Hepatitis C Virus*

Known to be a human carcinogen
First Listed in the *Eleventh Report on Carcinogens* (2004)

Carcinogenicity

Hepatitis C virus (HCV) is *known to be a human carcinogen* based on sufficient evidence from studies in humans. Numerous cohort and case-control studies conducted in populations differing by race or ethnicity and in various geographical locations have demonstrated that chronic HCV infection causes a malignant tumor of the liver (hepatocellular carcinoma) (NTP 2003). A meta-analysis (statistical overview) of 32 studies published between 1993 and 1997 reported a summary odds ratio of 11.5 (95% confidence interval = 9.9 to 13.3) (Donato *et al.* 1998), meaning that patients with chronic hepatitis C infection were 11.5 times as likely as uninfected individuals to develop hepatocellular carcinoma. These studies generally used relatively sensitive and specific serological markers (anti-HCV antibodies or HCV RNA in the blood) to assess chronic HCV infection. The association between HCV and hepatocellular carcinoma was independent of hepatitis B virus (HBV) infection (i.e., the association was clearly present when subjects did not include carriers of HBV), and it remained when studies controlled for potential confounders such as the use of alcohol or tobacco (NTP 2003). A number of recent studies have investigated whether some genotypes of HCV may be more potent carcinogens than others. Although the results are not entirely consistent, the evidence generally supports the hypothesis that HCV genotype 1b is more strongly associated with hepatocellular carcinoma than are other HCV genotypes (NTP 2003). A number of recent case-control studies and one cohort study have linked HCV infection to increased risk of B-cell lymphoma (cancer of the B lymphocytes, a type of white blood cell); however, many of these studies had relatively small sample sizes, and all were hospital-based (NTP 2003). In 1994, the International Agency for Research on Cancer classified HCV as carcinogenic to humans (Group 1) based on sufficient evidence of carcinogenicity in humans (IARC 1994).

Studies of HCV in experimental animals are limited, because the only animals known to be susceptible to HCV infection are chimpanzees and tree shrews. Hepatocellular carcinoma has been reported in one chimpanzee that had been infected with HCV for seven years (Linke *et al.* 1987, Muchmore *et al.* 1988, Xie *et al.* 1998). Hepatocellular carcinoma also developed in a few lines of transgenic mice carrying HCV genes; the cancer was observed primarily in males producing either the HCV core protein or low levels of the complete HCV polyprotein (components of the HCV virus, as discussed under "Properties," below) (Moriya *et al.* 1998, Koike *et al.* 2002, Lerat *et al.* 2002).

Additional Information Relevant to Carcinogenicity

The mechanism(s) by which HCV causes liver cancer has not been determined. HCV may cause cancer directly or indirectly, the latter as a result of liver inflammation and regeneration associated with chronic hepatitis. As an RNA virus, HCV does not integrate into the DNA of the hepatitis patient's cells; therefore, direct mechanisms of carcinogenesis would most likely involve the effects of viral protein on cell growth (Fong *et al.* 1991). The HCV core protein is the current leading suspect, based on its role in regulating cellular promoters of gene expression and proto-oncogenes (genes potentially associated with cancer) and on the studies in transgenic mice mentioned above. Studies with cell cultures have shown that the HCV core protein cooperates with the *ras* oncogene to transform primary rat embryo fibroblasts to a tumorigenic phenotype (a cell type that can proliferate to form tumors) (Ray *et al.* 1996). The roles of other HCV proteins in causing liver cancer remain largely unexplored. HCV-related liver cancer almost always arises in the presence of cirrhosis of the liver, suggesting the importance of indirect mechanisms such as inflammation, fibrosis (formation of fibrous tissue), and hepatocyte (liver-cell) regeneration in the development of cancer (Craig *et al.* 1991, Bralet *et al.* 2000). It is hypothesized that cirrhosis results in hepatocellular carcinoma when nodules within the cirrhotic liver become dysplastic (i.e., precancerous cells develop within the nodules) (Takayama *et al.* 1990). Several studies (though not all) have reported an association between HCV-associated liver cancer and β-catenin gene mutations (which are associated with other types of cancer); however, these studies were based on small numbers of tumors (Huang *et al.* 1999, Laurent-Puig *et al.* 2001, Ueta *et al.* 2002).

Properties

HCV is an enveloped RNA virus, which causes most non-B viral hepatitis that is transmitted parenterally (i.e., by injection, transfusion, or other contact with body fluids). It is a member of the *Flaviviridae* family of viruses and has a particle size of approximately 50 nm in diameter (He *et al.* 1987). The positive-sense RNA genome (9,600 nucleotides) codes for production of a polyprotein (3,000 amino acids); enzymes produced by the virus and the host cell then cleave the polyprotein into the smaller structural and nonstructural proteins that make up the mature virus particle. The structural proteins, which are incorporated into the viral envelope, consist of the core (nucleocapsid) protein and two glycoproteins (E1 and E2). The nonstructural proteins (NS2, NS3, NS4A, NS4B, NS5A, and NS5B) serve as enzymes essential for protein processing and RNA replication; their functions include protease, nucleotide triphosphatase, RNA helicase, and RNA polymerase activity (Rosenberg 2001).

Replication of HCV often results in random mutations that are not corrected by the RNA polymerase because it lacks a proofreading function. As a result, the genomes of HCV strains show extensive variability. However, some regions of the genome are more variable than others, and classification of HCV genotypes is based on differences in the less variable regions of the genome. HCVs can be divided into six phylogenetically distinct groups designated as clades (groups of genotypes that share a common ancestor). Within the clades, a number of subtypes (individual genotypes) have been defined (Simmonds *et al.* 1993, Bukh *et al.* 1995, Simmonds 1995, Robertson *et al.* 1998). All known types of HCV have the potential to cause serious liver disease.

Infection, Prevention, and Treatment

HCV can cause acute or chronic hepatitis. Acute hepatitis C usually is characterized by elevated or fluctuating levels of alanine aminotransferase (ALT, a liver enzyme). People with acute hepatitis C either have no symptoms (60% to 70%) or have mild clinical disease symptoms: 10% to 20% have nonspecific symptoms, such as nausea, vomiting, anorexia, or abdominal pain, and 20% to 30% may become jaundiced. The average time from exposure to symptoms is six to seven weeks (MMWR 1998). Most people infected with HCV (75% to 80%) go on to develop chronic hepatitis C. Individuals with chronic hepatitis C are the source for all new infections and are at increased risk for chronic liver disease, cirrhosis, and liver cancer (Bonkovsky and Mehta 2001). Chronic hepatitis is associated with chronic liver injury and inflammation. Liver injury appears to be a result of the patient's immune reaction to the virus, rather than damage by the virus itself. Chronic infection usually results in progressive fibrosis of the liver, which may progress to cirrhosis and other disease states. In the United States, HCV is the leading cause of liver disease and may account for 8,000 to 10,000 deaths per year. As of 1996 most HCV-infected individuals were between 30 and 49 years of age; thus, the number of deaths could substantially increase during the next 20 to 30 years, as

this group reaches the age at which complications from liver disease usually occur (MMWR 1998, Alter *et al.* 1999).

HCV infections are prevented by screening of the blood supply and reduction of contact with potentially contaminated fluids in health-care settings. The Occupational Safety and Health Administration has established a bloodborne pathogens standard, based on the concept of universal precautions, which requires that body fluids and materials be treated as infectious (OSHA 1992). Currently, HCV is treated with interferon-based therapies, and no vaccine is available.

Detection

HCV infection usually is confirmed by detection of antibodies against HCV proteins or by detection of HCV RNA. Anti-HCV antibodies are detected by serological assays, which have become more sensitive and specific. HCV RNA usually is detected by tests based on the polymerase chain reaction.

Exposure

The major risk factor for infection is illegal intravenous drug use, which accounts for 60% of acute HCV infections in adults. Since the screening of blood and blood products for HCV began in the 1990s, blood transfusion has accounted for only a small percentage of adult HCV cases (about 3%). Other routes of transmission include sexual, perinatal (from mother to infant at birth), familial (at low rates), and through health-care practices, including transmission by contaminated equipment or supplies, from patient to patient (at low rates), and through occupational exposure (at low rates). In U.S. surveillance studies from 1983 to 1996, no epidemiologic risk factors were identified for at least 10% of the cases of acute hepatitis C (Alter *et al.* 1999, Major *et al.* 2001).

The worldwide prevalence of HCV seropositivity (i.e., the percent of the population infected with HCV) is approximately 3% (170 million individuals); however, the prevalence varies geographically. Reported prevalence is very low (0.01% to 0.1%) in the United Kingdom and Scandinavia; low (less than 0.5%) in Western Europe, North America, Australia, most of Central and South America, and parts of Africa; intermediate (1% to 5%) in Eastern Europe, the Middle East, the Mediterranean, and parts of Africa and Asia; and highest (17% to 26%) in Egypt. Prevalence rates are unknown for much of Africa and parts of South America. (Wasley and Alter 2000).

In the United States, approximately 3 to 4 million people are infected with HCV (Alter *et al.* 1999). However, the annual number of newly acquired HCV infections declined from 180,000 in the mid 1980s to 28,000 by 1995, probably as a result of testing of blood donors and decreased numbers of cases among intravenous drug users (Alter 1997).

Regulations

OSHA

Any incidents that result in a diagnosis of hepatitis C must be recorded

Comprehensive regulations have been developed for employers to develop, and adhere to, exposure control plans for bloodborne pathogens

Public Health Service (PHS)

Rules have been set for packaging and transporting diagnostic specimens and products for hepatitis C-associated materials

*No separate CAS registry number is assigned to hepatitis C virus.

REFERENCES

Alter, M. J. 1997. Epidemiology of hepatitis C. Hepatology 26(3 Suppl 1): 62S-65S.

Alter, M. J., D. Kruszon-Moran, O. V. Nainan, G. M. McQuillan, F. Gao, L. A. Moyer, R. A. Kaslow and H. S. Margolis. 1999. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. N Engl J Med 341(8): 556-62.

Bonkovsky, H. L. and S. Mehta. 2001. Hepatitis C: a review and update. J Am Acad Dermatol 44(2): 159-82.

Bralet, M. P., J. M. Regimbeau, P. Pineau, S. Dubois, G. Loas, F. Degos, *et al.* 2000. Hepatocellular carcinoma occurring in nonfibrotic liver: epidemiologic and histopathologic analysis of 80 French cases. Hepatology 32(2): 200-4.

Bukh, J., R. H. Miller and R. H. Purcell. 1995. Genetic heterogeneity of hepatitis C virus: quasispecies and genotypes. Semin Liver Dis 15(1): 41-63.

Craig, J. R., E. C. Klatt and M. Yu. 1991. Role of cirrhosis and the development of HCC: Evidence from histologic studies and large population studies. In Etiology, Pathology, and Treatment of Hepatocellular Carcinoma in North America. E. Tabor, A. M. Di Bisceglie and R. H. Purcell, eds.: The Woodland: The Portfolio Publishing. 177-190.

Donato, F., P. Boffetta and M. Puoti. 1998. A meta-analysis of epidemiological studies on the combined effect of hepatitis B and C virus infections in causing hepatocellular carcinoma. Int J Cancer 75(3): 347-54.

Fong, T. L., M. Shindo, S. M. Feinstone, J. H. Hoofnagle and A. M. Di Bisceglie. 1991. Detection of replicative intermediates of hepatitis C viral RNA in liver and serum of patients with chronic hepatitis C. J Clin Invest 88(3): 1058-60.

He, L. F., D. Alling, T. Popkin, M. Shapiro, H. J. Alter and R. H. Purcell. 1987. Determining the size of non-A, non-B hepatitis virus by filtration. J Infect Dis 156(4): 636-40.

Huang, H., H. Fujii, A. Sankila, B. M. Mahler-Araujo, M. Matsuda, G. Cathomas and H. Ohgaki. 1999. Beta-catenin mutations are frequent in human hepatocellular carcinomas associated with hepatitis C virus infection. Am J Pathol 155(6): 1795-801.

IARC. 1994. Hepatitis viruses. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 59. Lyon, France: International Agency for Research on Cancer.

Koike, K., K. Moriya and S. Kimura. 2002. Role of hepatitis C virus in the development of hepatocellular carcinoma: transgenic approach to viral hepatocarcinogenesis. J Gastroenterol Hepatol 17(4): 394-400.

Laurent-Puig, P., P. Legoix, O. Bluteau, J. Belghiti, D. Franco, F. Binot, *et al.* 2001. Genetic alterations associated with hepatocellular carcinomas define distinct pathways of hepatocarcinogenesis. Gastroenterology 120(7): 1763-73.

Lerat, H., M. Honda, M. R. Beard, K. Loesch, J. Sun, Y. Yang, *et al.* 2002. Steatosis and liver cancer in transgenic mice expressing the structural and nonstructural proteins of hepatitis C virus. Gastroenterology 122(2): 352-65.

Linke, H. K., M. F. Miller, D. A. Peterson, E. Muchmore, R. R. Lesniewski, R. J. Carrick, G. D. Gagne and H. Popper. 1987. Documentation of non-A, non-B hepatitis in a chimpanzee with hepatocellular carcinoma. In Hepadna Viruses. W. Robinson, K. Koike and H. Well, eds. New York: Alan R. Liss. 357-370.

Major, M., B. Rehermann and S. M. Feinstone. 2001. Hepatitis C viruses. In Fields Virology. D. M. Knipe and P. M. Howley, eds. Philadelphia, PA: Lippincott Williams & Wilkins. pp. 1127-1161.

MMWR. 1998. Recommendations for Prevention and control of Hepatitis C Virus (HCV) Infection and HCV-Related Chronic Disease. Atlanta, GA: Morbidity and Mortality Weekly Report, U.S. Department of Health and Human Services.

Moriya, K., H. Fujie, Y. Shintani, H. Yotsuyanagi, T. Tsutsumi, K. Ishibashi, *et al.* 1998. The core protein of hepatitis C virus induces hepatocellular carcinoma in transgenic mice. Nat Med 4(9): 1065-7.

Muchmore, E., H. Popper, D. A. Peterson, M. F. Miller and H. M. Lieberman. 1988. Non-A, non-B hepatitis-related hepatocellular carcinoma in a chimpanzee. J Med Primatol 17(5): 235-46.

NTP. 2003. Report on Carcinogens Background Document for Hepatitis C. National Toxicology Program. http://ntp-server.niehs.nih.gov/newhomeroc/roc11/HCV_RG2Public.pdf.

OSHA. 1992. Bloodborne pathogens final standard, Fact Sheet No. OSHA 92-46. U.S. Department of Labor, Occupational Safety and Health Adminstration. http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=FACT_SHEETS&p_id=139.

Ray, R. B., L. M. Lagging, K. Meyer and R. Ray. 1996. Hepatitis C virus core protein cooperates with *ras* and transforms primary rat embryo fibroblasts to tumorigenic phenotype. J Virol 70(7): 4438-43.

Robertson, B., G. Myers, C. Howard, T. Brettin, J. Bukh, B. Gaschen, *et al.* 1998. Classification, nomenclature, and database development for hepatitis C virus (HCV) and related viruses: proposals for standardization. International Committee on Virus Taxonomy. Arch Virol 143(12): 2493-503.

Rosenberg, S. 2001. Recent advances in the molecular biology of hepatitis C virus. J Mol Biol 313(3): 451-64.

Simmonds, P. 1995. Variability of hepatitis C virus. Hepatology 21(2): 570-83.

Simmonds, P., E. C. Holmes, T. A. Cha, S. W. Chan, F. McOmish, B. Irvine, *et al.* 1993. Classification of hepatitis C virus into six major genotypes and a series of subtypes by phylogenetic analysis of the NS-5 region. J Gen Virol 74(Pt 11): 2391-9.

Takayama, T., M. Makuuchi, S. Hirohashi, M. Sakamoto, N. Okazaki, K. Takayasu, *et al.* 1990. Malignant transformation of adenomatous hyperplasia to hepatocellular carcinoma. Lancet 336(8724): 1150-3.

Ueta, T., M. Ikeguchi, Y. Hirooka, N. Kaibara and T. Terada. 2002. Beta-catenin and cyclin D1 expression in human hepatocellular carcinoma. Oncol Rep 9(6): 1197-203.

Wasley, A. and M. J. Alter. 2000. Epidemiology of hepatitis C: geographic differences and temporal trends. Semin Liver Dis 20(1): 1-16.

Xie, Z. C., J. I. Riezu-Boj, J. J. Lasarte, J. Guillen, J. H. Su, M. P. Civeira and J. Prieto. 1998. Transmission of hepatitis C virus infection to tree shrews. Virology 244(2): 513-20.