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Reviews

Obesity-associated mechanisms of hepatocarcinogenesis

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ABSTRACT

Obesity has been recognized as a key component of the metabolic syndrome, a cluster of risk factors associated with diabetes and cardiovascular morbidity. In addition, obesity has been linked to higher frequency of cancers in a variety of tissues including the liver. Liver cancer most often occurs as hepatocellular carcinoma (HCC) complicating cirrhosis due to chronic viral infection or toxic injury and remains the third leading cause of cancer death in the world. However, HCC is increasingly diagnosed among individuals with obesity and related disorders. As these metabolic conditions have become globally prevalent, they coexist with well-established risk factors of HCC and create a unique challenge for the liver as a chronically diseased organ. Obesity-associated HCC has recently been attributed to molecular mechanisms such as chronic inflammation due to adipose tissue remodeling and pro-inflammatory adipokine secretion, ectopic lipid accumulation and lipotoxicity, altered gut microbiota, and disrupted senescence in stellate cells, as well as insulin resistance leading to increased levels of insulin and insulin-like growth factors. These mechanisms synergize with those occurring in chronic liver disease resulting from other etiologies and accelerate the development of HCC before or after the onset of cirrhosis. Increasingly common interactions between oncogenic pathways linked to obesity and chronic liver disease may explain why HCC is one of the few malignancies with rising incidence in developed countries. Better understanding of this complex process will improve our strategies of cancer prevention, prediction, and surveillance.

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1. Introduction

In the past 30 years, overweight (abnormal accumulation of body fat defined by a body mass index [BMI] ≥ 25 kg/m^2) and obesity (BMI ≥ 30 kg/m^2) have become a great challenge to global health. According to the World Health Organization, there were at least 1.4 billion overweight adults in 2008 of whom 500 million were obese [1]. Obesity is a key component

Abbreviations: BMI, body mass index; ChREBP, carbohydrate-responsive element-binding protein; DCA, deoxycholic acid; DMBA, dimethylbenz(*a*)anthracene; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIF, hypoxia-inducible factor; IGF, insulin-like growth factor; IL, interleukin; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MIF, macrophage migration inhibitory factor; miRNA, microRNA; MMP, matrix metalloproteinase; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PAI, plasminogen activator inhibitor; PI3K, phosphatidyl-inositol-3-kinase; PPAR, peroxisome proliferator-activated receptor; SASP, senescence-associated secretory phenotype; SEER, Surveillance Epidemiology and End Results; SREBP, steroid response element binding protein; TIGAR, *Tp53*-induced glycolysis and apoptosis regulator; TLR, Toll-like receptor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

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of the metabolic syndrome, a cluster of risk factors associated with increased risk of diabetes and cardiovascular morbidity [2,3]. Obesity has been linked to increased frequency of many common types of malignancy including cancers of the breast, endometrium, prostate, kidney, esophagus, stomach, colon, pancreas, gallbladder, and liver [4–8]. In addition, obesity-associated tumors appear to be more aggressive, have an increased risk of recurrence, and result in higher mortality [9,10].

In this review we summarize current knowledge of the link between obesity and development of HCC. After briefly reviewing the epidemiology of this relationship, we discuss experimental and clinical evidence for obesity-associated molecular mechanisms of hepatocarcinogenesis, including those that may account for the development of liver cancer in the absence of cirrhosis. Identification of novel molecular targets in this process will hopefully improve our strategies for risk prediction, early detection, and effective therapy of HCC.

2. Epidemiology of obesity-associated HCC

2.1. Risk of primary liver cancer in obesity

Primary liver cancer is the fifth most commonly diagnosed malignancy in men and remains the third leading cause of cancer death in the world [11,12]. The major histological subtype of primary liver malignancies is hepatocellular carcinoma (HCC), which accounts for 70% to 85% of the total liver cancer burden [13]. HCC is one of the few cancers with rising incidence in developed societies [14]. Age-adjusted incidence of HCC among men in the United States has tripled in the past 20 years [15]. HCC has been mostly associated with cirrhosis due to chronic infection by hepatitis B virus (HBV) and hepatitis C virus (HCV), toxic injury from excessive alcohol consumption, or genetic disorders such as hemochromatosis [13].

While a substantial number of cases cannot be explained by these etiologies, HCC is increasingly diagnosed among obese individuals [16]. In a prospective cohort of the Cancer Prevention Study with more than 900,000 North American subjects, the relative risk of dying from liver cancer among men with a BMI $\geq$ 35 kg/m^2 was remarkably high (4.5 fold) compared to a reference group with normal body weight [4]. In a comparably large cohort study involving 362,552 Swedish men, the relative risk of HCC in individuals with a BMI $\geq$ 30 kg/m^2 was 3.1 fold higher than in normal weight controls [17]. Studies from other parts of the world indicate that the link between obesity and increased incidence of HCC has been globally recognized [5,6,18,19]. Importantly, the positive association between obesity and primary liver cancer is not limited to HCC. In a recent survey of the Surveillance, Epidemiology, and End Results (SEER)-Medicare database accounting for 25% of the general population in the United States, metabolic syndrome was linked to increased risk of not only HCC (odds ratio [OR], 2.13; 95% confidence interval [CI], 1.96–2.31), but also of intrahepatic cholangiocarcinoma (OR, 1.56; 95% CI, 1.32–1.83), a relatively rare primary malignancy of the liver [20].

2.2. Obesity-associated HCC occurring in NAFLD

What is the tissue-specific context of obesity-associated HCC? Hepatic manifestations of obesity and the metabolic syndrome are collectively termed nonalcoholic fatty liver disease (NAFLD) [21]. NAFLD is mostly limited to liver steatosis that is apparently benign and non-progressive (isolated fatty liver), but approximately 20% of all cases present as nonalcoholic steatohepatitis (NASH) featuring hepatocellular injury, inflammation, and variable degree of fibrosis with a risk of progression to cirrhosis and HCC [22–25]. Imaging data and autopsy records indicate that 70% to 80% of individuals with a BMI $\geq$ 30 kg/m^2 have increased liver fat content, suggesting that a remarkable 30% of the general adult population in the United States and other industrialized countries may have NAFLD [26–28]. Presence of biopsy-proven NAFLD among patients with type 2 diabetes has been reported to reach up to 74% [29,30], but NAFLD is commonly associated with insulin resistance and hyperinsulinemia even in lean subjects with normal glucose tolerance [31].

There is growing evidence for the risk of developing HCC in cirrhosis due to NAFLD in the absence of other risk factors [32–35]. In a prospective study conducted over 10 years, HCC developed in 10 out of 149 patients with NAFLD cirrhosis in comparison to 25 out of 147 American patients with HCV cirrhosis, which is currently the leading cause of HCC in this country [36]. In another analysis from the United States, yearly cumulative incidence of NAFLD cirrhosis was 2.6% compared to 4.0% among patients with HCV cirrhosis over an average follow-up period of 3.2 years [37]. In a Japanese study, HCC developed in 11.3% of patients with NAFLD-cirrhosis compared to 30.5% of patients with HCV-cirrhosis over 5 years [38]. A recent systematic review provided additional evidence that the risk of HCC in cirrhosis associated with NAFLD is lower compared to HCV cirrhosis [39].

The risk of liver cancer is markedly lower when patients with all stages of NAFLD are included in the analysis. Analysis of tumor incidence rates over a mean observation period of 8.2 years among 1600 Japanese patients with NAFLD indicated that HCC represented 6.0% (10/167) of all malignancies in comparison to 67.6% (267/395) in a matched group of patients with chronic hepatitis C [40]. In another cohort study from Japan, the annual incidence rate of HCC among patients with NAFLD was relatively low (0.043%) with a cumulative rate reaching 0.51% at year 12 following the original diagnosis of fatty liver made by sonography [41]. However, the overall public health impact of an association between NAFLD and HCC remains substantial considering the extraordinarily high prevalence of obesity and related metabolic conditions in modern society (Fig. 1).

2.3. Emergence of HCC in the non-cirrhotic liver

Although cirrhosis precedes the diagnosis of HCC in most individuals, the number of cases in which HCC develops in the absence of cirrhosis is not trivial. A clinico-histopathologic review of 804 American patients with HCC confirmed the lack of