

# Obesity as a cause of hepatocellular carcinoma

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## ABSTRACT

During recent years the incidence of obesity has increased significantly, and in some instances rapidly, in many resource-rich countries. Paralleling this increase has been an increase in the incidence of hepatocellular carcinoma. It has been estimated that as many as 90% of obese adults will develop the metabolic syndrome. The worldwide incidence of this syndrome in adults at this time ranges from 9 to 34%. Furthermore, obesity in childhood increases the risk of obesity in adulthood, and hence the development of the metabolic syndrome and hepatocellular carcinoma. Ten to 20% of patients with non-alcoholic fatty liver disease progress to non-alcoholic steatohepatitis, and 8.3% of the latter develop cirrhosis. Up to 50% of these patients with cirrhosis, and a significant proportion of those without cirrhosis, progress to hepatocellular carcinoma. Much remains to be learnt about the mechanisms by which obesity and the metabolic syndrome cause hepatocellular carcinoma, although insulin resistance, increased tissue necrosis factor activity, alterations in serum lipids, non-alcoholic fatty liver disease and non-alcoholic steatosis play important roles. There is also increasing evidence that gut microbiota play a role in the development of the metabolic syndrome and hence of hepatocellular carcinoma.

**Key words.** Metabolic syndrome. Non-Alcoholic Fatty Liver Disease. Non-alcoholic steatohepatitis. Cirrhosis. Gut microbiota.

## INTRODUCTION

In recent years it has become increasingly evident that obesity may be complicated by the development of hepatocellular carcinoma (HCC). During this time, the burgeoning incidence of obesity, at least in some resource-rich countries, has been the predominant reason for the striking increase in the incidence of the tumor in the populations of these countries.<sup>1</sup> For example, a meta-analysis of 11 studies conducted in the United States of America (USA), Europe and Asia showed an increased risk of HCC of 1.89 (95% confidence limits of 1.51 and 2.36), and that the tumor, paralleling the epidemic of obesity, is now the most rapidly increasing cause of cancer deaths in these,

and presumably, other countries.<sup>2</sup> In addition, a prospective study in Europe showed obesity to be closely associated with HCC: relative risk of 3.51, 95% confidence interval 2.09 to 5.87 ( $p < 0.0001$ ).<sup>3</sup> In another European analysis a relative risk of HCC development of 1.9 was reported in obese subjects.<sup>4</sup> Moreover, in the USA the incidence of HCC has tripled (1.6/100,000 to 4.9/100,000 of the population) in parallel with an increasing incidence of obesity.<sup>5</sup> Furthermore, a high body mass index (BMI) in childhood increases the risk of HCC in adulthood,<sup>6</sup> and may even result in the tumor developing during childhood.<sup>7</sup>

The rapidly increasing number of HCC-induced deaths in the USA has occurred at a time when it is estimated that 25% of the country's population (approximately 47 million people) meet the diagnostic criteria for the metabolic syndrome: the rates are 32% in Mexican Americans, 24% in European Americans and 22% in African Americans.<sup>8</sup> The metabolic syndrome is defined as a constellation of metabolic and other abnormalities in the form of central obesity (BMI in excess of 30 kg/m<sup>2</sup> or increased waist circumference), plus at least two of the following components: type 2 insulin resistance or

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*Manuscript received: September 14, 2014.*  
*Manuscript accepted: October 07, 2014.*

hyperinsulinemia, overt type 2 diabetes mellitus, raised triglycerides, and raised blood pressure.<sup>9</sup>

During the same time, evidence has accumulated of an association between the metabolic syndrome and the development of HCC, with the syndrome now being acknowledged to be the cause of the malignant transformation in the majority of the patients in the Western world previously labelled as having cryptogenic HCC.<sup>2,3,10-18</sup> The increasing incidence of the metabolic syndrome, as well as the resulting increase in the occurrence of HCC in affluent societies, are attributed to the increasing numbers of obese subjects, and it is estimated that as many as 90% of these obese adults will develop the metabolic syndrome.<sup>18</sup> Moreover, it is likely that the syndrome will result in substantial increases in the incidence of HCC in other resource-rich countries during the coming decades.<sup>19</sup>

Depending upon geographic location, socio-economic conditions, and ethnicity, the prevalence of the metabolic syndrome continues to increase in each of these locations and circumstances.<sup>19-23</sup> The highest incidences are believed to occur in the USA, where it has been estimated that obese adult males are 32 times as likely as normal-weight males to meet the diagnostic criteria for the metabolic syndrome, and the number continues to increase.<sup>20</sup> In a survey of adults in that country the prevalence of the metabolic syndrome showed an age-dependent increase: 6.7, 43.5 and 42% for ages 20 to 29, 60 to 69, and over 70 years, respectively.<sup>8</sup> It has been estimated that the prevalence of the metabolic syndrome is approximately 14% in China, 26% in South Asia, 19% in Australia, 9% in France and 18% in Italy.<sup>16</sup> Furthermore, it has been predicted that as many as 75% of obese adults will develop fatty liver.<sup>19</sup>

Worldwide, it is estimated that of some 400 million obese individuals, 75% have co-existing NAFLD.<sup>19-23</sup> The prevalence of NAFLD ranges, in different populations, from 9 to 37% and that of non-alcoholic steatohepatitis (NASH) from 5 to 7%.<sup>23</sup> NAFLD is currently the most common hepatic disorder in the USA and other industrialized countries, affecting as many as 18% of the general adult population and 90% of those with marked obesity.<sup>23-25</sup> During the course of 5 to 10 years between 5 and 14% of the latter will develop cirrhosis.<sup>19-22</sup>

Obesity is present in between 37% and more than 66% of patients with NAFLD, and the risk of steatosis is appreciably higher in obese than in non-obese individuals.<sup>21,23,25</sup> Obesity predisposes to the development of HCC by lipid accumulation within hepato-

cytes, which in turn leads to chronic low-grade inflammation.<sup>21,23,25</sup> Patients with steatosis are at risk for developing cirrhosis and HCC.<sup>24</sup> NAFLD is commonly associated with insulin resistance and hyperinsulinemia, and might therefore be considered to be a component of the metabolic syndrome.<sup>19</sup> Between 10 and 20% of patients with NAFLD progress to NASH, and 8 to 26% of those with NASH progress to cirrhosis,<sup>26</sup> although the latter progression may take many years. Cohorts of patients with NASH and cirrhosis are at risk of developing HCC, with a rate as high as 12.8% over a 3.2 years median follow-up.<sup>12,13</sup> NAFLD is currently the most common liver disease in resource-rich countries, although the incidence of HCC complicating NAFLD is lower than that complicating NASH (4-27%).<sup>25,27,29</sup> The risk of HCC developing in patients with NASH-related cirrhosis rivals that in patients with HCV-induced cirrhosis,<sup>21</sup> although a significant proportion of the patients with the metabolic syndrome (up to 50%) develop HCC without the intervention of cirrhosis.<sup>29-31</sup>

Type 2 diabetes is a common metabolic disorder strongly linked to obesity and is a component of the metabolic syndrome.<sup>30</sup> It carries a 2-3 fold increase in relative risk of developing HCC in a multivariate proportional hazards analysis:<sup>31,32</sup> the hazard ratio with less than 5 years of follow-up was 1.60 (95% confidence intervals 0.86 and 2.96), and with more than 5 years of follow-up 2.41 (95% confidence intervals 1.60 to 3.62).<sup>31</sup> In another analysis, diabetes was an independent risk factor for HCC with an odds ratio of 2.87 (95% confidence interval 2.49 and 3.30).<sup>31</sup>

### POSSIBLE PATHOGENETIC MECHANISMS OF OBESITY- INDUCED HEPATOCELLULAR CARCINOMA

Much remains to be learnt about the mechanisms by which obesity and the metabolic syndrome cause malignant transformation, although insulin resistance, hyperinsulinemia, increased tumor necrosis factor (TNF) signalling pathways, alterations in cellular lipid, NASH and NAFLD, and gut microbiota may play key roles.

Insulin resistance is the principle denominator that links all the components of the metabolic syndrome. It also causes fat accumulation in hepatocytes, even in subjects with normal glycemic control, and plays a major role in the development of NAFLD.<sup>32,33</sup> Patients with NAFLD demonstrate significantly increased insulin resistance, which

facilitates the accumulation of free fatty acids in the liver and leads to the development of NAFLD.<sup>23,24</sup> Chronic hepatosteatosis leads to hepatosteatitis, which in turn progresses ultimately to tumor initiation and formation.<sup>19</sup>

Obesity predisposes to HCC development by lipid accumulation within hepatocytes, which leads to a chronic low-grade inflammation involving cytokines and adipokines.<sup>19</sup> Aberrant accumulation of adipose tissue, release of pro-inflammatory cytokines, inhibition of anti-inflammatory cytokines, and lipotoxicity collectively promote and propagate both systemic and hepatic insulin resistance, leading to hyperinsulinemia.<sup>34,35</sup> Hyperinsulinemia, in turn, results in increased levels of insulin growth factor-1 (IGF-1), which have important proliferative and anti-apoptotic effects. IGF-1 also promotes angiogenesis through increased vascular endothelial growth factor production, which in turn leads to proliferation of cancer cells.<sup>36,37</sup>

Toll-like receptors 4 (TLR4) have a role in Kupffer cells in mediating progression of simple steatosis to NASH by introducing reactive oxygen species-dependent activation of X binding protein 1 (XBP-1).<sup>38</sup> In addition, up-regulation of peroxisome proliferator-activated receptors (PPARs) regulate a network of genes encoding protein involved in fatty acid uptake, enzymes required for the beta-oxidation of fatty acids, and enzymes required for ketogenesis.<sup>38</sup> In experimental animals, the expression of TLR4 mediated the progression of simple steatosis to NASH.<sup>38</sup> Interleukin-6 (IL-6) has been linked to the obesity-associated response, in that it activates signal transducer and activator of transcription-3 (STAT-3), potentiating cell proliferation and anti-apoptotic mechanisms.<sup>39</sup> In addition, IL-6 plays a key role in the obesity-associated inflammatory response and tumorigenesis, and exerts cell proliferative and anti-apoptotic effects.<sup>40</sup>

TNF, an adipose-derived cytokine, is a potent activator of pro-oncogenic pathways, including jun kinases (JNK), nuclear factor  $\kappa$ B (NF $\kappa$ B), and mammalian target of rapamycin (mTOR).<sup>41</sup> Both dietary and genetic obesity promote hepatic inflammation and tumorigenesis by enhancing interleukin-6 (IL-6) and TNF expression.

Furthermore, high circulating levels of leptin in NAFLD exert pro-inflammatory and pro-fibrogenic effects.<sup>42,43</sup>

Evidence is accumulating for a role for gut microbiota in the pathogenesis of fatty liver disease and HCC.<sup>44</sup> Metabolic activity of the gut microbiota normally provides considerable benefit to human health

by supplying essential nutrients and maximizing the efficiency of harvesting energy from ingested food.<sup>44</sup> But the microbiota also contain numerous potentially opportunistic pathogens. Gut microbiota have long been known to be a key determinant of intestinal inflammation, and have very recently been shown to play a role in generating chronic inflammation of the liver.<sup>45</sup> They appear to cause the latter by activating the innate immune system to drive proinflammatory gene expression, thereby promoting chronic inflammatory disease of the liver.<sup>45</sup> This effect seems to be achieved through the intervention of NAFLD and the metabolic syndrome, and may ultimately be complicated by malignant transformation of hepatocytes.<sup>45</sup> Alterations in the composition of microbiota, as well as increases in gut permeability and serum levels of endotoxin, suggest that gut microbiota promote NAFLD formation and function. The increasing incidence of NAFLD over the last half-century may indicate that environmental and/or lifestyle factors in association with the metabolic syndrome are driving this alarming trend.<sup>45</sup>

A central component of the mucosal immune system is the system of receptors that recognise conserved features of the microbial products. Primary classes of the receptors include TLR and NLR receptors that protect against microbes.<sup>45</sup> Thus, these receptors normally play a key role in keeping gut bacteria in check. But activation of these receptors may also drive a variety of inflammatory diseases, including liver diseases.<sup>45</sup> The concept that reduced or impaired intestinal barrier function can result in gut microbiota products breaching the intestine is increasingly thought to play a central role in liver disease by promoting inflammation.<sup>45</sup>

Microbiota products might also activate TLR/NLR in the liver, promoting the formation of NAFLD.<sup>45</sup> This finding suggests that the rapidly increasing occurrence of NAFLD during recent times may, in part, result from increased consumption of western diets. Increased activation of proinflammatory signals as a result of increased intestinal permeability and/or changes in microbiota composition results.<sup>45</sup> NAFLD has been shown to be associated with altered microbiota composition and a predisposition to develop the metabolic syndrome.<sup>45</sup> Strong evidence that microbiota can promote NAFLD is supported by recent studies in mice.<sup>45</sup> There is also evidence that microbiota cause NASH, especially by inducing activation of X box binding protein-1 (XBP-1).<sup>46</sup>

Recent evidence also supports the notion of microbiota playing a role in the development of

fibrosis and cirrhosis.<sup>45</sup> This hypothesis is supported by the finding that intestinal microbiota, as well as TLR4/CD14, are essential for the appearance of hepatic fibrosis, and that hepatic stem cells are the predominant target by which TLR4 ligands promote hepatic fibrosis.<sup>45</sup>

## CONFLICT OF INTEREST

The author has had no financial support in respect to this publication.

The author is solely responsible for the authorship of this manuscript.

The author has no conflict of interest in the writing of the manuscript.

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