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REVIEW

Hyperinsulinemia, Insulin Resistance, Vitamin D, and Colorectal Cancer Among Whites and African Americans

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Abstract African Americans have the highest incidence and mortality rates of colorectal cancer among all US racial and ethnic groups. Dietary factors, lifestyle factors, obesity, variability in screening rates, socioeconomic differences, barriers to screening, and differences in access to health care may be contributory factors to racial and ethnic disparities. African Americans are more likely to demonstrate microsatellite instability in their colorectal tumors leading to malignancy. However, these differences do not completely explain all the variances. Ample evidence implicates insulin resistance and its associated conditions, including elevated insulin and insulin-like growth factor-1 (IGF-1), in colorectal carcinogenesis. African Americans have a high risk for and a high prevalence of insulin resistance and subsequent overt type 2 diabetes. Recent clinical studies revealed that ethnic differences between whites and African Americans in early diabetes-related conditions including hyperinsulinemia already exist during childhood. African Americans have a much higher prevalence of vitamin D deficiency than whites throughout their life spans. Vitamin D deficiency has been associated with higher rates of diabetes and colorectal cancer, particularly in individuals with high serum insulin and IGF-1 levels. Moreover, African Americans have lower insulin sensitivity in tissues, independent of obesity, fat distribution, and inflammation. Further development of measures of biomarkers of tumor biology and host susceptibility may provide further insight on risk stratification in African Americans.

Keywords Hyperinsulinemia · Insulin resistance · Blacks · Vitamin D · Colorectal cancer · African Americans

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Introduction

Colorectal cancer, in both men and women, is the third most commonly diagnosed cancer and the third leading cause of cancer death in the United States [1–3]. The American Cancer Society estimated that about 141,210 people will be diagnosed with colorectal cancer and about 49,380 people will die of this disease in the US in 2011. At current rates, Americans have an approximately 5.6 % lifetime risk of diagnosis of colorectal cancer [3]. More than 1 million Americans have been cured of or are currently under treatment for this disease. Significant racial and ethnic variance exists in both the incidence and mortality rates of colorectal cancer. African Americans have the highest incidence and mortality rates among all US racial and ethnic groups [4–8]. The incidence rates are nearly 20 % higher and mortality rates are nearly 45 % higher for African Americans than those for white Americans. A higher proportion of African Americans present with colorectal cancer under 50 years of age compared with white Americans. Distribution of colorectal cancer is more likely to be right-sided, proximal in African

Americans. Colorectal cancer in African Americans is more likely to be diagnosed at a later stage, to have distal spread, and is less likely to be localized. Five-year survival rate is lower in African Americans compared with that in white Americans. Although stage of colorectal cancer at diagnosis and access to health care may play a part in lower survival rates for African Americans, they are unlikely to account for all the disparities found because, even after survival is adjusted for sociodemographic and lifestyle factors and for treatment patterns, survival differences remain [9]. In addition, known tumor characteristics and markers of aggressiveness do not explain racial differentials in survival, which suggests the importance of other environmental exposure factors and the need for improved measures of biomarkers of tumor biology and host susceptibility. Hence, reducing the high mortality and morbidity rates of colorectal cancer in African Americans remains to be a major health care challenge in the United States.

The reasons for the high incidence rates of colorectal cancer in African Americans are not clear. Dietary factors, lifestyle factors, obesity, variability in screening rates, socioeconomic differences, barriers to screening, and differences in access to health care may be contributory [4–8]. There are also observations that polymorphisms within the P 53 gene are more prevalent in African Americans and that African Americans are more likely to demonstrate microsatellite instability in their colorectal tumors leading to malignancy [10–12]. However, these differences do not completely explain all the variances.

Hyperinsulinemia and Colorectal Cancer

The incidence of colorectal cancer rose dramatically in parallel with industrialization and westernization of lifestyles worldwide over the last century. Migration studies demonstrated that the incidence of colorectal cancer increased among immigrants from low-incidence to high-incidence industrialized countries [13]. The strong relationship between westernization of lifestyles, particularly increased consumption of animal fats, and colorectal cancer has spawned many hypotheses. Many studies focused on the hypotheses that high fat and low fiber consumption increase the risk of colorectal cancer [14–17]. Higher fat consumption induces increased secretion of bile acids. Colonic bacteria convert them into secondary and tertiary bile acids which may promote tumor formation by increasing colonic cell proliferation or by mutagenesis. Higher fiber consumption could limit colonic transit time and dilute potential colonic carcinogens. However, recent investigations, including cohort studies and randomized trials, have cast doubt on the central roles of fat and fiber in the colonic carcinogenesis [18, 19]. The fat and fiber hypotheses do not explain adequately all the observations and findings and are often contradictory. An increasing amount of evidence has indicated that hyperinsulinemia may account for many risk factors of colorectal cancer and for its high incidence in industrialized countries [20].

Ample evidence indicates that insulin resistance and its associated pathological conditions, including elevated fasting glucose, insulin, and insulin-like growth factor-1 (IGF-1), are implicated in colorectal carcinogenesis [20–26]. Risk factors for colorectal cancer, including abdominal obesity, physical inactivity, and type 2 diabetes mellitus, are all linked to insulin resistance and hyperinsulinemia. Insulin reduces the hepatic production of IGF binding protein (IGFBP-1) with resultant increase in the levels of circulating, bioactive, free IGF-1. Studies showed that high blood insulin, glucose, IGF-1, and C-peptide, a marker of insulin secretion, are associated with an increased risk of colorectal cancer [27–31]. Patients with acromegaly have a higher risk of colonic neoplasia; the high insulin levels in acromegalic patients seem to be most closely related to the higher risk [32]. In addition, chronic insulin therapy in type 2 diabetes patients has been shown to be associated with an increased risk of colorectal cancer [33]. The risk increase correlates with the duration of insulin therapy, and may be due to enhanced colonic cellular proliferation as a consequence of increased levels of insulin and IGF-1.

Insulin resistance is also considered to be a major etiologic factor in the development of the metabolic syndrome [34]. According to the criteria set by the national cholesterol education treatment program–adult treatment panel III (NCEP/ATPIII), the diagnosis of metabolic syndrome requires at least 3 out of 5 characteristics to be present [34]. These characteristics are central obesity, hypertension, fasting hyperglycemia, increased triglyceride levels, and low high-density lipoprotein (HDL) levels. Diabetes, hypertension, obesity, cardiovascular disease, and insulin resistance are more common in African Americans than whites. In the presence of the metabolic syndrome, there is a twofold increased risk of cardiovascular disease and a fivefold increased risk of type 2 diabetes [35]. Epidemiologic data collected in the past decade indicate that the risk of colorectal cancer is increased overall in individuals with metabolic syndrome [31, 36, 37]. The data include studies that examined determinants and clinical consequences of metabolic syndrome, plasma components of the definition of metabolic syndrome, and markers of hyperinsulinemia or insulin resistance in relation to risk of colorectal cancer or adenoma. However, it remains unclear to what extent the metabolic syndrome components individually account for such an association. A recent large epidemiological study suggested that simple assessment of abnormal glucose metabolism or abdominal

obesity, or both, to identify individuals at colorectal cancer risk may have higher clinical utility compared to applying more complex metabolic syndrome definitions [36].

The causality of these associations cannot be directly established through the epidemiologic associations, but strong evidence implicating cancer-enhancing effects of insulin also comes from animal models in which animals were treated with insulin injections. Insulin injections have been shown to enhance the growth of aberrant crypt foci, a colorectal cancer precursor, and increase the number and size of colorectal tumors [38, 39]. In various animal experiments, modulation of insulin and IGF-1 levels through various means, including genetically-induced obesity, caloric excess or restriction, inhibition of normal insulin secretion, and pharmacological inhibition of IGF-1, influences colonic carcinogenesis.

Mechanistic evidence is supported by in vivo results demonstrating a tumor promoting effect of insulin [40–43]. The proliferative mitogenic effect of insulin is mediated via its cognate insulin receptor and IGF-1 receptors. IGF-1 inhibits apoptosis and increases the risk of cellular transformation by enhancing cell turnover. Both normal colorectal epithelial cells and cancerous cells express IGF-1 receptors. When IGF-1 activates its receptor, the receptor–ligand complex inhibits apoptosis and allows progression through the cell cycle. In addition, IGF-1 increases production of vascular endothelial growth factor, an angiogenic factor supporting tumor growth, in colonic cancerous cell lines [40]. The insulin-induced pro-proliferative effect has only been shown with supra-physiological serum insulin levels typically in adults; however, re-expression of the fetal type A insulin receptor isoform in neoplastic cells renders them more sensitive to typically circulating levels of insulin and IGFs [44]. The insulin and IGF-1 signal transduction pathway involved in the regulation of gene expression and mitogenicity is mediated by activation of the ras protein. Ras mutations, which increase activity of the ras protein, occur in colonic cancerous cells and may enhance growth of colonic adenomas into cancers [45].

Insulin Resistance in African Americans

African American adults, adolescents, and children have a high risk for insulin resistance and subsequent development of overt type 2 diabetes [46–50]. African American men have a 60 % higher incidence of type 2 diabetes than white men, and African American women have a 100 % higher incidence of type 2 diabetes than white women [51]. Diet and obesity, particularly abdominal adiposity, play significant roles in the development of type 2 diabetes. African Americans have a higher prevalence of obesity compared with whites. It is commonly assumed that diet and obesity are the causes of the increased risk of type 2 diabetes in African Americans. However, recent clinical studies revealed that ethnic differences between whites and African Americans in early diabetes-related pathological conditions, including hyperinsulinemia and insulin resistance, already exist during childhood, and are not the result of differences in dietary consumption or abdominal adiposity [52, 53]. On the contrary, African American children have higher vegetable and fruit intakes than do white children [52, 53]. In addition, African American children, compared with white children, have lower visceral fat mass despite similar overall adiposity, but higher fasting insulin and lower fasting C-peptide levels [54]. These findings imply that there is a derangement in insulin clearance and impairment in pancreatic beta-cell function in African Americans [55]. Even when normal-weight adults are compared, insulin resistance is greater in African Americans than in white Americans [56]. African Americans have higher insulin and C-peptide responses to glucose during childhood, adolescence, and adulthood [57–60]. Moreover, African Americans have lower insulin sensitivity in tissues, independent of obesity, fat distribution, and inflammation, which indicates that the metabolic action of insulin is impaired [61]. African American youths also have higher rates of acanthosis nigricans, a cutaneous abnormality commonly associated with primary insulin resistance, than their white counterparts [62–64]. In addition, despite similar declines in insulin action during puberty, there is no compensatory increase in insulin secretion in African American children, contrary to the observation in white children [64–66]. These observations indicate that insulin resistance may manifest itself differently in African Americans. Furthermore, despite the fact that African Americans have a higher risk for and a higher prevalence of insulin resistance, paradoxically, the prevalence of metabolic syndrome is lower in African Americans than in whites [50, 59]. It is likely that the paradox is due to the relative absence of the dyslipidemia of insulin resistance in African Americans. African American children, despite being more insulin-resistant and hyperinsulinemic compared with their white counterparts, have favorable lipid concentrations including lower LDL-cholesterol, higher HDL-cholesterol, and lower serum fatty acid and triacylglycerol levels compared with white children [52, 54, 67, 68]. In addition, unlike in whites, in blacks the relation of insulin resistance to blood pressure is weak, referred to as the blood pressure and insulin resistance paradox in blacks [69]. Similarly, among blacks, there is a weak relationship between insulin resistance and dyslipidemia, referred to as the insulin resistance and HDL-cholesterol/triglyceride paradox in blacks [69]. The relationship between metabolic syndrome and risk of colorectal cancer is still not clear in blacks.

Obesity is a major health issue worldwide and the prevalence of obesity increases exponentially in blacks residing in urban areas in various regions including the United States. Abdominal circumference, as a surrogate for visceral adipose tissue and determinant of insulin resistance, is a greater predictor of metabolic syndrome than body mass index in non-black populations. However, this relationship in blacks remains controversial, because blacks, despite increased insulin resistance, have, in general, lower visceral adiposity for similar body mass index when compared with whites [69], which is referred to as the insulin resistance and visceral adipose tissue paradox in blacks. There is a dissociation between body fat distribution and insulin resistance among blacks.

Pro-inflammatory cytokines are predominantly derived from adipose tissues associated with metabolic syndrome. They are associated with increased visceral adiposity. It is believed that these adipocyte-derived cytokines could be the link between insulin resistance and metabolic syndrome, type 2 diabetes, and cardiovascular disease. Some studies have shown higher levels of these pro-inflammatory cytokines including tumor necrosis factor-alpha, resistin, leptin, interleukin-6, and C-reactive protein in African Americans than in whites [70]. Recently, several studies have revealed lower serum levels of adipopectic and its isomers, which are potent endogenous insulin sensitizers, in African Americans than in whites [71]. It is hypothesized that adipocytokines and other pro-inflammatory cytokines might play a significant role in the development of insulin resistance and type 2 diabetes in African Americans.

A potentially important modifying factor is vitamin D status. Vitamin D insufficiency has been associated with increased risk of colonic adenoma and colorectal cancer [72–84], and this deficiency is much more common in African Americans than in whites throughout their life spans [72, 73, 85], primarily due to the greater melanin pigmentation in the skin [86]. Vitamin D deficiency has been associated with increased risk of type 2 diabetes and abnormalities in insulin resistance and secretion [87–89]. Serum vitamin D levels were shown to be inversely associated with risks of prediabetic conditions and overt diabetes. Although evidence is mixed, early and long-term vitamin D supplementation may decrease the risk of developing diabetes [90–95]. Some clinical intervention studies also support that vitamin D and its active metabolites may improve insulin sensitivity [96–98]. An increasing amount of evidence suggests that vitamin D directly and adversely affects beta cells of pancreas [90, 98, 99]. A recent study demonstrated that higher circulating 25-hydroxy-vitamin D levels reduced the higher risk of colorectal cancer associated with high IGF-1 and insulin levels [100]. Because African Americans suffer from very high rates of vitamin D deficiency, and better vitamin D status has been associated with improvements in insulin secretion and insulin resistance and lower rates of colorectal cancer, especially in those with high serum insulin and IGF-1 levels, further study of the role of vitamin D deficiency in contributing to racial disparities in colorectal cancer incidence and mortality should be a high priority.

Discussion

Insulin resistance and hyperinsulinemia may be major risk factors for colorectal cancer. Although obesity and unhealthy lifestyles are on the rise globally, the susceptibility of metabolic derangements toward these changes may differ among populations. Due to differences in the environmental and genetic backgrounds, the risks for insulin resistance and for subsequent development of type 2 diabetes vary among various racial and ethnic populations. Although the cause of insulin resistance remains uncertain, the relationships of components of metabolic syndrome to insulin resistance are well established in whites, while they remain controversial in blacks [50, 59, 69]. At present, it is still not clear if these racial differences in insulin resistance are based on metabolic disturbance due to lifestyle changes or are an ethnically and genetically grounded phenomenon. For example, studies have revealed that there were genetic variants in the beta-cell specific transcription factor insulin promoter factor 1 gene and defective insulin secretion and a significant association between a certain polymorphism and type 2 diabetes in African Americans but not in whites [101–104]. Through gene–gene or gene–environment interactions, these variants might increase the susceptibility of African Americans to type 2 diabetes. In addition, it has been demonstrated that hyperinsulinemia in African Americans is not merely a compensatory response to lower insulin sensitivity [60]. Studies have suggested that increased insulin secretion and decreased insulin clearance might precede the development of insulin resistance in African Americans [54, 55]. The increased pancreatic demand may result in early pancreatic beta-cell exhaustion and earlier development of type 2 diabetes. Genome-wide association studies have uncovered numerous variants related to obesity and type 2 diabetes, but the preponderance of these studies have been conducted in whites. Potential genetic determinants of racial differences, if any, remain to be uncovered.

On the basis of the findings from mechanistic and epidemiologic studies, it appears evident that hyperinsulinemia–insulin resistance in metabolic syndrome may be a critical factor associated with risk of colorectal cancer. African Americans, compared with whites, have higher serum insulin levels and insulin resistance. African

Americans have the highest incidence of colorectal cancer when compared to other ethnic and racial groups in the United States. Further development of measures of biomarkers of tumor biology and host susceptibility in African Americans may provide further insight on risk stratification.

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