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

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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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