance [10, 11]. However, social determinants influence the quality of the environments that impact these same behaviors [12, 13]. Exposure to environments of negative quality can impact the onset of obesity at the earliest stages of life. Methods for addressing and halting the intergenerational obesity epidemic are needed to prevent an epidemic of cancer manifested among our youth, further contributing to health disparities. Policy interventions promote opportunities supporting children in attaining healthy behaviors across the multiple environments where they spend time [14–16]. Evidence-based policies help to assure the health quality of those environments.

The purpose of this chapter is to further describe (1) the prevalence of obesity disparities in youth, (2) social determinants and dimensions of obesity disparities, (3) the influences on stages of obesity development, and (4) the role and types of policies designed to prevent obesity disparities in young children. Figure 12.1 present an organizing model for the chapter, which promotes the understanding

of how populations at risk are impacted by dimensions of disparities and how evidence-based policies can reduce disparities by promoting the quality of target environments across key stages of obesity development.

Obesity Disparities in Youth

Cancer disparities associated with obesity in adulthood have their beginnings in early childhood. Approximately 17 % (or 12.5 million) of children and adolescents aged 2–19 years are obese [2]. One-third of babies are overweight or obese by age 9 months [1]. Rapid weight gain contributes to 34 % of overweight or obese children by age 2 years [17]. By age 5, 21 % of children are overweight or obese, a number that has doubled in the past 30 years [18]. Older children and adolescents had higher obesity prevalence than preschool children [19]. In addition to the prevalence of obesity, the type of obesity has shifted. Specifically, youth are becoming more centrally obese as defined by higher waist circumference in contrast to body mass index (BMI) with several minority groups exhibiting increases in overall fat in contrast to white counterparts [20].

Obesity disparities are pronounced across various racial ethnic groups including African Americans, Hispanics, American Indian and Alaskan Natives, Asian Americans, Hawaiian, and Pacific Islanders [21, 22]. Wang [19] analyzed national survey data concluding that American Indians had the highest obesity prevalence while blacks and Mexican Americans had rates higher than those in whites and Asians. Numerous studies support these conclusions noting Hispanic (21 %) and non-Hispanic black (24 %) youth have higher rates of obesity than non-Hispanic white youth (14 %) [23]. Obesity is most prevalent in children aged 2–4 years who are American Indian or Alaska Natives (21.1 %) and Hispanic (17.6 %); Hawaiian–Pacific Islanders (Samoan children) report 17.5–27 % prevalence among 1–4-year-olds [24]. The early onset and cumulative effects of obesity increase the risk for cancer and poor health outcomes that track into adulthood with Native Hawaiians/Pacific Islanders 70 % more likely to be obese than non-Hispanic whites [23, 25] and non-Hispanic adult blacks with the highest age-adjusted rates of obesity (49.5 %) compared with Mexican Americans (40.4 %), all Hispanics (39.1 %), AI/AN (39.9 %), and whites (34.3 %) [23, 25].

Gender disparities are also evident at a young age. Among boys, Mexican Americans report the highest combined prevalence (40.5 % vs. 34.5 % in whites and 32.1 % in blacks) [19]. In girls, blacks have the highest prevalence (44.5 % vs. 31.7 % in whites and 37.1 % in Mexican Americans). In all age groups, between 1988–1994 and 2007–2008, the estimated average annual increase in obesity was ~0.6 percentage points. Among children, boys had a faster increase in obesity than girls (0.7 vs. 0.5 percentage points), although the increases were similar in adolescents (~0.5 %) [19]. These obesity disparities place children from high-risk racial ethnic groups at greater risk chronic diseases including cancer [9].

Disparities not only are present by racial ethnic groups but also exist among children with disabilities. For example, adolescents with autism and Down syndrome

were two to three times more likely to be obese than adolescents in the general population; obesity among adolescents with physical and cognitive disabilities (17.5 %) is significantly higher than among adolescents without disabilities (13.0 %) [26, 27].

Finally, obesity also varies by urban versus rural geographic location. YRBSS data have shown considerable disparities in obesity rates across the covered states and cities in the USA [28]; nine of the ten states with the highest rates of obese children are in the South with evidence that rural children are more likely than urban children to be obese [29, 30]. More than one-third of children in both large (34.6 %) and small rural areas (35.2 %) had a BMI at or above the 85th percentile for their age and sex, compared to 30.9 % of urban children, a finding further enhanced by children living in poverty [31]. In 2007, across the 39 included states, obesity prevalence ranged from 8.7 to 17.9 % and was 20.4 to 35.8 % for the combined prevalence [32]. Utah (8.7 %) had the lowest and Mississippi (17.9 %) had the highest obesity prevalence [19]. In children aged 6–9 years, the combined prevalence was higher in urban areas (26.1 % vs. 22.8 %), but in adolescents, it was slightly higher in rural areas (27.2 % vs. 24.4 %) [19].

The prevalence of obesity among disadvantaged youth, and resulting health risks for cancer and related chronic diseases, identifies the critical need to better define and understand factors that influence or cause these disparities.

Dimension of Disparities and Childhood Obesity

Health disparities have been defined by Braveman et al. [33, 34] as a "difference in health that can be shaped by policies, in which disadvantaged social groups systematically experience worse health or more health risks than do more advantaged social groups." Determinants of disparities in obesity are complex driven by interacting factors across multiple levels of influence. These "upstream" determinants have been defined by socioeconomic, sociocultural, living conditions, and life course influences that, in turn, impact "downstream" outcomes defined by individual behavior among populations at risk for obesity disparities.

The health behavior of a child cannot be divorced from *socioeconomic influences* that impact healthy choices (e.g., wealth vs. poverty, food security, quality of education) [35, 36]. Several studies show that education or occupation, as indicators of economic resources and social class, can influence the risk for obesity [37–39]. In 2008, over 14 million children less than 18 years of age lived in families with incomes at or below the federal poverty level while almost 30 million children lived in low-income families [40–43]. Children less than 6 years of age accounted for 44 % of those living in low-income families. African American, Hispanic, or American Indians were twice as likely as other racial-ethnic groups to be living in economic deprivation [9, 44]. Children living in poverty are at higher risk for obesity and its negative health outcomes including cancer, diabetes, and early cardiovascular disease [12, 45, 46]. For example, poverty impacts food security, a

driver of obesity and cancer risk [47]. Food security exists when people have physical, social, and economic access to sufficient and nutritious food that meets their dietary needs [48]; food insecurity describes an environment which lacks access to sufficient quality and quantity of foods with periods of hunger common [49–53]. In 2008, nearly 23 % of children (16.7 million) lived in food-insecure households defined by interrupted food intake.

Sociocultural influences, such as racism and discrimination, are associated with poorer living conditions due to residential segregation and chronic stress related to racial/ethnic bias [37, 54, 55]. Children exposed to discrimination and limited educational or occupational benefits are at risk for the development of early obesity [56, 57]. Discrimination contributes to poor *living and working conditions* described by the quality of the physical or the built environment including housing conditions, access to healthy food outlets, and street connectivity or density [13, 35, 58, 59]. Appropriate and stable housing, safe living conditions, and access to healthy food outlets can have a direct impact on physical activity and eating behaviors associated with the prevention and control of childhood obesity [60]. Poor-quality living conditions limit access to other services that impact young children. For example, children of the working poor are at high risk for poor-quality childcare services further exacerbating the lack of quality nutrition during the early years [61–63]. Approximately 60 % of young children are cared for in out-of-home childcare settings [64, 65]. Lack of ability to pay for quality childcare services places children at risk for obesity due to poorer access to quality nutrition and physical activity [64, 66].

Finally, *life course exposure* to childhood disadvantage has been associated with increased risk of obesity into adulthood; those with the longest exposure to disadvantaged circumstances across the life course are at highest risk for negative health outcomes [67]. The pervasive role of stress associated with disadvantaged environments influences neuroendocrine, inflammatory, or immune outcomes that lead to cancer, diabetes, and heart disease [68]. The cumulative burden of adverse dimensions of disparities significantly impacts the health of minority populations in contrast to short-term exposure [69, 70].

Evidence-Based Policy and Target Environments

Over the past decade, the role of policy as a means of altering upstream factors to positively influence eating and activity behaviors has become central to obesity prevention efforts. Evidence-based policies provide a mechanism for creating an environment that eliminates barriers and provides support for healthy behavioral choices. Policies can be initiated at the local, organizational, state, or federal level. They hold promise as a strategy that will "level the playing field" by assuring that all populations have access to, and are supported by, resources and environments that promote healthy outcomes and reduce cancer risk. Policies can promote health and eliminate disparities associated with economic, cultural, or physical factors.

Table 12.1 Examples of upstream obesity policies by target environment

Environment	Sample policies	Applied examples
Food and beverage	Policies related to agriculture, food availability, and access	Adopt nutrition standards for federal child nutrition programs that are aligned with guidance on optimal nutrition ensure food literacy
		Government agencies should maximize participation in federal nutrition assistance programs and increase access to healthy foods at the community level
Physical activity	Policies related to urban planning, housing and the built environment, land use and transportation, recreational facilities	Increase access to safe places for physical activity, joint use agreements between parks and schools
School–childcare	Policies related to quality childcare, education, and services	Increase the number of states with licensing regulation for physical activity in childcare that require the number of minutes of physical activity per day or by length of time
		Require schools to implement policies to assure that students meet national guidelines for physical activity and nutrition; implement curriculum designed to support healthy lifestyle behaviors
Health Care–worksite	Policies related to businesses and work environments	Promote support for breastfeeding at the workplace
	Policies on health care infrastructure and financing, public health systems, and access to and delivery of care	Institute baby-friendly hospital practices; educate community on importance of prepregnancy weight control and prenatal care
Message	Policies on media, marketing, and information	Implement social marketing campaign to promote consistent messaging of healthy foods and physical activity, reduce marketing of poor-quality foods to children

Modified from Institute of Medicine Reports on Childhood Obesity [71–73]

They can target societal or social factors that can create support for obesity prevention behaviors.

The Institute of Medicine (IOM) identified evidence-based policy as a mechanism for influencing five environments or settings targeted as critical to eliminating childhood obesity depicted previously in Fig. 12.1, with examples of upstream policies provided in Table 12.1 [71]. The food and beverage environment is defined by policies promoting access and availability to healthy, quality foods [74, 75]. Policies targeting the physical activity environment address the distribution of resources that encourage physical activity or active play for children [76, 77]. School and early childcare environments are focused on assuring that the

youngest of our children have access to healthy food and physical activity delivered by qualified caregivers trained in practices designed to prevent the onset of obesity [78]. Health care and work environments are focused on assuring access to quality health care and supportive food and physical activity across environments [70, 71]. Finally, the message environment addresses marketing strategies that promote consumption of healthy food or physical activity [66–68].

Stages of Obesity Development

Limiting exposure to negative influences and stressors is critical to impacting the life course of obesity development and halting the intergenerational obesity and cancer risk. Policies can serve as an upstream intervention with promise to support healthy, individual behaviors of children yielding optimal health outcomes [34, 79]. Policy can impact the development of obesity in children across the life course defined for purposes of this chapter as pregnancy and the intrauterine environment, early childhood (0–5 years), and school-aged youth (6–18 years) [79].

Pregnancy and the intrauterine environment. The earliest risk for the onset of childhood obesity occurs during pregnancy. In the USA, more than one-half of pregnant women are overweight or obese putting them at a greater risk of pregnancy complications [80]. The prevalence of racial-ethnic disparities among women in general is also present among pregnant women [81–83]. The pathways that link the mother's prenatal status to her offspring include metabolic effects of obesity on the intrauterine environment of the child, maternal behaviors that impact gestational weight gain (GWG), and a genetic predisposition transmitted to the child [83, 84]. Maternal obesity before and during pregnancy and excess GWG increase both maternal and neonatal morbidity and mortality [84]. Obesity is associated with adverse pregnancy outcomes including stillbirth, neonatal death, miscarriage, congenital malformations, preeclampsia, gestational diabetes mellitus, preterm birth, macrosomia, and cesarean delivery [15, 85]. It disrupts glucose homeostasis, insulin sensitivity, amino acid synthesis, and fat metabolism, directly increasing the risk for obesity in the child [86–88]. Additionally, there is evidence that the food choices a mother makes during her pregnancy may set the stage for an infant's later acceptance of solid foods, influencing childhood obesity development past pregnancy [89]. The experiences of taste and smell function during fetal life provide a "flavor bridge" that plays a key role in the acquisition of food and flavor preferences of the child [90].

An important step in preventing obesity is to design evidence-based policies that interrupt the pathways contributing to obesity that begin in early life and are prevalent in populations at risk for disparities [72]. Interventions that encourage ideal preconception weight, appropriate GWG, and reduction in postpartum weight retention (PPWR) can interrupt the pathway that links maternal and child obesity. Table 12.2 gives examples of these interventions, introduced next.

Table 12.2 Sample policy and practice recommendations

Sample policy or practice recommendations	Application to practice
Prenatal, pregnancy, and postpartum	
Promote early prenatal, postnatal, and interconceptual care	Health care providers should incorporate most recent IOM/ACOG guidelines in prenatal/interconceptual care
Achieve health gestational weight gain Encourage postpartum return to healthy weight	Health care providers should offer consistent health recommendations regarding breastfeeding and infant nutrition across prenatal and postnatal health care providers
Early childhood (0–5 years)	
Assess, monitor, and track growth from birth to age 5	Health care providers should track growth from birth to 5 using standardized approaches and WHO or CDC growth charts AND assess parent BMI in routine assessment of child risk
Promote the consumption of a variety of nutrition foods and encourage and support breastfeeding during infancy	Implement baby-friendly initiatives in hospitals
Create a healthful eating environment responsive to children's hunger and fullness cues	Encourage employers to implement policies that support breastfeeding mothers after they return to work
	State child care regulatory agencies should require childcare providers to practice responsive feeding in accordance with CACFP guidelines
Increase physical activity and decrease sedentary activity in young children	Childcare regulatory agencies should require childcare providers to provide opportunities for the infant to move freely and explore their environments and for toddlers to engage in physical activity 15 min per hour
Limit young children's screen time and exposure to food and beverage marketing	Childcare settings should limit screen time
	Health care providers should counsel parents to limit screen time
Promote age-appropriate sleep durations among children	Childcare agencies should adopt practices that promote age-appropriate sleep durations for children
	Childcare regulatory agencies should require childcare agencies to environments, behaviors, and practices that promote restful sleep
Childhood to adolescence (6–18 years)	
Require quality physical education and opportunities for physical activity in schools	Increase the numbers of school districts that require elementary schools recess for an appropriate amount of time
Ensure strong nutritional standards for all foods and beverages sold or provided through schools	Increase the availability of fruits and vegetables with foods offered in school
	Assure that meals meet 2012 federal nutrition standards for school meals
Promote food literacy in schools	Schools should require curriculum that meets National Health Education Standards

Modified from Institute of Medicine [71, 91] and Nader et al. [73]

There is a strong link between maternal *preconception weight* and the likelihood that these women will give birth to infants and children who will develop obesity [92]. There appears to be a dose–response association with the magnitude of maternal obesity related to that of her child [93, 94]. Strategies for improving women's preconception health include greater individual responsibility across the life-span, preventive visits and intervening for identified risks, interconception care, prepregnancy checkup, public health programs and strategies, and monitoring improvements [94]. Policies that encourage ideal maternal weight prior to pregnancy are likely to impact the prevalence of early childhood obesity.

Increased *GWG* elevates the risk for excessive weight in the offspring of the mother [91]. Recent studies found a preponderance of evidence to support the association between GWG and childhood weight as a continuous measure and risk of overweight and obesity [86, 87, 95]. In 2009, the IOM published revised GWG guidelines that are based on prepregnancy BMI ranges for underweight, normal-weight, overweight, and obese women recommended by the World Health Organization [95]. Recent studies underscore the importance of dietary therapy, and encouraging an increase in exercise, for controlling GWG among obese women [3, 96–98]. Women who routinely participate in exercise during pregnancy reduce their incidence of gestational diabetes, have less GWG, have less PPWR, and give birth to smaller but normal weight range infants than those who do not exercise [49, 99, 100]. In general these studies identify strategies that promote ideal nutrition and physical activity during pregnancy, coupled with close monitoring of weight, which are protective against excessive GWG [15, 85, 101–103]. These findings suggest the importance of encouraging weight control within the IOM-ACOG guidelines to promote the optimal uterine environment and infant outcomes.

Maternal obesity is associated with *PPWR* that is exacerbated by obesity and multiple pregnancies [95, 104, 105]. PPWR is associated with preconception weight and gestational weight gain [106]. Nehring et al. found that women who gained above the IOM recommendations retained an additional 3.06 kg after 3 years and 4.72 kg on average after $\geq$15 years postpartum [107]. Several provider-based interventions have been designed with a goal to reduce PPWR [108, 109]. For example, the Fit for Pregnancy study included one face-to-face visit; weekly mailed materials that promoted an appropriate weight gain, healthy eating, and exercise; individual graphs of weight gain; and telephone-based feedback. This intervention reduced excessive GWG and prevented PPWR in normal-weight, overweight, and obese women [96]. Policies that encourage provider-based interventions can impact the risk for postpartum weight gain and obesity onset and reduce the risk for cancer and related disease for a long term.

Early Childhood (0–5 Years)

Offspring born to obese mothers have a greater risk of neurodevelopmental delay, atypical neurodevelopment, becoming obese, and other sequelae when compared to those born to healthy, lean women [5]. These offspring are also at risk for the onset of rapid weight gain during infancy that is associated with the onset of early-childhood obesity [17].

Policy interventions hold promise for preventing obesity and related illnesses, such as cancer, in very young children from disadvantaged populations. The IOM targeted several key areas in which policies can support behavioral and practice changes that impact young children [91]. These include growth monitoring, breastfeeding, healthy eating, physical activity, screen time and marketing, and adequate sleep.

Growth monitoring, defined by routine tracking of height and weight from birth to age 5, is needed to assure optimal child growth and development and identify early-onset obesity. Parental perceptions about weight can influence their behaviors in child feeding [110]. Recent studies suggest that parents are unlikely to recognize overweight in their young child [111]. Additionally, overweight mothers tend to underestimate the weight of their child, a finding associated with disparities of less income and education [112]. Continual monitoring of infant and child weight through well child visits affords health care providers the opportunity to encourage appropriate child feeding and activity [91]. This also allows for early intervention at the first sign of excessive weight gain.

Breastfeeding is recommended as the optimal feeding method for the first 6 months of life, followed by the introduction of solids and continued breastfeeding for a minimum of 1 year [113]. Breast milk supports normal growth, has immunological properties that provide some early protection from infection, and may protect against obesity [114, 115]. Breastfeeding may also impact food acceptance and encourage the infant to self-regulate or control energy intake [90, 116]. For example, Mennella and colleagues found that experience with different flavors in breast milk facilitated the infant's acceptance of foods of the adult diet, especially those foods consumed by the mother during lactation [89]. In contrast to bottle-fed infants, breastfeeding encourages infants to self-regulate by adjusting the volume of milk consumed [113, 117–120]. Despite these advantages, disparities in the breastfeeding practices of the US women are quite evident [121]. Breastfeeding initiation rates are markedly lower among black women (60 %) compared with other ethnic groups. Also of concern, Hispanic and black women have the highest rates of formula supplementation of breast-fed infants [121, 122]. The low rates and rapid attrition of breastfeeding by mothers in general, and those from minority groups in particular, suggest a need for strategies to promote the consumption of a variety of nutritious foods and encourage and support breastfeeding during infancy [123, 124]. Policies are needed that adequately prepare a mother to breastfeed through educational initiatives and to encourage adults who care for infants to

support breastfeeding [74, 75]. Examples of policies are provided in Table 12.1 [115, 121, 123, 125] designed to promote breastfeeding.

In addition to support for breastfeeding, strategies also need to create a *healthful eating environment* responsive to children's hunger and fullness cues. The majority of young children in this country are not consuming healthy diets [120]. Parental understanding of the normal growth and development of their child, and the negative sequelae of excessive weight gain, is critical as they promote the food environment of the infant [126, 127]. The feeding practices of parents influence the development of food preference beginning in infancy [90]. Infants respond to differences in energy density early in life, self-regulating their intake to accommodate nutritional needs [128, 129]. Parental feeding practices focused on type, amount, and patterns of child feeding can influence the child's ability to self-regulate energy intake, a finding that has been associated with differences in weight status [130–133]. Parents should be encouraged to practice responsive feeding practices, including age-appropriate foods and portion sizes, provided through daily routines for timing of snacks and meals [90, 132, 133]. Policies are needed to maximize access to healthy foods, critical to eliminating obesity disparities associated with poverty and low-income areas [134–137]. Strategies that maximize participation in federal nutrition assistance programs are one means of increasing access to healthy foods for the youngest children.

Another goal for young children is to *increase physical activity and decrease sedentary activity*. This goal is based on the extensive evidence base suggesting that physical activity benefits older children. Safety concerns often confine the young child to cribs, car seats, and strollers for extended periods of time [91]. Infants and young children need opportunities to engage in unrestricted play to encourage physical activity, prevent excessive weight gain, and maximize the developmental potential of the child [138, 139]. A recent report by the IOM identified policy initiatives to promote physical activity in the very young, primarily focused on educational interventions for parents and caregivers, as well as regulatory guidance to childcare facilities [91]. Recommendations include the provision of opportunities for safe physical activity with guidance suggesting that infants should have access to "tummy time"; toddlers and preschoolers should be active at least 15 min per hour of physical activity [91]. Table 12.2 provides additional examples of recommendations.

Marketing strategies encourage excess consumption of food or discourage physical activity and contribute to obesity disparities in children [140–142]. The use of media to entertain infants, by television and other screen time equipment, has also become common [143]. This suggests that adults and caregivers of the very young should *limit their exposure to screen time and marketing*. There is substantial research to suggest that marketing works to influence food preferences, purchases, and immediate consumption of older children and adults [144–146]. Exposure to TV and advertising is also associated with inactivity and increased snacking and overweight–obesity [143, 147, 148]. Additionally, the American Academy of Pediatrics statement recommending no television viewing for children under 2 years of age is based on concerns that significant brain development that occurs

during the first 18–24 months of life can be impacted by exposure to media [149]. The evidence supports strategies to eliminate screen time exposure of children from birth to age 2 and limit exposure to less than 2 h per day for children aged 3–5 [91]. Health care providers should communicate these guidelines to parents and caregivers.

Finally, it is important to promote age-appropriate *sleep duration* among children [8]. Sleep deprivation and shorter durations of sleep are a risk factor for obesity and related disease [150–154]. Less sleep or irregular sleeping habits are inversely associated with elevated BMI among young children 4 years of age [155]. This association between sleep deprivation and obesity appears to track into adulthood [156]. Insufficient childhood sleep may yield metabolic dysfunction [157–159]. Poor sleep habits might also be associated with environmental distractions such as televisions in the bedroom [117, 160–162]. Support for healthy sleep patterns, without food soothing, is critical.

Childhood to Adolescence (6–18 Years)

Over the past three decades, obesity has more than doubled for adolescents 12–19 years and tripled for children 1–6 years of age [163]. The prevalence of obesity is even higher among youth from diverse racial ethnic backgrounds [23]. Approximately 60 % of children and adolescents consume high-fat diets, 79 % do not eat the recommended amount of fruits and vegetables, and 40 % drink soda at least once per day. Children also report watching television for 3 or more hours on an average school day, and 65 % do not meet the recommended levels of moderate and vigorous exercise [164]. Minority youth have higher use of media per day compared to white youth, up to 8 h per day [140, 165–167].

The focus on intervention across the target environments, as noted in early childhood, is relevant for school-aged and adolescent youth as well. Strategies to promote the physical activity environment, food and beverage environments, and message environments parallel those of early childhood. The influence of health care and work environments is also relevant, particularly as adolescent youth enter the workforce or, in some cases, become parents. Of particular relevance to youth is the role of the school environment. Children spend more time in schools than in any other environment away from home. More than 48 million students attend 94,000 public elementary, middle, and secondary schools each day, and an additional 5.3 million students attend 30,000 private schools [168]. More than 95 % of American youth aged 5–17 are enrolled in school, and no other institution has as much continuous and intensive contact and influence on children during their first two decades of life. Health and education success are intertwined: schools cannot achieve their primary mission of education if students are not healthy and fit [169–171]. While the schools alone cannot solve the childhood obesity epidemic, it also is unlikely that childhood obesity rates can be reversed without strong school-based policies and programs to support healthy eating and physical activity.

The IOM identified several policy strategies relevant to the role of schools in preventing obesity and risk for chronic disease and cancer in children and youth [71]. First, the report urged communities to make schools a focal point of obesity prevention efforts. The school environment is interrelated with all aspects of the community and can have a powerful and influential role in structuring healthy environments for children. The 2005 IOM report Preventing Childhood Obesity: Health in the Balance recommends that children and adolescents participate in a minimum of 30 min of physical activity during the school day [172]. Actions that reflect this include requiring quality physical education and opportunities for physical activity in schools [71]. There is substantial evidence documenting the value of recess and activity in schools [173–175]. Despite this, there is also a wide variation in number, timing, and quality of physical activity breaks and recess afforded in schools. In 2006, only 4 % of elementary schools and 2 % of high schools required daily physical education. Among all school districts across the country, only 39 % required 30 min or more of recess per day. While this is an improvement over the past decade, additional work is needed to enable students to achieve the goal of 60 min of activity per day.

The role of nutrition in schools is critical to obesity prevention among youth. The goal of school nutrition programs is to assure that children are nourished effectively and educated as to healthy dietary patterns. Youth with access to healthy foods are more likely to consume those foods [176–180]. Knowledge about healthy choices is also critical to long-term nutrition and health. The Healthy Hunger Free Kids Act of 2010 gave USDA the mandate to develop regulations governing all foods sold and served on school campuses. Children participating in government nutrition programs (e.g., school lunch), many of who are minority children living in poverty, receive nearly half their daily calories from foods received in these programs. Schools provide a mechanism for encouraging appropriate eating patterns, portion sizes, and foods that meet the 2010 dietary guidelines (e.g., fruits and vegetables, low-fat dairy products). Policy strategies to encourage schools and communities to implement these approaches to a broad and comprehensive extent can have immediate and direct impacts on the local youth.

Finally, schools have an important role in assuring the food literacy of children and adolescents [181, 182]. Nutrition education can have a positive impact on a child's food and nutrition intake by changing knowledge and attitudes [183]. While several studies note the importance and impact of nutrition education, more instructional time is needed. Current data suggests that students are exposed to 1–2 min per day of information on nutrition [71]. The success of several school-based programs in preventing obesity, including the CATCH trial and others, suggests the value of nutrition education within a multicomponent intervention [184–186].

Conclusion

The national obesity epidemic is even more devastating among disadvantaged populations. The prevalence of obesity disparities in youth, and the subsequent risk for developing cancer and related chronic disease, suggests the need to behaviorally disrupt the intergenerational cycle of obesity that begins in early life. Dimensions of disparities as defined by socioeconomic, sociocultural, living and working conditions, and life course exposures influence obesity onset. Evidence-based policies can influence the qualities of the environments where children spend time and interrupt the pathways that link behaviors to obesity, reducing the risk for cancer development.

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Index

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