

Obesity and Liver Cancer

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KEYWORDS

- Obesity • Hepatocellular carcinoma • Nonalcoholic fatty liver disease
- Carcinogenesis

KEY POINTS

- Obesity has become an alarming threat to health worldwide, because of its pandemic spread and increasing prevalence among children.
- Hepatocellular carcinoma (HCC) is the cancer most strongly enhanced by obesity, mainly through the increased risk for nonalcoholic fatty liver disease (NAFLD).
- The lower rates of HCC incidence compared with virus or alcohol-related etiology are outweighed by the much larger spread of NAFLD, thus foreseeing the future trends of HCC in the general population.
- The diagnosis of nonalcoholic steatohepatitis-related HCC is often made at the first referral, when the tumor is at a more advanced stage.
- HCC may also develop in noncirrhotic livers with NAFLD.
- The mechanisms of obesity-induced hepatocarcinogenesis are under active investigation to identify new targets for therapeutic interventions.

INTRODUCTION

Obesity and cancer represent 2 of the most important public health challenges of the twenty-first century. The prevalence of obesity has reached epidemic proportions, with a steep increase over the last decades (Fig. 1). In 2005 approximately 1.6 billion people worldwide were overweight and 400 million adults were obese; according to World Health Organization estimates, by 2015 these figures will have doubled.¹ One of the most worrisome aspects of this pandemic spread of obesity is the constant increase among children and adolescents; in 2006, one-third of children aged 2 to 19 years had a body mass index (BMI) above the 85th percentile, with 16% above the 95th percentile.² Overweight in early childhood increases the likelihood of being obese in later childhood,³ and in up to one-half of cases leads to obesity and its complications in adulthood.⁴

Obesity is an established risk factor for cancers in several sites. In a well-known study from the American Cancer Society, death rates from all cancers in the heaviest

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Clin Liver Dis 18 (2014) 191–203
<http://dx.doi.org/10.1016/j.cld.2013.09.001>

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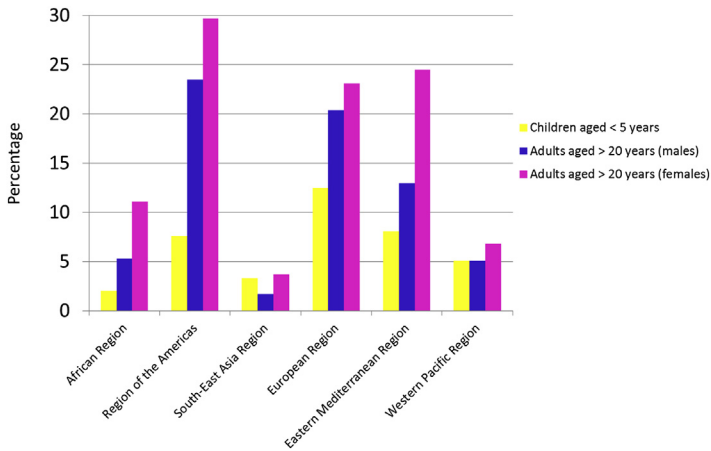


Fig. 1. Global burden of increased body mass index ($>25 \text{ kg/m}^2$) in children and of obesity in adults. (Data from World Health Organization. World Health Statistics Report 2013.)

members of the cohort ($\text{BMI} \geq 35 \text{ kg/m}^2$) were 52% higher in men and 62% higher in women when compared with lean subjects. Based on the relative risks observed in this study and on the current patterns of overweight and obesity, the proportion of all cancer deaths in United States adults older than 50 years that is attributable to overweight/obesity may be as high as 14% in men and 20% in women.⁵ An important and still controversial point is the relative importance of fat distribution. Visceral fat (VF), evaluated as waist circumference or by computed tomography (CT), can be more important than general adiposity for cancer induction, although the threshold for the increased risk is still unclear.⁶ Regarding obesity, VF is also associated with worse clinical outcomes, such as recurrence of the primary cancer, shorter disease-free survival, reduced overall survival, and reduced responsiveness to chemotherapy.⁶

Sites of cancer whose risk is increased by obesity include endometrium, breast, kidney, and bone marrow. Regarding the gastrointestinal tract, obesity increases the risk of colorectal, esophageal, pancreatic, and, above all, primary liver cancer (Fig. 2).⁷

OBESITY AND HEPATOCELLULAR CARCINOMA

Liver cancer is the fifth most common cancer in men (7.9% of the total), the seventh most common in women (6.5% of the total), and the third most common cause of death from cancer worldwide.⁸ Hepatocellular carcinoma (HCC) accounts for 70% to 85% of the total burden of liver cancer. Most cases of HCC (70%–90%) develop against a background of advanced chronic liver disease, related mainly to hepatitis B virus (HBV), hepatitis C virus (HCV), and alcohol abuse.⁸ Whereas in eastern Asia and sub-Saharan Africa the dominant risk factor is HBV, in the developed countries time trends in the incidence of HCC paralleled the timing of HCV spread, but in approximately 15% to 50% of HCC cases the etiology is unrelated to viruses or alcohol. Lately, a strong association between HCC and the metabolic syndrome (MS) has become evident.⁹ The definition of the MS is constantly updated, but basically refers to a cluster of interrelated risk factors, including visceral obesity, atherogenic dyslipidemia, arterial hypertension, and hyperglycemia/type 2 diabetes, which exponentially increase the risk of developing cardiovascular diseases.¹⁰ Among the components of the MS, both obesity and type 2 diabetes are independent risk factors

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