Hepatitis C Virus

CAS No.: none assigned

Known to be a human carcinogen

First listed in the *Eleventh Report on Carcinogens* (2004)

Also known as HCV

Carcinogenicity

Hepatitis C virus (HCV) is *known to be a human carcinogen* based on sufficient evidence from studies in humans.

Cancer Studies in Humans

In epidemiological research, 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 liver cancer (hepatocellular carcinoma) (NTP 2003). A meta-analysis 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 HCV 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, and it remained when studies controlled for potential confounders such as the use of alcohol or tobacco. 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. A number of recent case-control studies and one cohort study have linked HCV infection to increased risk of B-cell lymphoma; 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 based on sufficient evidence of carcinogenicity in humans (IARC 1994).

Cancer Studies in Experimental Animals

Studies of HCV in experimental animals are limited, because the only animals known to be susceptible to HCV infection are chimpanzees and tree shrews. Liver cancer (hepatocellular carcinoma) was reported in one chimpanzee that had been infected with HCV for seven years, but not in HCV-infected tree shrews (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).

Studies on Mechanisms of Carcinogenesis

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 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 (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, and hepatocyte 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 about 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 transaminase (ALT). 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 infection can be 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 route of HCV transmission is through contaminated blood. 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, 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 epidemiological 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 based on published studies that used both enzyme immunoassays and supplemental testing is about 3% (170 million individuals. Prevalence varies geographically, ranging from 0.01% to 0.1% in the United Kingdom and Scandinavia to 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, the third National Health and Nutrition Examination Survey (NHANES III, conducted from 1988 to 1994) found that about 3 million to 4 million people were infected with HCV, based on anti-HCV assays (Alter *et al.* 1999). However, the annual incidence of HCV infection 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). Based on NHANES data for 1999 through 2002, about 4.1 million people (95% confidence interval = 3.4 million to 4.9 million) were anti-HCV-positive, with peak prevalence (4.3%) among individuals aged 40 to 49 years. A large percentage (85.1%) of anti-HCV-positive individuals aged 20 to 59 years had a risk factor such as abnormal serum ALT levels, a history of injection drug use, or a history of blood transfusion before 1992 (Armstrong *et al.* 2006).

Regulations

Food and Drug Administration (FDA)

Regulations have been established to guard against the spread of hepatitis C through donation of blood, serum, and human immune globulin, including requirements for donor screening, product testing, and product labeling.

Regulations in 21 CFR 1270 and 1271 prescribe procedures, including donor screening and tissue testing, to ensure that tissues intended for human transplant or other human cells, tissues, and cellular and tissue-based products are free of hepatitis C.

Each donation of blood or blood product to be used in preparing a biological product shall be tested for the presence of hepatitis C surface antigen.

Occupational Safety and Health Administration (OSHA)

All work-related needlestick injuries and cuts from sharp objects that are contaminated with another person's blood or other potentially infectious material must be recorded.

First-aid training program trainees must have adequate instruction in the value of universal precautions for preventing infectious diseases.

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

Public Health Service (PHS)

Regulations have been established to control the spread of hepatitis from hemodialysis treatment.

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