2

The Relationship Between Nonalcoholic Fatty Liver Disease and Hepatocellular Carcinoma

Misael Uribe, Jesús Román-Sandoval,
Norberto C. Chávez-Tapia and Nahum Méndez-Sánchez
Medica Sur Clinic and Foundation, Biomedical Research Department and Liver Research Unit, Mexico City Mexico

1. Introduction

Hepatocellular carcinoma (HCC) is the most prevalent type of primary liver cancer, the fifth most common type of solid tumor, and the third highest cause of cancer mortality worldwide (Parkin et al., 2005, Motola-Kuba et al., 2006). On the other hand, nonalcoholic fatty liver disease (NAFLD) is now recognized as one of the most common liver disorders (Lazo and Clark, 2008). The subclinical nature of this disease has prompted research to improve its diagnosis and prevent its progression to nonalcoholic steatohepatitis (NASH), liver cirrhosis, and HCC. An increasing number of reports indicate that NAFLD is the key link between obesity and HCC (Chavez-Tapia et al., 2009, Mendez-Sanchez et al., 2007). It has been suggested that most cases of HCC involve progression of NASH to cirrhosis (Caldwell et al., 2004). In 1980, Ludwig et al. described NASH as an advanced form of fatty liver disease. They defined it as a well-recognized clinical pathological syndrome that occurs primarily in obese women with diabetes mellitus and has histological similarities to alcoholic liver disease in the absence of heavy alcohol consumption (Ludwig et al., 1980). Some reports suggest that 10–24% of the populations of various countries have NAFLD. The prevalence of NAFLD is higher among obese and diabetic patients (70–86%). NASH is estimated to occur in 10% of NAFLD patients. NASH has been posited as a possible cause of cryptogenic cirrhosis (CC) (Bellentani et al., 2000). Patients with CC also develop HCC (Caldwell et al., 1999). In this review, we discuss the associations between obesity and cancer, between metabolic syndrome and NAFLD, and between NAFLD and HCC.

2. Obesity and cancer

The World Health Organization defines obesity as fat accumulation in adipose tissue to the extent that health is impaired. For epidemiological purposes, overweight is defined as a body mass index (BMI) greater than 25 kg/m^2 and obesity is defined as a BMI greater than 30 kg/m^2.

Epidemiological studies provide convincing evidence of an association between obesity and cancer of the esophagus (adenocarcinoma), pancreas, colorectum, breast (postmenopausal), endometrium, and kidney (WCR, 2007). The largest meta-analysis to date involved 282,000 patients from prospective observational studies and more than 133 million person-years of

follow-up. It showed that a high BMI is associated with a high incidence of cancer. The association is modest and risk estimates range from 1.1 to 1.6 for an increase in BMI of 5 kg/m². For people with an average BMI (23 kg/m²), a 5 kg/m² increase in BMI corresponds to a weight gain of 15 kg (men) or 13 kg (women). The associations between obesity and cancer are sex and site specific but are broadly consistent across geographic populations (Renehan et al., 2008). Emerging evidence suggests that weight loss after bariatric surgery reduces the incidence of cancer (Sjostrom et al., 2009). Furthermore, a prospective study of 900,000 adults in the United States showed that obesity accounts for 14% of all deaths from cancer in men and for 20% of all deaths from cancer in women (Calle et al., 2003) (Fig.1). Men and women with a BMI greater than 40 kg/m² have death rates 52% and 62%, respectively, higher than those of people with normal BMIs. This indicates that obesity also affects the outcome of cancer and this finding is supported by studies showing increased perioperative mortality rates for obese people (Li et al., 2009, Meyerhardt et al., 2003, Haydon et al., 2006, Dignam et al., 2006). There appears to a sex differential with respect to the risk of developing cancer: men have a higher risk than women of developing cancer when their BMI is elevated (Renehan et al., 2008, Moore et al., 2004). This may be due to hormonal differences or it may indicate that BMI is a poor index of central adiposity in females. As females generally only deposit adipose tissue centrally when the total volume of deposited fat is elevated, overweight BMIs do not correspond with visceral fat volume in females to the same extent as in males, which may account for the differences in cancer risk observed when BMI is used to determine obesity status.

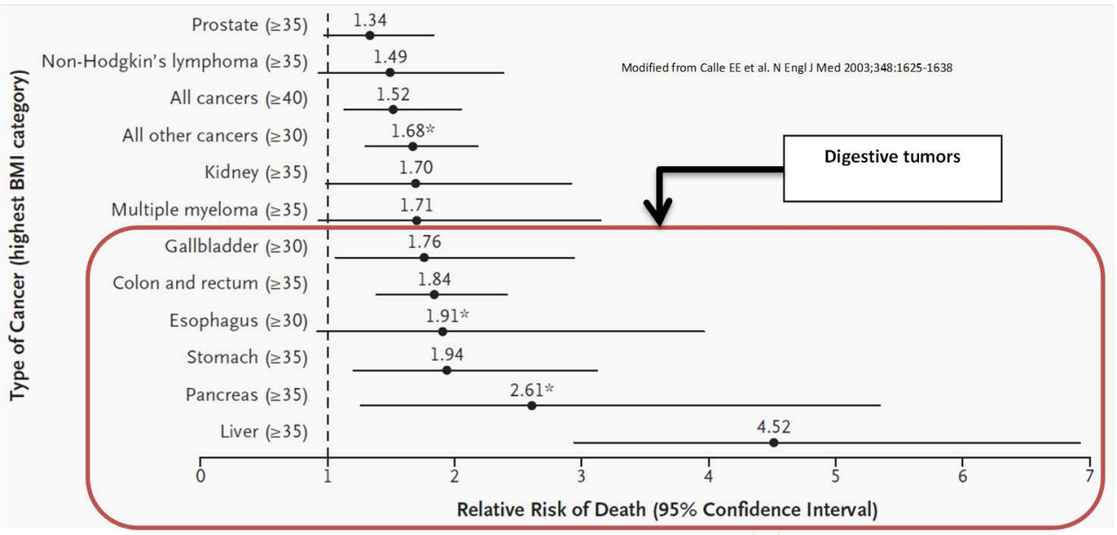


Fig. 1. Mortality from cancer in obese men in the USA.
The highest relative risk was observed in liver cancer. It is also important to note that gastrointestinal tumors are associated with the highest relative risk of death according to BMI and obesity.

In studies in which measures of visceral adiposity such as waist circumference (WC) or visceral fat adiposity (VFA) were used, visceral adiposity was associated with an increased risk of cancer (Moore et al., 2004, Wang et al., 2008, Steffen et al., 2009); it is a stronger predictor of cancer than BMI (Moore et al., 2004), and the cancer risk is similar for males and females (Moore et al., 2004, Wang et al., 2008). Large-scale studies on visceral adiposity

across cancer sites are needed to clarify whether there is a clear differential effect of visceral versus subcutaneous obesity. Visceral adiposity (and not subcutaneous adiposity) is associated with development of features of metabolic syndrome (a proxy for a dysmetabolic profile in viscerally obese patients) (Donohoe et al., 2010). Most of the components of the syndrome, alone (Cowey and Hardy, 2006, Giovannucci, 2007) or in combination (Colangelo et al., 2002, Bowers et al., 2006, Trevisan et al., 2001), have been individually linked to cancer at various sites. A prospective international population-based study of 580,000 people (the Me-Can Study) is under way to identify whether metabolic syndrome is independently associated with cancer. Initial findings suggest that a combination of components of metabolic syndrome is associated with colorectal cancer (men RR, 1.25 [95% CI, 1.18–1.32]; women RR, 1.14 [95% CI, 1.02–1.18]) (Stocks et al., 2010), endometrial cancer (RR, 1.37; [95% CI, 1.28–1.46]) (Bjorge et al., 2010), bladder cancer in men (RR, 1.1; [95% CI, 1.01–1.18]) (Stocks et al., 2010), and pancreatic cancer in women (RR, 1.58; [95% CI, 1.34–1.87])(Johansen et al., 2010).

3. Metabolic syndrome and NAFLD

Metabolic syndrome is a condition characterized by a cluster of symptoms, including glucose intolerance/insulin resistance, abdominal obesity, atherogenic dysfunction, dyslipidemia (low concentrations of high-density lipoprotein cholesterol and high concentrations of triglycerides), elevated blood pressure, a proinflammatory state, and a prothrombotic state. It increases morbidity and mortality, especially in respect of cardiovascular disease (Reaven, 2002, Grundy et al., 2004). NAFLD can be considered the hepatic manifestation of metabolic syndrome (Fig. 2) (Rector et al., 2008). NAFLD is strongly associated with metabolic syndrome; 90% of patients with NAFLD have more than one feature of metabolic syndrome and 33% have three or more features (Marchesini et al., 2003). Furthermore, the risk of steatosis increases exponentially as the number of components of metabolic syndrome increases (Marceau et al., 1999). NAFLD has been consistently associated with obesity (60–95%), type 2 diabetes (28–55%), and dyslipidemia (27–92%) (Bugianesi et al., 2005). Metabolic syndrome is associated with liver disease, which may progress and become severe. In addition, the likelihood of developing NASH increases with

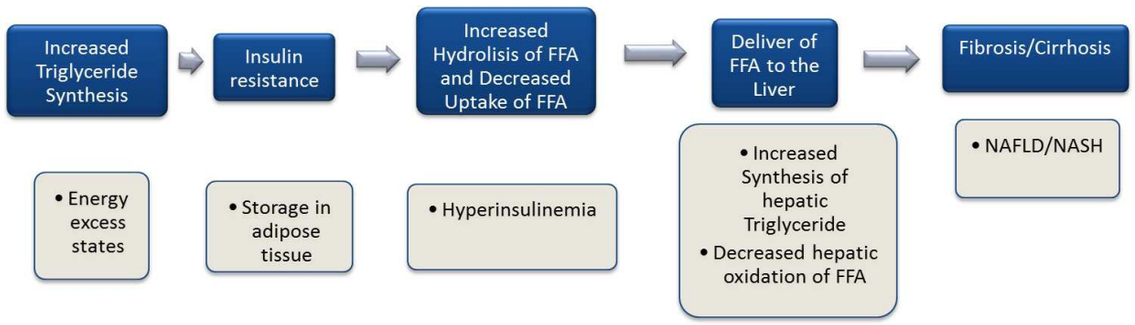


Fig. 2. Triglyceride synthesis and NAFLD.
Triglyceride synthesis increases in states of energy excess. Insulin resistance and hyperinsulinemia increase lipolysis of triglyceride depots in adipose tissue, amplifying the delivery of free fatty acids Free Fatty Acids (FFA) to the liver. Insulin further stimulates liver triglyceride synthesis while inhibiting fatty acid oxidation, inhibiting the production of very-low-density lipoproteins.

the severity of obesity (Bugianesi et al., 2005, Marchesini et al., 2003). There is a universal association between NASH and insulin resistance regardless of BMI, suggesting that insulin resistance is a central factor in the pathogenesis of NASH (Chitturi et al., 2002). The elevated expression of tumor necrosis factor-alpha (TNF-α) in the liver observed in NAFLD may represent a link between insulin resistance and hepatic steatosis. TNF-α has been proposed as an important component of peripheral insulin resistance in obesity and type 2 diabetes. It is linked to increased oxidative stress and cell death in the liver, and potentiates the development of liver fibrosis and progression to NASH (Jiang and Torok, 2008).

4. NAFLD and HCC

It is clear that cirrhosis is linked to the development of HCC regardless of the underlying etiology of liver disease. The exact mechanism responsible for the development of HCC in NASH remains unclear, although the pathophysiological mechanisms responsible for the development of NASH associated with insulin resistance and the subsequent inflammatory cascade likely contribute to the carcinogenic potential of NASH.

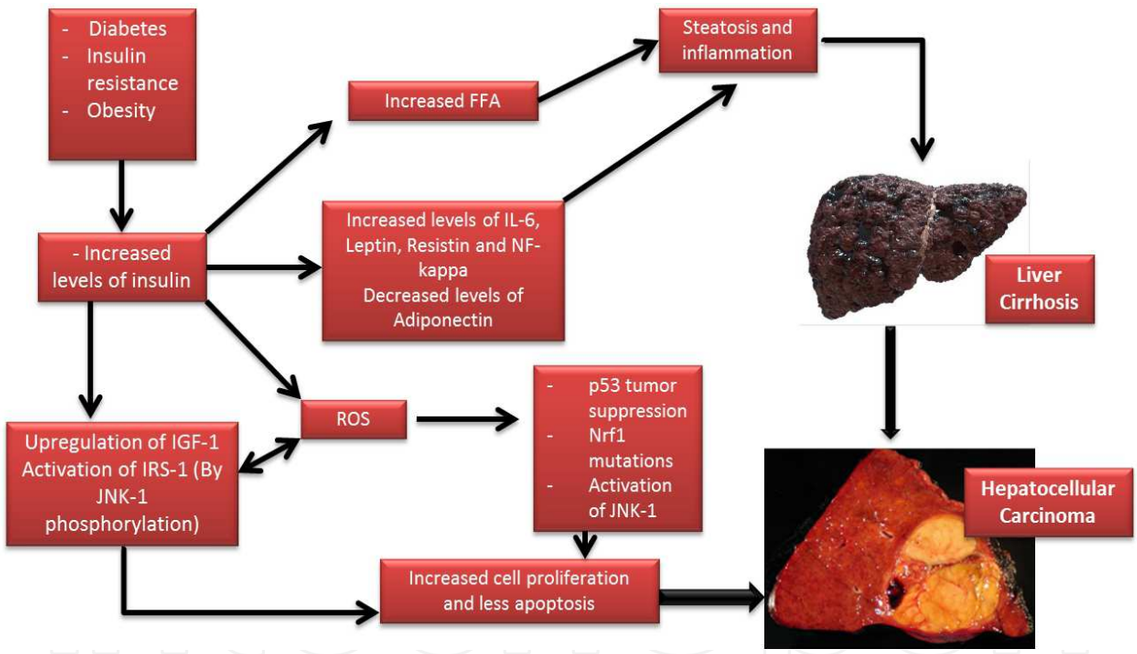


Fig. 3. Proposed pathogeneses of HCC in NAFLD/NASH.
Obesity, diabetes, and insulin resistance are strongly associated with hyperinsulinemia, which can trigger upregulation of IGF-1, activation of IRS-1, increased FFA release, increased secretion of TNF-α, IL-6, leptin, resistin, and NF-κ, and decreased production of adiponectin. Suppression of p53 and activation of JNK-1 result in cell proliferation and decreased apoptosis, which in turn result in HCC. ROS are also important in the pathogenesis of HCC. IGF-1, insulin growth factor-1; IRS-1, insulin receptor substrate-1; FFA, free fatty acid; TNF-α, tumor necrosis factor-alpha; IL-6, interleukin-6; NF-κ, nuclear factor-kappa; JNK-1, Jun amino-terminal kinase-1; HCC, hepatocellular carcinoma; ROS, reactive oxygen species.

Obesity and diabetes are risk factors for NASH and CC and have been implicated in multiple cancers, including HCC (Bugianesi et al., 2007). Insulin resistance associated with obesity, metabolic syndrome, and diabetes results in increased release of FFAs from adipocytes, increased secretion of proinflammatory cytokines such as TNF-α, increased secretion of interleukin-6, leptin, and resistin, and decreased secretion of adiponectin. These processes favor the development of hepatic steatosis and inflammation (Fig. 3) (Bugianesi et al., 2007, Harrison, 2006).

Hyperinsulinemia upregulates the production of insulin-like growth factor-1 (IGF1), a peptide hormone that stimulates growth through cellular proliferation and inhibition of apoptosis (Page and Harrison, 2009, Calle and Kaaks, 2004, Ish-Shalom et al., 1997). Insulin also activates insulin receptor substrate-1 (IRS-1), which is involved in cytokine signaling pathways and has been shown to be upregulated in HCC (Tanaka et al., 1997). The mannose 6-phosphate/IGF2 receptor (M6P/IGF2R) is involved by regulating cell growth and functions as a tumor suppressor. Mutations resulting in loss of heterozygosity for this receptor have been detected in 61% of patients with HCC (Yamada et al., 1997). Adiponectin is an anti-inflammatory polypeptide specific to adipose tissue that is decreased in insulin-resistant states and has been shown to inhibit angiogenesis via modulation of apoptosis in an animal model (Ukkola and Santaniemi, 2002, Brakenhielm et al., 2004). In an insulin-resistant state, these factors promote uninhibited cell growth and appear to play a significant role in the development of HCC in patients with NASH.

NASH is also associated with oxidative stress and the release of reactive oxygen species (ROS), which likely contribute to the development of HCC. An insulin-resistant obese mouse model demonstrated that ROS production is increased in the mitochondria of hepatocytes with fatty infiltration and that oxidative stress may be implicated in hepatic hyperplasia (Bugianesi et al., 2007, Yang et al., 2000). During carcinogenesis, epithelial hyperplasia and dysplasia generally precede cancer by many years (Bugianesi et al., 2007). C-Jun amino-terminal kinase 1 (JNK1) has also recently been linked to obesity, insulin resistance, NASH, and HCC. JNK1 is a ubiquitously expressed mitogen-activated protein kinase. Obesity is associated with abnormally elevated JNK activity (Hirosumi et al., 2002). In hyperinsulinemia, FFA, TNF-α, and ROS are potent activators of JNK, which in turn phosphorylates IRS-1 (Hirosumi et al., 2002, Gomaa et al., 2008). Evidence suggests that statins significantly decrease the risk of HCC in diabetic patients, presumably because of their anti-inflammatory properties (El-Serag and Rudolph, 2007, Huether et al., 2005, Kawata et al., 2001, El-Serag et al., 2009). Interestingly, atorvastatin therapy has been shown to acutely decrease expression of JNK and other inflammatory cells in patients with abdominal aortic aneurysms (Kajimoto et al., 2009). That statin treatment reduces JNK expression may explain, in part, the decreased risk of HCC in diabetic patients who receive statin therapy, although this has yet to be proven. Further studies linking statins and JNK activity with NASH and HCC may enable the development of therapeutic drugs for the prevention and treatment of NASH as well as HCC secondary to NASH. There is a lack of randomized controlled trials on the benefits of bariatric surgery for patients with NASH and obese patients in terms of prevention of HCC (Chavez-Tapia et al., 2010). (Fig. 4)

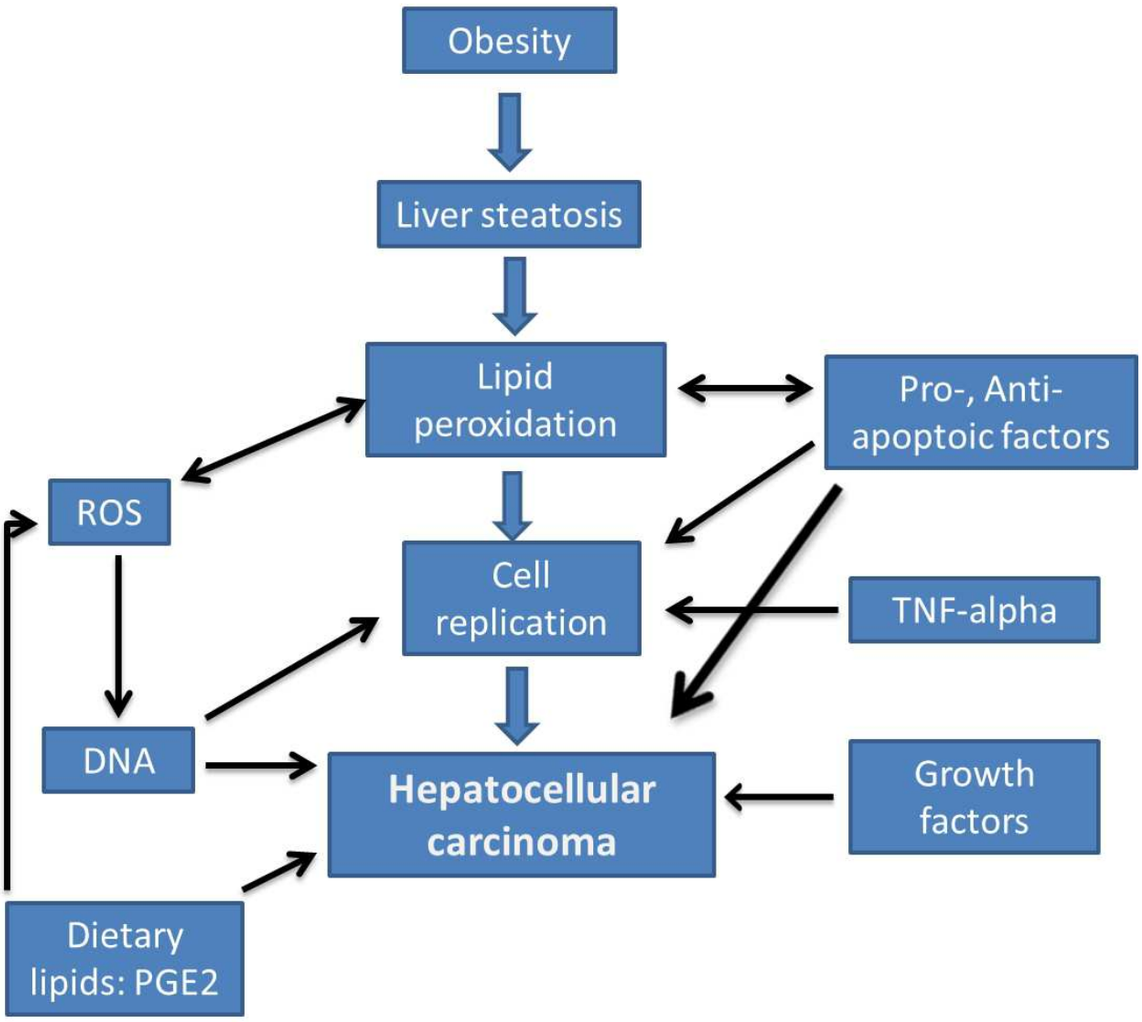


Fig. 4. Proposed progression of and significant factors in the pathogenesis of HCC in NAFLD. ROS, reactive oxygen species; DNA, deoxyribonucleic acid; PGE2, prostaglandin type 2; TNF-α, tumor necrosis factor-alpha

5. Conclusion

The most common cause of liver disease in developed countries is NAFLD, which includes NASH and its associated complications. The prevalence of NAFLD and NASH is likely higher than previously estimated and is associated with the growing epidemics of obesity and diabetes. There is increasing evidence showing that NASH may progress to HCC. The overall prevalence of HCC in patients with NAFLD remains low, although the incidence of HCC in developed countries is rising. HCC secondary to NASH typically develops when cirrhosis is present, although rare cases of HCC arising in cases of NASH without cirrhosis raise the possibility that carcinogenesis secondary to NAFLD can occur in the absence of advanced liver disease. The connection between NAFLD and progression to HCC is becoming clearer, and the increasing burden of NASH, diabetes mellitus, and obesity is becoming heavier. Community awareness of the potential for this disease to progress to

HCC is critical. Complications of NASH are expected to increase with the continuing epidemics of obesity and diabetes. Once a diagnosis of cirrhosis is made, screening for HCC should be pursued. Given recent epidemiological data on diabetes, thought should be given to the use of statins for NASH patients, particularly those with diabetes and hyperlipidemia. Further research is urgently needed to better elucidate the signaling pathways that result in HCC when insulin resistance is present. Studies evaluating potential targets for the treatment of NASH and HCC, including those targeting JNK activation, should be actively pursued.

6. References

Bellentani, S., Saccoccio, G., Masutti, F., Croce, L. S., Brandi, G., Sasso, F., Cristanini, G. & Tiribelli, C. 2000. Prevalence of and risk factors for hepatic steatosis in Northern Italy. *Annals of internal medicine,* 132, 112-7.

Bjorge, T., Stocks, T., Lukanova, A., Tretli, S., Selmer, R., Manjer, J., Rapp, K., Ulmer, H., Almquist, M., Concin, H., Hallmans, G., Jonsson, H., Stattin, P. & Engeland, A. 2010. Metabolic syndrome and endometrial carcinoma. *American journal of epidemiology,* 171, 892-902.

Bowers, K., Albanes, D., Limburg, P., Pietinen, P., Taylor, P. R., Virtamo, J. & Stolzenberg-Solomon, R. 2006. A prospective study of anthropometric and clinical measurements associated with insulin resistance syndrome and colorectal cancer in male smokers. *American journal of epidemiology,* 164, 652-64.

Brakenhielm, E., Veitonmaki, N., Cao, R., Kihara, S., Matsuzawa, Y., Zhivotovsky, B., Funahashi, T. & Cao, Y. 2004. Adiponectin-induced antiangiogenesis and antitumor activity involve caspase-mediated endothelial cell apoptosis. *Proceedings of the National Academy of Sciences of the United States of America,* 101, 2476-81.

Bugianesi, E., Mccullough, A. J. & Marchesini, G. 2005. Insulin resistance: a metabolic pathway to chronic liver disease. *Hepatology,* 42, 987-1000.

Bugianesi, E., Vanni, E. & Marchesini, G. 2007. NASH and the risk of cirrhosis and hepatocellular carcinoma in type 2 diabetes. *Current diabetes reports,* 7, 175-80.

Caldwell, S. H., Crespo, D. M., Kang, H. S. & Al-Osaimi, A. M. 2004. Obesity and hepatocellular carcinoma. *Gastroenterology,* 127, S97-103.

Caldwell, S. H., Oelsner, D. H., Iezzoni, J. C., Hespenheide, E. E., Battle, E. H. & Driscoll, C. J. 1999. Cryptogenic cirrhosis: clinical characterization and risk factors for underlying disease. *Hepatology,* 29, 664-9.

Calle, E. E. & Kaaks, R. 2004. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. *Nature reviews. Cancer,* 4, 579-91.

Calle, E. E., Rodriguez, C., Walker-Thurmond, K. & Thun, M. J. 2003. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *The New England journal of medicine,* 348, 1625-38.

Colangelo, L. A., Gapstur, S. M., Gann, P. H., Dyer, A. R. & Liu, K. 2002. Colorectal cancer mortality and factors related to the insulin resistance syndrome. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology,* 11, 385-91.

Cowey, S. & Hardy, R. W. 2006. The metabolic syndrome: A high-risk state for cancer? *The American journal of pathology,* 169, 1505-22.

Chavez-Tapia, N. C., Mendez-Sanchez, N. & Uribe, M. 2009. Role of nonalcoholic fatty liver disease in hepatocellular carcinoma. *Annals of hepatology : official journal of the Mexican Association of Hepatology,* 8 Suppl 1, S34-9.

Chavez-Tapia, N. C., Tellez-Avila, F. I., Barrientos-Gutierrez, T., Mendez-Sanchez, N., Lizardi-Cervera, J. & Uribe, M. 2010. Bariatric surgery for non-alcoholic steatohepatitis in obese patients. *Cochrane database of systematic reviews*, CD007340.

Chitturi, S., Abeygunasekera, S., Farrell, G. C., Holmes-Walker, J., Hui, J. M., Fung, C., Karim, R., Lin, R., Samarasinghe, D., Liddle, C., Weltman, M. & George, J. 2002. NASH and insulin resistance: Insulin hypersecretion and specific association with the insulin resistance syndrome. *Hepatology,* 35, 373-9.

Dignam, J. J., Polite, B. N., Yothers, G., Raich, P., Colangelo, L., O'connell, M. J. & Wolmark, N. 2006. Body mass index and outcomes in patients who receive adjuvant chemotherapy for colon cancer. *Journal of the National Cancer Institute,* 98, 1647-54.

Donohoe, C. L., Pidgeon, G. P., Lysaght, J. & Reynolds, J. V. 2010. Obesity and gastrointestinal cancer. *The British journal of surgery,* 97, 628-42.

El-Serag, H. B., Johnson, M. L., Hachem, C. & Morgana, R. O. 2009. Statins are associated with a reduced risk of hepatocellular carcinoma in a large cohort of patients with diabetes. *Gastroenterology,* 136, 1601-8.

El-Serag, H. B. & Rudolph, K. L. 2007. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. *Gastroenterology,* 132, 2557-76.

Giovannucci, E. 2007. Metabolic syndrome, hyperinsulinemia, and colon cancer: a review. *The American journal of clinical nutrition,* 86, s836-42.

Gomaa, A. I., Khan, S. A., Toledano, M. B., Waked, I. & Taylor-Robinson, S. D. 2008. Hepatocellular carcinoma: epidemiology, risk factors and pathogenesis. *World journal of gastroenterology : WJG,* 14, 4300-8.

Grundy, S. M., Brewer, H. B., Jr., Cleeman, J. I., Smith, S. C., Jr. & Lenfant, C. 2004. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation,* 109, 433-8.

Harrison, S. A. 2006. Liver disease in patients with diabetes mellitus. *Journal of clinical gastroenterology,* 40, 68-76.

Haydon, A. M., Macinnis, R. J., English, D. R. & Giles, G. G. 2006. Effect of physical activity and body size on survival after diagnosis with colorectal cancer. *Gut,* 55, 62-7.

Hirosumi, J., Tuncman, G., Chang, L., Gorgun, C. Z., Uysal, K. T., Maeda, K., Karin, M. & Hotamisligil, G. S. 2002. A central role for JNK in obesity and insulin resistance. *Nature,* 420, 333-6.

Huether, A., Hopfner, M., Baradari, V., Schuppan, D. & Scherubl, H. 2005. EGFR blockade by cetuximab alone or as combination therapy for growth control of hepatocellular cancer. *Biochemical pharmacology,* 70, 1568-78.

Ish-Shalom, D., Christoffersen, C. T., Vorwerk, P., Sacerdoti-Sierra, N., Shymko, R. M., Naor, D. & De Meyts, P. 1997. Mitogenic properties of insulin and insulin analogues mediated by the insulin receptor. *Diabetologia,* 40 Suppl 2, S25-31.

Jiang, J. & Torok, N. 2008. Nonalcoholic steatohepatitis and the metabolic syndrome. *Metabolic syndrome and related disorders,* 6, 1-7.

Johansen, D., Stocks, T., Jonsson, H., Lindkvist, B., Bjorge, T., Concin, H., Almquist, M., Haggstrom, C., Engeland, A., Ulmer, H., Hallmans, G., Selmer, R., Nagel, G., Tretli,

S., Stattin, P. & Manjer, J. 2010. Metabolic factors and the risk of pancreatic cancer: a prospective analysis of almost 580,000 men and women in the Metabolic Syndrome and Cancer Project. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology,* 19, 2307-17.

Kajimoto, K., Miyauchi, K., Kasai, T., Shimada, K., Kojima, Y., Shimada, A., Niinami, H., Amano, A. & Daida, H. 2009. Short-term 20-mg atorvastatin therapy reduces key inflammatory factors including c-Jun N-terminal kinase and dendritic cells and matrix metalloproteinase expression in human abdominal aortic aneurysmal wall. *Atherosclerosis,* 206, 505-11.

Kawata, S., Yamasaki, E., Nagase, T., Inui, Y., Ito, N., Matsuda, Y., Inada, M., Tamura, S., Noda, S., Imai, Y. & Matsuzawa, Y. 2001. Effect of pravastatin on survival in patients with advanced hepatocellular carcinoma. A randomized controlled trial. *British journal of cancer,* 84, 886-91.

Lazo, M. & Clark, J. M. 2008. The epidemiology of nonalcoholic fatty liver disease: a global perspective. *Seminars in liver disease,* 28, 339-50.

Li, D., Morris, J. S., Liu, J., Hassan, M. M., Day, R. S., Bondy, M. L. & Abbruzzese, J. L. 2009. Body mass index and risk, age of onset, and survival in patients with pancreatic cancer. *JAMA : the journal of the American Medical Association,* 301, 2553-62.

Ludwig, J., Viggiano, T. R., Mcgill, D. B. & Oh, B. J. 1980. Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. *Mayo Clinic proceedings. Mayo Clinic,* 55, 434-8.

Marceau, P., Biron, S., Hould, F. S., Marceau, S., Simard, S., Thung, S. N. & Kral, J. G. 1999. Liver pathology and the metabolic syndrome X in severe obesity. *The Journal of clinical endocrinology and metabolism,* 84, 1513-7.

Marchesini, G., Bugianesi, E., Forlani, G., Cerrelli, F., Lenzi, M., Manini, R., Natale, S., Vanni, E., Villanova, N., Melchionda, N. & Rizzetto, M. 2003. Nonalcoholic fatty liver, steatohepatitis, and the metabolic syndrome. *Hepatology,* 37, 917-23.

Mendez-Sanchez, N., Arrese, M., Zamora-Valdes, D. & Uribe, M. 2007. Current concepts in the pathogenesis of nonalcoholic fatty liver disease. *Liver international : official journal of the International Association for the Study of the Liver,* 27, 423-33.

Meyerhardt, J. A., Catalano, P. J., Haller, D. G., Mayer, R. J., Benson, A. B., 3rd, Macdonald, J. S. & Fuchs, C. S. 2003. Influence of body mass index on outcomes and treatment-related toxicity in patients with colon carcinoma. *Cancer,* 98, 484-95.

Moore, L. L., Bradlee, M. L., Singer, M. R., Splansky, G. L., Proctor, M. H., Ellison, R. C. & Kreger, B. E. 2004. BMI and waist circumference as predictors of lifetime colon cancer risk in Framingham Study adults. *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity,* 28, 559-67.

Motola-Kuba, D., Zamora-Valdes, D., Uribe, M. & Mendez-Sanchez, N. 2006. Hepatocellular carcinoma. An overview. *Annals of hepatology : official journal of the Mexican Association of Hepatology,* 5, 16-24.

Page, J. M. & Harrison, S. A. 2009. Nash and HCC. *Clinics in liver disease,* 13, 631-47.

Parkin, D. M., Bray, F., Ferlay, J. & Pisani, P. 2005. Global cancer statistics, 2002. *CA: a cancer journal for clinicians,* 55, 74-108.

Reaven, G. 2002. Metabolic syndrome: pathophysiology and implications for management of cardiovascular disease. *Circulation,* 106, 286-8.

Rector, R. S., Thyfault, J. P., Wei, Y. & Ibdah, J. A. 2008. Non-alcoholic fatty liver disease and the metabolic syndrome: an update. *World journal of gastroenterology : WJG,* 14, 185-92.

Renehan, A. G., Tyson, M., Egger, M., Heller, R. F. & Zwahlen, M. 2008. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet,* 371, 569-78.

Sjostrom, L., Gummesson, A., Sjostrom, C. D., Narbro, K., Peltonen, M., Wedel, H., Bengtsson, C., Bouchard, C., Carlsson, B., Dahlgren, S., Jacobson, P., Karason, K., Karlsson, J., Larsson, B., Lindroos, A. K., Lonroth, H., Naslund, I., Olbers, T., Stenlof, K., Torgerson, J. & Carlsson, L. M. 2009. Effects of bariatric surgery on cancer incidence in obese patients in Sweden (Swedish Obese Subjects Study): a prospective, controlled intervention trial. *The lancet oncology,* 10, 653-62.

Steffen, A., Schulze, M. B., Pischon, T., Dietrich, T., Molina, E., Chirlaque, M. D., Barricarte, A., Amiano, P., Quiros, J. R., Tumino, R., Mattiello, A., Palli, D., Vineis, P., Agnoli, C., Misirli, G., Boffetta, P., Kaaks, R., Rohrmann, S., Bueno-De-Mesquita, H. B., Peeters, P. H., May, A. M., Spencer, E. A., Allen, N. E., Bingham, S., Tjonneland, A., Halkjaer, J., Overvad, K., Stegger, J., Manjer, J., Lindkvist, B., Hallmanns, G., Stenling, R., Lund, E., Riboli, E., Gonzalez, C. A. & Boeing, H. 2009. Anthropometry and esophageal cancer risk in the European prospective investigation into cancer and nutrition. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology,* 18, 2079-89.

Stocks, T., Borena, W., Strohmaier, S., Bjorge, T., Manjer, J., Engeland, A., Johansen, D., Selmer, R., Hallmans, G., Rapp, K., Concin, H., Jonsson, H., Ulmer, H. & Stattin, P. 2010. Cohort Profile: The Metabolic syndrome and Cancer project (Me-Can). *International journal of epidemiology,* 39, 660-7.

Tanaka, S., Mohr, L., Schmidt, E. V., Sugimachi, K. & Wands, J. R. 1997. Biological effects of human insulin receptor substrate-1 overexpression in hepatocytes. *Hepatology,* 26, 598-604.

Trevisan, M., Liu, J., Muti, P., Misciagna, G., Menotti, A. & Fucci, F. 2001. Markers of insulin resistance and colorectal cancer mortality. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology,* 10, 937-41.

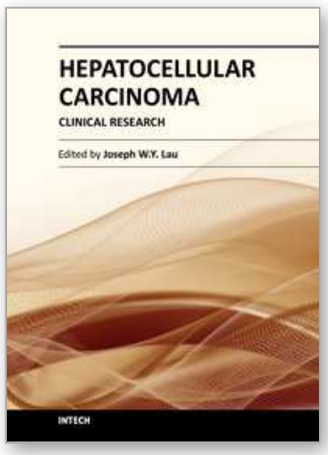
Ukkola, O. & Santaniemi, M. 2002. Adiponectin: a link between excess adiposity and associated comorbidities? *Journal of molecular medicine,* 80, 696-702.

Wang, Y., Jacobs, E. J., Patel, A. V., Rodriguez, C., Mccullough, M. L., Thun, M. J. & Calle, E. E. 2008. A prospective study of waist circumference and body mass index in relation to colorectal cancer incidence. *Cancer causes & control : CCC,* 19, 783-92.

WCR, F. 2007. Food, nutrition, physical activity and the prevention of cancer: a global perspective. *American Institute for Cancer Research,* 2nd edition.

Yamada, T., De Souza, A. T., Finkelstein, S. & Jirtle, R. L. 1997. Loss of the gene encoding mannose 6-phosphate/insulin-like growth factor II receptor is an early event in liver carcinogenesis. *Proceedings of the National Academy of Sciences of the United States of America,* 94, 10351-5.

Yang, S., Zhu, H., Li, Y., Lin, H., Gabrielson, K., Trush, M. A. & Diehl, A. M. 2000. Mitochondrial adaptations to obesity-related oxidant stress. *Archives of biochemistry and biophysics,* 378, 259-68.



Hepatocellular Carcinoma - Clinical Research
Edited by Dr. Joseph W.Y. Lau

ISBN 978-953-51-0112-3
Hard cover, 330 pages
Publisher InTech
Published online 02, March, 2012
Published in print edition March, 2012

This book covers the clinical aspects of hepatocellular carcinoma. This book is a compendium of papers written by experts from different parts of the world to present the most up-to-date knowledge on the clinical aspects of hepatocellular carcinoma. This book is divided into three sections: (I) Diagnosis / Differential Diagnosis; (II) Surgical Treatment; (III) Non-surgical Treatment. There are 19 chapters covering topics from novel diagnostic methods to hepatic lesions mimicking hepatocellular carcinoma, from laparoscopic liver resection to major hepatectomy without allogeneic blood transfusion, from molecular targeted therapy to transarterial radioembolization, and from local ablative therapy to regional therapy. This volume is an important contribution to the clinical management of patients with hepatocellular carcinoma. The intended readers of this book are clinicians who are interested in hepatocellular carcinoma, including hepatologists, liver surgeons, interventional and diagnostic radiologists, pathologists and epidemiologists. General surgeons, general physicians, trainees, hospital administrators, and instruments and drug manufacturers will also find this book useful as a reference.

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following:

Misael Uribe, Jesús Román-Sandoval, Norberto C. Chávez-Tapia and Nahum Méndez-Sánchez (2012). The Relationship Between Nonalcoholic Fatty Liver Disease and Hepatocellular Carcinoma, Hepatocellular Carcinoma - Clinical Research, Dr. Joseph W.Y. Lau (Ed.), ISBN: 978-953-51-0112-3, InTech, Available from: http://www.intechopen.com/books/hepatocellular-carcinoma-clinical-research/the-relationship-between-nonalcoholic-fatty-liver-disease-and-hepatocellular-carcinoma

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen