telomerase is inactive liver but the activation occurs during transition of pre-malignant lesions to HCC (Luedde T, et al. 2007).

Hygiene of HCV transmission

Hepatitis C virus is greater fluently broadcast by direct percutaneous exposure to contamination blood, such as through blood transfusion from contamination donors and giving of contaminated accessories among injecting drug consumers .(Mansell CJ. Et al.1995) Haemodialysis patients and healthcare workers who are apparent to needle stick injuries in a career setting are also at risk from uncovering to infectious blood, as are baby born to infected women. In addition, HCV can be communicated by sexual or domestic exposure to a contaminated contact; however, the efficiency of transposal in these settings appears to be short.

Despite an common popularity of HCV infection of 4–5% has been found among family and sex contacts of infected guy in a number of analysis, most of these analysis were preside over in countries where transmission of HCV infection may be affiliate with common display to contaminated accessories used in acceptable and non acceptable medical agenda in the past . (Alter MJ et al. 1998) There are still huge break in our understanding of the al round epidemiology of HCV. The comparative addition of the various sources of infection has infrequently been investigated in population-based epidemiological studies in most terrestrial areas. In addition, many ignored questions are living about the roles of risk factors and way of life circumstances that may be linked with HCV spread in different areas of the world. Epidemiological studies on the act of inherent risk factors, such as medical processes, injections for medications and booster dose, injections used outside of medical background, tattooing, and incision methods, have shown wide terrestrial variations with basic implications for local populations and inherent prevention and control programmes. As HCV can be sexually send (although not often between healthy persons), the role of co infection with other sexually communicated diseases, such as HIV/AIDS, need to be additional studied, specifically for those that can result in open genital rash, such as gonorrhea infection, scabies and herps. **(**D. Lavanchy et al. 2010)

Diagnosis

The patients (atleast 70 percent) with infection of HCV are non-symptomatic, but when signs do occur, they are not specific and include weakness, weight loss fatigue, myalgias, arthralgias nausea and anorexia (Wasley et al. 2008: Koff, R.S.1981).). Laboratory tests or symptoms of cirrhosis should prompt HCV antibody testing, that followed by confirmatory tests (Chou R et al. 2004).SevreHCV infection caused to cirrhosis in almost 10 to 20 percent patients, by increasing the risk of chronic liver disease complications, also including hypertension, hemorrhage, ascites and hepatocellular carcinoma (Chou R et al., 2004: Jou JH et al. 2008).

Diagnostic tests for the detection of HCV infection

The diagnostic test used for HCV infection detection isthe recombinant immunoblotassay, HCV antibody enzyme immunoassay and quantitative HCV RNA polymerase chain reaction (PCR). The common diagnostic tests are listed in Table 2 (Ghany MG et al. 2009;) Most commonly used assay for HCV detection antibodies is the immunoassay of enzyme. Positive enzyme immunoassay must be used by a confirmatory test. It gives false positive results when it is used in the low-risk groups (González V, et al. 2008). For HCV antibody detection a saliva-based test may be available soon.

The Recombinant immunoblot assay that is a confimatory test for immunoassay of enzyme, sense antibodies to individual antigens of HCV. (Scott JD and Gretch DR. 2007).

Laboratory Test

There are two classes of assays that are used in the detection and management for HCVinfection: The serologic assay sense the specific antibody to hepatitis C virus (anti-HCV) and the molecular assays detect the nucleic acid of virus. Both of these have no role in the estimation of severity of the disease or its progression (Ghany, M. Get al. 2009).

Serologic Assays

The tests that detect anti-HCV are used both to detect and screen HCV infection. Anti-HCV can be detected in theplasma or serum by using a number of immunoassays. There are two enzyme immunoassays (EIAs) are recommended by the U.S. Food and Drug Administration (FDA) for clinical use, HCV Version 3.0 ELISA (Ortho-Clinical Diagnostics, Raritan, NJ), Abbott HCV EIA 2.0 (Abbott Laboratories, Abbott Park, IL) and as well as one enhanced chemiluminescence immunoassay (CIA) VITROS Anti-HCV assay, (Ortho-Clinical Diagnostics, Specificity of recent EIAs for anti-HCV is higher than 99% (Colin C, at al. 2001).

Molecular Assays

Qualitative assays have been more efficient than quantitative assays. There is no need for the qualitative assay due to the availability of transcription-mediated amplification(TMA) assays and real time polymerase chain reaction (PCR)- based assays with the sensitivity of 10-50 IU/mL (Stramer SL, et al. 2000; Scott JD and Gretch DR. 2007). The highly detectable assay with this lesser detection limit is considered appropriate for therapy during monitoring., With the specificity range of 98% to 99%, all the easily available assays have excellent., The World Health Organization in 1997 formed the first International standard for HCV RNA nucleic acid technology (Saldanha J, et al. 1999)and IU rather than copies of virus is now most commonly used unit to find test results (Pawlotsky JM, et al. 2000).

Utility of the Liver Biopsy and Noninvasive

Tests of Fibrosis

Three main reasons for doing a liver biopsy: it gives beneficial information on the current status of liver injury, it detect the features that are useful in the decision for therapy and it can be showed severe fibrosis or cirrhosis that is necessary for hepatocellular carcinoma (HCC) and viruses screening. Liver biopsy is performed for stage and grade of the liver injury, but it also gives information on other histopathological features that may have facing proliferation of liver disease (Kleiner DE. 2005). Grade defines the limit of necro-inflammatory activity, while the stage marked the limit of fibrosis or the occurrence of cirrhosis. There are many scoring systems have been recieved, the most common being the French METAVIR, the Batts-Ludwig, the International Association for the Study of the Liver (IASL) and the Ishak Scoring systems (Scheuer PJ. 1991)

Signs and Symptoms

The symptoms of hepatitis C tend to be intermittent, mild and non specific. The most common symptom of chronic hepatitis C is fatigue which can be described as lethargy, malaise, lack of stamina and the patient's fatiguability rate is high. The other symptoms which are less frequent include feverishness, nausea, weight loss, muscle aches and poor appetite. There is a decrease in the quality of life of patient because these symptoms are rarely incapacitating. The severity

of disease depends upon the symptoms. The asymptomatic person has less severe disease than symptomatic. Due to non specificity of the symptoms of HCV it is very difficult to define what percentage of people were symptomatic but it is always less than 25%. According to a study in which 108 patients participated 70% had one or more of six symptoms (fatigue, nausea, abdominal pain, anorexia, itching and dark urine). 62% patients showed a most common symptom which was fatigue. Other symptoms such as abdominal pain, itching and dark urine were also significantly present but in a minority of patients (Hoofnagle 1997).

Treatment

Sustained virologic response is the delegate counter used by most studies to assess the effectiveness of therapy and is correlate with bettered outcomes, such as low likelihood of viral relapse, reduced mortality, and reduced exposure of cirrhosis and hepatocellular carcinoma.(Mangia A, Minerva N and Bacca D, et al. 2008). All persons with chronic HCV infection should be examined applicant for treatment; however, several factors power the decision to continue with therapy. Treatment for HCV infection is widely acknowledged in persons at least 18 years of age who are consenting to be treated and to conform to treatment necessity, with abnormal serum alanine transaminase (ALT) principles, denoting liver fibrosis or committed cirrhosis, and normal renal function, and without anemia or neutropenia. Before starting therapy, diagnostic blood work should be achieved, including a complete blood count, complete metabolic board, and measurement of thyroid-stimulating hormone level, because interferon therapy is affiliated with leukopenia, thrombocytopenia, and autoimmune thyroiditis. Human being with chronic HCV infection and anemia, renal deficiency, autoimmune hepatitis, de compensated cirrhosis, pregnancy, caustic cardiopulmonary disease, unrestrained major abasement, or unrestrained hyperthyroidism are not good applicant for treatment.(Strader DB, Wright T and Thomas DL et al. 2004)

Blood urea nitrogen and serum creatinine levels should be assess because ribavirin (Rebetol) is renally discharged and should be used with carefulness in patients with renal efficiency. (Koff RS et al. 2008) Genotype assimilation aid in predicting reaction to treatment because persons with genotype 1 have lower degree of reaction to therapy than patients with genotypes 2 and liver biopsy to determine disease cruelty may be thought out when determining whether to initiate treatment in patients with chronic HCV infection and actively normal transaminase levels or with relative conflict to therapy, or for predictive purposes (e.g., in patients with genotype 1). (Scott JD et al. 2007)

Options Treatment

Approved therapy for the treatment of chronic HCV contamination is pegylated interferon and ribavirin.,38(Mc Hutchison JG et al. 2001) Oral ribavirin monotherapy is not productive for encourage sustained virologic response (relative risk = 1.01; 95% confidence interval, 0.96 to 1.07).(Brok J et al. 2009)

There are two conceptions of pegylated interferon that arecertified for HCV therapy: pegylated interferon alfa-2a (Pegasys) and pegylated interferon alfa-2b (Pegintron). Sustained virologic response ratio for pegylated interferon monotherapy and pegylated interferon plus ribavirin is 25 to 39 percent and 54 to 60 percent,The assessable HCV RNA level is used to evaluate response to therapy and as a adviser to blow off treatment. A negative viral charge test after four weeks of therapy is divining of sustained virologic response. (Ghany MG and Strader DB et al. 2009)

Opposite to failure to accomplish a 100-fold reduction in viral load by week 12 of therapy has a strong negative predictive value for sustained virologic response and convey advice that treatment is likely useless and should be blocked. (Schade, R. R. 2010)

Medical care

In contrast to hepatitis A and B, advancement to chronic hepatitis C is plenty greater common. The conclusive object of hepatitis C treatment is blockage of hepatocellular carcinoma (HCC).The good action to decrease the long-term risk of HCC is to accomplish sustained virological response (SVR).(Messori and Andrea et al. 2015) SVR is defined as an imponderable viral load at 12 weeks after cure close and display cure.At present available treatments involve indirect and direct acting antiviral drugs. The indirect acting anti virals involve pegylated interferon (PEG IFN) and ribavirin (RBV), which in mixture have historically been the support of therapy for HCV. Continuation and reaction to these treatments alter based on genotype. (Stephen D et al. 2015)

Genotype 1 (GT1), which is the most prevalent genotype in the United States and around the world, can now be cured with a direct acting antiviral regimen. (Raymond T et al. 2015) The American Association for the Study of Liver Diseases and the Infectious Diseases Society of America (AASLD-IDSA) advise antiviral treatment for all patients with chronic hepatitis C infection other than for those with extra chronic medical circumstances that brink their life assurance. (Guidance Panel et al. 2015).

Strategies to prevent and control hepatitis C

Scope to avert and mastery hepatitis C is confined. The addition of a vaccine is not likely in the account able future, and immune globulin is not active for post-exposure prophylaxis. At present available prevention measures involve primary prevention activities that decrease the risk of flattering contaminated with HCV and secondary prevention activities that decrease the chance taken for chronic disease in HCV-contaminated creature.(Locarnini SA et al. 1995)

Primary prevention

From a worldwide perspective, the greatest impact on the disease stress affiliated with HCV contamination will likely be accomplished by focusing exertion on primary prevention. Primary prevention action can reduce or remove the risk of transposable from

(1) No socomial exposures, involve transfusion of blood and blood amount, and other percutaneous exposures to blood such as through use of unsterile medical and dental accessories and un intensional needle sticks

(2) Giant risk practices (e.g. injecting drug use, unprotected sex with multiple partners).

The primary methods to prevent HCV transmission from blood and blood products are absolute of donors who are appreciate to be at increased risk of germs by history or who have serologic markers of HCV communicability. Extraneous, plasma derivatives (e.g. clotting factor concentrates, immune globulin) should either abide viral calm or be HCV RNA negative by polymerase chain reaction. Conveyance of HCV connect in mind with high-risk practices (e.g. injecting drug use, defenseless sex with multiple colleague) can be prevented by analyze and adminish persons with a

history these convention and by educational work to prevent beginning of these conventions. Educational struggle to prevent beginning of drug injection are particularly important for children and pre adult or immature because HCV infection is very quickly accomplished after beginning of injecting drug employment. (E.E. Mast et al. 1999)

Secondary prevention

Secondary prevention activities make less the danger for chronic disease by recognize HCV-infected persons through demonstrative testing and by providing applicable medical administration and antiviral therapy. In appropriate, counseling of HCV infected persons to reduce or avoid from alcohol consumption may prevent disease advancement. Antiviral treatment is also accessible, and treatment direction has been matured. Nevertheless, treatment is expensive and outside limits the resources accessible in many countries. Additionally, the benefits of early discovery and treatment of persons with asymptomatic infection have not been clearly settled, a high relative amount of persons do not act in response to at present available treatment, and the long-term benefit of treatment has not been driven.(E.E. Mast et al. 1999)

Future Burden of HBV- and HCV-Related HCC

Among the United States, incidence of HBV-linkedHCC is likely to remain steady. Even vaccinationsagainst the HBV could prevent HCC; it does not stopcancer in persons with severe or chronic infections. Most recent (1999–2006). National Health and Nutrition Examination Survey noticed that only 0.27% of US population, 6 years or older, had severe or chronic HBV infection (Bugianesi E, et al. 2004). National Health and Nutrition Examination Survey also reported that 1.3% of civilian US population had severe or chronic HCV infection; at least 66% of those infected were born between 1945 and 1964, and have been living with this disease for several decades. This study was also related to many risk factors for proliferation, such as alcohol consumption and the obesity. A report estimated that almost 50% of individuals with lethal HCV infections in United States are not diagnosed. Studies suggested that, without the effective treatment, total number of patients with HCC or cirrhosis will be double in 2020 (El Serag HB. 2004).

The World Health Organization data showed that a massive increase in the all of the people diagnosed with primary liver cancer, massively HCC, from 437,408 cases in 1990 to 714,600 in 2002 (Adami HO, Chow WH, Nyren O, et al. 1996)Percentage of HCC infection linked with HBV has reduced speedily while percentage linked with HCV has been greater. So, after reviewing literature we can say that each country or region country might be has its own case study. The World Health Organization death data from many European countries showed that between 1980 and 2004, total mortality by HCC among males increased inGermany, and Switzerland andAustria, while it reduced to a greater extent inItaly France and Italy (Wideroff L and Schottenfeld, D. 2006). In 2010 The Institute of Medicine study onLiver Cancer and Hepatitis marked the awareness inability about HCV and HBV infections and lesser understanding and knowledge about the limit and effective loss of their public health impact. HCV- and HBV-linked HCC can be prohibited by increasing the screening and diagnosis of patients, by various approaches such as vaccination of juvenile and adults susceptibility against HBV, a flatoxin exposure reduction, treating the infected patients with severe HCV and HBV infections, co-factors reducing for proliferation (metabolic syndrome and alcohol drinking) at the early stage diagnosis and treatment.

References

Gogela, N. A., Lin, M. V., Wisocky, J. L., & Chung, R. T. (2015). Enhancing our understanding of current therapies for hepatitis C virus (HCV). *Current HIV/AIDS Reports*, *12*(1), 68-78.

Zimmerman, J. J., Akhtar, S. R., Caldwell, E., & Rubenfeld, G. D. (2009). Incidence and outcomes of pediatric acute lung injury. *Pediatrics*, *124*(1), 87-95.

Bernal, W., & Wendon, J. (2013). Acute liver failure. *New England Journal of Medicine*, *369*(26), 2525-2534.

Bari, A., Akhtar, S., Rahbar, M. H., & Luby, S. P. (2001). Risk factors for hepatitis C virus infection in male adults in Rawalpindi–Islamabad, Pakistan. *Tropical medicine & international health*, *6*(9), 732-738.

Shukla, R., Bansal, V., Chaudhary, M., Basu, A., Bhonde, R. R., & Sastry, M. (2005). Biocompatibility of gold nanoparticles and their endocytotic fate inside the cellular compartment: a microscopic overview. *Langmuir*, *21*(23), 10644-10654.

Hamid, S., Umar, M., Alam, A., Siddiqui, A., Qureshi, H., & Butt, J. (2004). PSG consensus statement on management of hepatitis C virus infection--2003. *JPMA. The Journal of the Pakistan Medical Association*, *54*(3), 146.

Rudolph, K. L., Chang, S., Millard, M., Schreiber-Agus, N., & DePinho, R. A. (2000). Inhibition of experimental liver cirrhosis in mice by telomerase gene delivery. *Science*, *287*(5456), 1253-1258.

Alter, M. J., Margolis, H. S., Krawczynski, K., Judson, F. N., Mares, A., Alexander, W. J., ... & Meeks, E. L. (1992). The natural history of community-acquired hepatitis C in the United States. *New England journal of medicine*, *327*(27), 1899-1905.

Choo, Q. L., Kuo, G., Weiner, A. J., Overby, L. R., Bradley, D. W., & Houghton, M. (1989). Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. *Science*, *244*(4902), 359-362.

Lindenbach, B. D., & Rice, C. M. (2001). Flaviviridae: the viruses and their replication, vol. 1.

Akinyemiju, T., Abera, S., Ahmed, M., Alam, N., Alemayohu, M. A., Allen, C., ... & Ayele, T. A. (2017). The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level: results from the global burden of disease study 2015. *JAMA oncology*, *3*(12), 1683-1691.

Parkin, D. M., Bray, F., Ferlay, J., & Pisani, P. (2001). Estimating the world cancer burden: Globocan 2000. *International journal of cancer*, *94*(2), 153-156.

Chang, M. H., Chen, C. J., Lai, M. S., Hsu, H. M., Wu, T. C., Kong, M. S., ... & Chen, D. S. (1997). Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. *New England Journal of Medicine*, *336*(26), 1855-1859.

Choo, Q. L., Kuo, G., Weiner, A. J., Overby, L. R., Bradley, D. W., & Houghton, M. (1989). Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. *Science*, *244*(4902), 359-362. Adami, H. O., Chow, W. H., Nyrén, O., Berne, C., Linet, M. S., Ekbom, A., ... & Fraumeni, J. F. (1996). Excess risk of primary liver cancer in patients with diabetes mellitus. *JNCI: Journal of the National Cancer Institute*, *88*(20), 1472-1477.

Anderson, D., Bishop, J. B., Garner, R. C., Ostrosky-Wegman, P., & Selby, P. B. (1995). Cyclophosphamide: review of its mutagenicity for an assessment of potential germ cell risks. *Mutation research/fundamental and molecular mechanisms of mutagenesis*, *330*(1-2), 115-181.

Artandi, S. E., Chang, S., Lee, S. L., Alson, S., Gottlieb, G. J., Chin, L., & DePinho, R. A. (2000). Telomere dysfunction promotes non-reciprocal translocations and epithelial cancers in mice. *Nature*, *406*(6796), 641.

Barbason, H., Rassenfosse, C., & Betz, E. H. (1983). Promotion mechanism of phenobarbital and partial hepatectomy in DENA hepatocarcinogenesis cell kinetics effect. *British journal of cancer*, *47*(4), 517.

Boffetta., Brennan, P., Gajalakshmi, V., Mathew, A., Shanta, V., Varghese, C., & Znaor, A.,. (2003). Independent and combined effects of tobacco smoking, chewing and alcohol drinking on the risk of oral, pharyngeal and esophageal cancers in Indian men. *International journal of cancer*, *105*(5), 681-686.

Bugianesi, E., Manzini, P., D'Antico, S., Vanni, E., Longo, F., Leone, N., ... & Rizzetto, M. (2004). Relative contribution of iron burden, HFE mutations, and insulin resistance to fibrosis in nonalcoholic fatty liver. *Hepatology*, *39*(1), 179-187.

Calle, E. E., Rodriguez, C., Walker-Thurmond, K., & Thun, M. J. (2003). Overweight, obesity, and mortality from cancer in a prospectively studied cohort of US adults. *New England Journal of Medicine*, *348*(17), 1625-1638.

Chiba, T., Kita, K., Zheng, Y. W., Yokosuka, O., Saisho, H., Iwama, A., ... & Taniguchi, H. (2006). Side population purified from hepatocellular carcinoma cells harbors cancer stem cell–like properties. *Hepatology*, *44*(1), 240-251.

Chiu, C. M., Chiu, C. S., & Chang, H. C. (2007). Examining the integrated influence of fairness and quality on learners' satisfaction and Web- based learning continuance intention. *Information systems journal*, *17*(3), 271-287.

Cho, L. Y., Yang, J. J., Ko, K. P., Park, B., Shin, A., Lim, M. K., & Yoo, K. Y. (2011). Coinfection of hepatitis B and C viruses and risk of hepatocellular carcinoma: systematic review and meta- analysis. *International journal of cancer*, *128*(1), 176-184.

Colnot, S., Decaens, T., Niwa-Kawakita, M., Godard, C., Hamard, G., Kahn, A., ... & Perret, C. (2004). Liver-targeted disruption of Apc in mice activates β-catenin signaling and leads to hepatocellular carcinomas. *Proceedings of the National Academy of Sciences*, *101*(49), 17216-17221.

di Fagagna, F. D. A., Reaper, P. M., Clay-Farrace, L., Fiegler, H., Carr, P., von Zglinicki, T., ... & Jackson, S. P. (2003). A DNA damage checkpoint response in telomere-initiated senescence. *Nature*, *426*(6963), 194.

Djojosubroto, M. W., Chin, A. C., Go, N., Schaetzlein, S., Manns, M. P., Gryaznov, S., ... & Rudolph, K. L. (2005). Telomerase antagonists GRN163 and GRN163L inhibit tumor growth and increase chemosensitivity of human hepatoma. *Hepatology*, *42*(5), 1127-1136.

Donato, F., Boffetta, P., & Puoti, M. (1998). A meta- analysis of epidemiological studies on the combined effect of hepatitis B and C virus infections in causing hepatocellular carcinoma. *International journal of cancer*, *75*(3), 347-354.

El-Serag, H. B. (2004). Hepatocellular carcinoma: recent trends in the United States. *Gastroenterology*, *127*(5), S27-S34.

Farazi, P. A., Glickman, J., Jiang, S., Yu, A., Rudolph, K. L., & DePinho, R. A. (2003). Differential impact of telomere dysfunction on initiation and progression of hepatocellular carcinoma. *Cancer research*, *63*(16), 5021-5027.

Feld, J. J., Modi, A. A., El–Diwany, R., Rotman, Y., Thomas, E., Ahlenstiel, G., ... & Ghany, M. G. (2011). S-adenosyl methionine improves early viral responses and interferon-stimulated gene induction in hepatitis C nonresponders. *Gastroenterology*, *140*(3), 830-839.

Fiore, G., Fera, G., Napoli, N., Vella, F., & Schiraldi, O. (1996). Liver steatosis and chronic hepatitis C: a spurious association?. *European journal of gastroenterology & hepatology*, *8*(2), 125-129.

Freedman, N. D., Everhart, J. E., Lindsay, K. L., Ghany, M. G., Curto, T. M., Shiffman, M. L., ... & Hoefs, J. C. (2009). Coffee intake is associated with lower rates of liver disease progression in chronic hepatitis C. *Hepatology*, *50*(5), 1360-1369.

Gallus, S., Colombo, P., Scarpino, V., Zuccaro, P., Apolone, G., & La Vecchia, C. (2002). Smoking in Italy, 2002. *Tumori Journal*, *88*(6), 453-456.

He, X. C., Yin, T., Grindley, J. C., Tian, Q., Sato, T., Tao, W. A., ... & Wiedemann, L. M. (2007). PTEN-deficient intestinal stem cells initiate intestinal polyposis. *Nature genetics*, *39*(2), 189.

Hu, T. H., Huang, C. C., Lin, P. R., Chang, H. W., Ger, L. P., Lin, Y. W., ... & Tai, M. H. (2003). Expression and prognostic role of tumor suppressor gene PTEN/MMAC1/TEP1 in hepatocellular carcinoma. *Cancer: Interdisciplinary International Journal of the American Cancer Society*, *97*(8), 1929-1940.

Hwang, S. J., Bellocq, N. C., & Davis, M. E. (2001). Effects of structure of β-cyclodextrin-containing polymers on gene delivery. *Bioconjugate chemistry*, *12*(2), 280-290.

Iakova, P., Awad, S. S., & Timchenko, N. A. (2003). Aging reduces proliferative capacities of liver by switching pathways of C/EBPα growth arrest. *Cell*, *113*(4), 495-506.

Ikeda, K., Saitoh, S., Suzuki, Y., Kobayashi, M., Tsubota, A., Koida, I., ... & Kumada, H. (1998). Disease progression and hepatocellular carcinogenesis in patients with chronic viral hepatitis: a prospective observation of 2215 patients. *Journal of hepatology*, *28*(6), 930-938.

Jee, S. H., Ohrr, H., Sull, J. W., & Samet, J. M. (2004). Cigarette smoking, alcohol drinking, hepatitis B, and risk for hepatocellular carcinoma in Korea. *Journal of the national cancer institute*, *96*(24), 1851-1856.

Kanwal, F., Hoang, T., Kramer, J. R., Asch, S. M., Goetz, M. B., Zeringue, A., ... & El–Serag, H. B. (2011). Increasing prevalence of HCC and cirrhosis in patients with chronic hepatitis C virus infection. *Gastroenterology*, *140*(4), 1182-1188.

Kawai, H., Imanaga, S., & Kobayashi, T. (2000). *U.S. Patent No. 6,064,082*. Washington, DC: U.S. Patent and Trademark Office.

Kurozawa, Y., Ogimoto, I., Shibata, A., Nose, T., Yoshimura, T., Suzuki, H., ... & Tamakoshi, A. (2005). Coffee and risk of death from hepatocellular carcinoma in a large cohort study in Japan. *British journal of cancer*, *93*(5), 607.

Lechel, A., Holstege, H., Begus, Y., Schienke, A., Kamino, K., Lehmann, U., ... & Rudolph, K. L. (2007). Telomerase deletion limits progression of p53-mutant hepatocellular carcinoma with short telomeres in chronic liver disease. *Gastroenterology*, *132*(4), 1465-1475.

Levy, M. Z., Allsopp, R. C., Futcher, A. B., Greider, C. W., & Harley, C. B. (1992). Telomere end-replication problem and cell aging. *Journal of molecular biology*, *225*(4), 951-960.

Luedde, T., Beraza, N., Kotsikoris, V., van Loo, G., Nenci, A., De Vos, R., ... & Pasparakis, M. (2007). Deletion of NEMO/IKKγ in liver parenchymal cells causes steatohepatitis and hepatocellular carcinoma. *Cancer cell*, *11*(2), 119-132.

Micsenyi, A., Tan, X., Sneddon, T., Luo, J. H., Michalopoulos, G. K., & Monga, S. P. (2004). β-Catenin is temporally regulated during normal liver development. *Gastroenterology*, *126*(4), 1134-1146.

Møller, H., Mellemgaard, A., Lindvig, K., & Olsen, J. H. (1994). Obesity and cancer risk: a Danish record-linkage study. *European journal of cancer*, *30*(3), 344-350.

Montella, M., Polesel, J., La Vecchia, C., Maso, L. D., Crispo, A., Crovatto, M., ... & Franceschi, S. (2007). Coffee and tea consumption and risk of hepatocellular carcinoma in Italy. *International journal of cancer*, *120*(7), 1555-1559.

Plentz, R. R., Park, Y. N., Lechel, A., Kim, H., Nellessen, F., Langkopf, B. H. E., ... & Roncalli, M. (2007). Telomere shortening and inactivation of cell cycle checkpoints characterize human hepatocarcinogenesis. *Hepatology*, *45*(4), 968-976.

Poynard, T., Yuen, M. F., Ratzin, V., & Lai, C. L. (2003). Viral hepatitis C. *The Lancet*, *362*(9401), 2095-2100.

Ratziu, V., Bonyhay, L., Di Martino, V., Charlotte, F., Cavallaro, L., Sayegh- Tainturier, M. H., .. & Poynard, T. (2002). Survival, liver failure, and hepatocellular carcinoma in obesity- related cryptogenic cirrhosis. *Hepatology*, *35*(6), 1485-1493.

Rodriguez-Abreu, D., Bordoni, A., & Zucca, E. (2007). Epidemiology of hematological malignancies. *Annals of oncology*, *18*(suppl_1), i3-i8.

Rubbia-Brandt, L., Quadri, R., Abid, K., Giostra, E., Malé, P. J., Mentha, G., ... & Negro, F. (2000). Hepatocyte steatosis is a cytopathic effect of hepatitis C virus genotype 3. *Journal of hepatology*, *33*(1), 106-115.

Satyanarayana, L., Reddy, K. M., & Manorama, S. V. (2003). Nanosized spinel NiFe2O4: a novel material for the detection of liquefied petroleum gas in air. *Materials Chemistry and Physics*, *82*(1), 21-26.

Shachaf, C. M., Kopelman, A. M., Arvanitis, C., Karlsson, Å., Beer, S., Mandl, S., ... & Yang, Q. (2004). MYC inactivation uncovers pluripotent differentiation and tumour dormancy in hepatocellular cancer. *Nature*, *431*(7012), 1112..

Shimazu, T., Inoue, I., Araki, N., Asano, Y., Sawada, M., Furuya, D., ... & Greenberg, J. H. (2005). A peroxisome proliferator-activated receptor-γ agonist reduces infarct size in transient but not in permanent ischemia. *Stroke*, *36*(2), 353-359.

Sicklick, J. K., Li, Y. X., Melhem, A., Schmelzer, E., Zdanowicz, M., Huang, J., ... & Reid, L. M. (2006). Hedgehog signaling maintains resident hepatic progenitors throughout life. *American Journal of Physiology-Gastrointestinal and Liver Physiology*, *290*(5), G859-G870.

Smogorzewska, A., & de Lange, T. (2002). Different telomere damage signaling pathways in human and mouse cells. *The EMBO journal*, *21*(16), 4338-4348.

Talamini, R., Polesel, J., Montella, M., Maso, L. D., Crispo, A., Tommasi, L. G., ... & Franceschi, S. (2006). Food groups and risk of hepatocellular carcinoma: a multicenter case- control study in Italy. *International journal of cancer*, *119*(12), 2916-2921.

V., Wolk, Pisani, P., Tenet, A Bergström, A.., & Adami, H. O. (2001). Overweight as an avoidable cause of cancer in Europe. *International journal of cancer*, *91*(3), 421-430.

Wagayama, H., Shiraki, K., Yamanaka, T., Sugimoto, K., Ito, T., Fujikawa, K., ... & Nakano, T. (2001). p21WAF1/CTP1 expression and hepatitis virus type. *Digestive diseases and sciences*, *46*(10), 2074-2079.

Wang, Y., & Zhang, Q. (2006). Are American children and adolescents of low socioeconomic status at increased risk of obesity? Changes in the association between overweight and family income between 1971 and 2002. *The American journal of clinical nutrition*, *84*(4), 707-716.

Westin, J., Nordlinder, H., Lagging, M., Norkrans, G., & Wejstål, R. (2002). Steatosis accelerates fibrosis development over time in hepatitis C virus genotype 3 infected patients. *Journal of hepatology*, *37*(6), 837-842.

White, D. L., Thrift, A. P., Kanwal, F., Davila, J., & El-Serag, H. B. (2017). Incidence of hepatocellular carcinoma in all 50 United States, from 2000 through 2012. *Gastroenterology*, *152*(4), 812-820.

Adami, H. O., Chow, W. H., Nyrén, O., Berne, C., Linet, M. S., Ekbom, A., ... & Fraumeni, J. F. (1996). Excess risk of primary liver cancer in patients with diabetes mellitus. *JNCI: Journal of the National Cancer Institute*, *88*(20), 1472-1477.

Anderson, D., Bishop, J. B., Garner, R. C., Ostrosky-Wegman, P., & Selby, P. B. (1995). Cyclophosphamide: review of its mutagenicity for an assessment of potential germ cell risks. *Mutation research/fundamental and molecular mechanisms of mutagenesis*, *330*(1-2), 115-181.

Artandi, S. E., Chang, S., Lee, S. L., Alson, S., Gottlieb, G. J., Chin, L., & DePinho, R. A. (2000). Telomere dysfunction promotes non-reciprocal translocations and epithelial cancers in mice. *Nature*, *406*(6796), 641.

Barbason, H., Rassenfosse, C., & Betz, E. H. (1983). Promotion mechanism of phenobarbital and partial hepatectomy in DENA hepatocarcinogenesis cell kinetics effect. *British journal of cancer*, *47*(4), 517.

Boffetta., Brennan, P., Gajalakshmi, V., Mathew, A., Shanta, V., Varghese, C., & Znaor, A.,. (2003). Independent and combined effects of tobacco smoking, chewing and alcohol drinking on the risk of oral, pharyngeal and esophageal cancers in Indian men. *International journal of cancer*, *105*(5), 681-686.

Bugianesi, E., Manzini, P., D'Antico, S., Vanni, E., Longo, F., Leone, N., ... & Rizzetto, M. (2004). Relative contribution of iron burden, HFE mutations, and insulin resistance to fibrosis in nonalcoholic fatty liver. *Hepatology*, *39*(1), 179-187.

Calle, E. E., Rodriguez, C., Walker-Thurmond, K., & Thun, M. J. (2003). Overweight, obesity, and mortality from cancer in a prospectively studied cohort of US adults. *New England Journal of Medicine*, *348*(17), 1625-1638.

Chiba, T., Kita, K., Zheng, Y. W., Yokosuka, O., Saisho, H., Iwama, A., ... & Taniguchi, H. (2006). Side population purified from hepatocellular carcinoma cells harbors cancer stem cell–like properties. *Hepatology*, *44*(1), 240-251.

Chiu, C. M., Chiu, C. S., & Chang, H. C. (2007). Examining the integrated influence of fairness and quality on learners' satisfaction and Web- based learning continuance intention. *Information systems journal*, *17*(3), 271-287.

Colnot, S., Decaens, T., Niwa-Kawakita, M., Godard, C., Hamard, G., Kahn, A., ... & Perret, C. (2004). Liver-targeted disruption of Apc in mice activates β-catenin signaling and leads to hepatocellular carcinomas. *Proceedings of the National Academy of Sciences*, *101*(49), 17216-17221.

di Fagagna, F. D. A., Reaper, P. M., Clay-Farrace, L., Fiegler, H., Carr, P., von Zglinicki, T., ... & Jackson, S. P. (2003). A DNA damage checkpoint response in telomere-initiated senescence. *Nature*, *426*(6963), 194.

Djojosubroto, M. W., Chin, A. C., Go, N., Schaetzlein, S., Manns, M. P., Gryaznov, S., ... & Rudolph, K. L. (2005). Telomerase antagonists GRN163 and GRN163L inhibit tumor growth and increase chemosensitivity of human hepatoma. *Hepatology*, *42*(5), 1127-1136.

Donato, F., Boffetta, P., & Puoti, M. (1998). A meta- analysis of epidemiological studies on the combined effect of hepatitis B and C virus infections in causing hepatocellular carcinoma. *International journal of cancer*, *75*(3), 347-354.

El-Serag, H. B. (2004). Hepatocellular carcinoma: recent trends in the United States. *Gastroenterology*, *127*(5), S27-S34.

Farazi, P. A., Glickman, J., Jiang, S., Yu, A., Rudolph, K. L., & DePinho, R. A. (2003). Differential impact of telomere dysfunction on initiation and progression of hepatocellular carcinoma. *Cancer research*, *63*(16), 5021-5027.

Feld, J. J., Modi, A. A., El–Diwany, R., Rotman, Y., Thomas, E., Ahlenstiel, G., ... & Ghany, M. G. (2011). S-adenosyl methionine improves early viral responses and interferon-stimulated gene induction in hepatitis C nonresponders. *Gastroenterology*, *140*(3), 830-839.

Fiore, G., Fera, G., Napoli, N., Vella, F., & Schiraldi, O. (1996). Liver steatosis and chronic hepatitis C: a spurious association?. *European journal of gastroenterology & hepatology*, *8*(2), 125-129.

Freedman, N. D., Everhart, J. E., Lindsay, K. L., Ghany, M. G., Curto, T. M., Shiffman, M. L., ... & Hoefs, J. C. (2009). Coffee intake is associated with lower rates of liver disease progression in chronic hepatitis C. *Hepatology*, *50*(5), 1360-1369.

Gallus, S., Colombo, P., Scarpino, V., Zuccaro, P., Apolone, G., & La Vecchia, C. (2002). Smoking in Italy, 2002. *Tumori Journal*, *88*(6), 453-456.

He, X. C., Yin, T., Grindley, J. C., Tian, Q., Sato, T., Tao, W. A., ... & Wiedemann, L. M. (2007). PTEN-deficient intestinal stem cells initiate intestinal polyposis. *Nature genetics*, *39*(2), 189.

Hu, T. H., Huang, C. C., Lin, P. R., Chang, H. W., Ger, L. P., Lin, Y. W., ... & Tai, M. H. (2003). Expression and prognostic role of tumor suppressor gene PTEN/MMAC1/TEP1 in hepatocellular carcinoma. *Cancer: Interdisciplinary International Journal of the American Cancer Society*, *97*(8), 1929-1940.

Hwang, S. J., Bellocq, N. C., & Davis, M. E. (2001). Effects of structure of β-cyclodextrin-containing polymers on gene delivery. *Bioconjugate chemistry*, *12*(2), 280-290.

Iakova, P., Awad, S. S., & Timchenko, N. A. (2003). Aging reduces proliferative capacities of liver by switching pathways of C/EBPα growth arrest. *Cell*, *113*(4), 495-506.

Ikeda, K., Saitoh, S., Suzuki, Y., Kobayashi, M., Tsubota, A., Koida, I., ... & Kumada, H. (1998). Disease progression and hepatocellular carcinogenesis in patients with chronic viral hepatitis: a prospective observation of 2215 patients. *Journal of hepatology*, *28*(6), 930-938.

Jee, S. H., Ohrr, H., Sull, J. W., & Samet, J. M. (2004). Cigarette smoking, alcohol drinking, hepatitis B, and risk for hepatocellular carcinoma in Korea. *Journal of the national cancer institute*, *96*(24), 1851-1856.

Kanwal, F., Hoang, T., Kramer, J. R., Asch, S. M., Goetz, M. B., Zeringue, A., ... & El–Serag, H. B. (2011). Increasing prevalence of HCC and cirrhosis in patients with chronic hepatitis C virus infection. *Gastroenterology*, *140*(4), 1182-1188.

Kawai, H., Imanaga, S., & Kobayashi, T. (2000). *U.S. Patent No. 6,064,082*. Washington, DC: U.S. Patent and Trademark Office.

Kurozawa, Y., Ogimoto, I., Shibata, A., Nose, T., Yoshimura, T., Suzuki, H., ... & Tamakoshi, A. (2005). Coffee and risk of death from hepatocellular carcinoma in a large cohort study in Japan. *British journal of cancer*, *93*(5), 607.

Lechel, A., Holstege, H., Begus, Y., Schienke, A., Kamino, K., Lehmann, U., ... & Rudolph, K. L. (2007). Telomerase deletion limits progression of p53-mutant hepatocellular carcinoma with short telomeres in chronic liver disease. *Gastroenterology*, *132*(4), 1465-1475.

Lee, J. S., & Bowen, N. K. (2006). Parent involvement, cultural capital, and the achievement gap among elementary school children. *American educational research journal*, *43*(2), 193-218.

Levy, M. Z., Allsopp, R. C., Futcher, A. B., Greider, C. W., & Harley, C. B. (1992). Telomere end-replication problem and cell aging. *Journal of molecular biology*, *225*(4), 951-960.

Llovet, J. M., Chen, Y., Wurmbach, E., Roayaie, S., Fiel, M. I., Schwartz, M., ... & Battiston, C. (2006). A molecular signature to discriminate dysplastic nodules from early hepatocellular carcinoma in HCV cirrhosis. *Gastroenterology*, *131*(6), 1758-1767.

Luedde, T., Beraza, N., Kotsikoris, V., van Loo, G., Nenci, A., De Vos, R., ... & Pasparakis, M. (2007). Deletion of NEMO/IKKγ in liver parenchymal cells causes steatohepatitis and hepatocellular carcinoma. *Cancer cell*, *11*(2), 119-132.

Micsenyi, A., Tan, X., Sneddon, T., Luo, J. H., Michalopoulos, G. K., & Monga, S. P. (2004). β-Catenin is temporally regulated during normal liver development. *Gastroenterology*, *126*(4), 1134-1146.

Mobasheri, A., Mobasheri, R., Francis, M. J. O., Trujillo, E., Alvarez De La Rosa, D., & Martin-Vasallo, P. (1998). Ion transport in chondrocytes: membrane transporters involved in intracellular ion homeostasis and the regulation of cell volume, free [Ca^ 2^+] and pH. *Histology and histopathology*, *13*(3), 893-910.

Møller, H., Mellemgaard, A., Lindvig, K., & Olsen, J. H. (1994). Obesity and cancer risk: a Danish record-linkage study. *European journal of cancer*, *30*(3), 344-350.

Montella, M., Polesel, J., La Vecchia, C., Maso, L. D., Crispo, A., Crovatto, M., ... & Franceschi, S. (2007). Coffee and tea consumption and risk of hepatocellular carcinoma in Italy. *International journal of cancer*, *120*(7), 1555-1559.

Plentz, R. R., Park, Y. N., Lechel, A., Kim, H., Nellessen, F., Langkopf, B. H. E., ... & Roncalli, M. (2007). Telomere shortening and inactivation of cell cycle checkpoints characterize human hepatocarcinogenesis. *Hepatology*, *45*(4), 968-976.

Poynard, T., Yuen, M. F., Ratzin, V., & Lai, C. L. (2003). Viral hepatitis C. *The Lancet*, *362*(9401), 2095-2100.

Ratziu, V., Bonyhay, L., Di Martino, V., Charlotte, F., Cavallaro, L., Sayegh- Tainturier, M. H., ... & Poynard, T. (2002). Survival, liver failure, and hepatocellular carcinoma in obesity- related cryptogenic cirrhosis. *Hepatology*, *35*(6), 1485-1493.

Rubbia-Brandt, L., Quadri, R., Abid, K., Giostra, E., Malé, P. J., Mentha, G., ... & Negro, F. (2000). Hepatocyte steatosis is a cytopathic effect of hepatitis C virus genotype 3. *Journal of hepatology*, *33*(1), 106-115.

Shi, J., Shen, W., Dong, X., Feng, J., Ruan, M., & Li, Y. (2005). Stimuli- responsive controlled drug release from a hollow mesoporous silica sphere/polyelectrolyte multilayer core–shell structure. *Angewandte Chemie International Edition*, *44*(32), 5083-5087.

Shimazu, T., Inoue, I., Araki, N., Asano, Y., Sawada, M., Furuya, D., ... & Greenberg, J. H. (2005). A peroxisome proliferator-activated receptor-γ agonist reduces infarct size in transient

Talamini, R., Polesel, J., Montella, M., Maso, L. D., Crispo, A., Tommasi, L. G., ... & Franceschi, S. (2006). Food groups and risk of hepatocellular carcinoma: a multicenter case- control study in Italy. *International journal of cancer*, *119*(12), 2916-2921.

V., Wolk, Pisani, P., Tenet, A Bergström, A.., & Adami, H. O. (2001). Overweight as an avoidable cause of cancer in Europe. *International journal of cancer*, *91*(3), 421-430.

Wagayama, H., Shiraki, K., Yamanaka, T., Sugimoto, K., Ito, T., Fujikawa, K., ... & Nakano, T. (2001). p21WAF1/CTP1 expression and hepatitis virus type. *Digestive diseases and sciences*, *46*(10), 2074-2079.

Wang, Y., & Zhang, Q. (2006). Are American children and adolescents of low socioeconomic status at increased risk of obesity? Changes in the association between overweight and family income between 1971 and 2002. *The American journal of clinical nutrition*, *84*(4), 707-716.

White, D. L., Thrift, A. P., Kanwal, F., Davila, J., & El-Serag, H. B. (2017). Incidence of hepatocellular carcinoma in all 50 United States, from 2000 through 2012. *Gastroenterology*, *152*(4), 812-820.

Arena, U., Vizzutti, F., Corti, G., Ambu, S., Stasi, C., Bresci, S., &Marra, F. (2008). Acute viral hepatitis increases liver stiffness values measured by transient elastography. *Hepatology*, *47*(2), 380-384.

Cadranel, J. F., Rufat, P., &Degos, F. (2000). Practices of liver biopsy in France: results of a prospective nationwide survey. *Hepatology*, *32*(3), 477-481.

Castéra, L., Vergniol, J., Foucher, J., Le Bail, B., Chanteloup, E., Haaser, M., ...& de Lédinghen, V. (2005). Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. *Gastroenterology*, *128*(2), 343-350.

Colin, C., Lanoir, D., Touzet, S., Meyaud- Kraemer, L., Bailly, F., Trepo, C., & HEPATIS Group. (2001). Sensitivity and specificity of third- generation hepatitis C virus antibody detection assays: an analysis of the literature. *Journal of viral hepatitis*, *8*(2), 87-95.

Crockett, S. D., Kaltenbach, T., &Keeffe, E. B. (2006). Do we still need a liver biopsy? Are the serum fibrosis tests ready for prime time?. *Clinics in liver disease*, *10*(3), 513-34.

Dienstag, J. L. (2002). The role of liver biopsy in chronic hepatitis C. *Hepatology*, *36*(S1), S152-S160.

Ghany, M. G., Strader, D. B., Thomas, D. L., &Seeff, L. B. (2009). Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology*, *49*(4), 1335-1374.

Gonzalez, M. C., Hidalgo, C. A., &Barabasi, A. L. (2008).Understanding individual human mobility patterns. *nature*, *453*(7196), 779.

Jou, J. H., Chen, C. C., Chung, Y. C., Hsu, M. F., Wu, C. H., Shen, S. M., ... &Shyue, J. J. (2008). Nanodot- Enhanced High- Efficiency Pure- White Organic Light- Emitting Diodes with Mixed- Host Structures. *Advanced Functional Materials*, *18*(1), 121-126.

Koff, R. S. (1981). Management of the hepatitis B surface antigen (HBsAg) carrier.In *Seminars in liver disease* (Vol. 1, No. 01, pp. 33-43).© 1981 by Thieme Medical Publishers, Inc.

Moriya, T., Naito, H., Ito, Y., & Nakajima, T. (2009)." Hypothesis of Seven Balances": Molecular Mechanisms behind Alcoholic Liver Diseases and Association with PPARα. *Journal of occupational health*, *51*(5), 391-403.

Pawlotsky, J. M., Bouvier-Alias, M., Hezode, C., Darthuy, F., Remire, J., &Dhumeaux, D. (2000). Standardization of hepatitis C virus RNA quantification. *Hepatology*, *32*(3), 654-659.

Kasper, D. L., Fauci, A. S., Hauser, S. L., Longo, D. L., Jameson, J. L., & Loscalzo, J. (2015). *Harrison's principles of internal medicine*. McGraw Hill Education,.

Mahboobi, N., Agha- Hosseini, F., Mahboobi, N., Safari, S., Lavanchy, D., & Alavian, S. M. (2010). Hepatitis B virus infection in dentistry: a forgotten topic. *Journal of viral hepatitis*, *17*(5), 307-316.

Crofts, N., Stewart, T., Hearne, P., Ping, X. Y., Breschkin, A. M., & Locarnini, S. A. (1995). Spread of bloodborne viruses among Australian prison entrants. *Bmj*, *310*(6975), 285-288.

Mast, E. E., Alter, M. J., & Margolis, H. S. (1999). Strategies to prevent and control hepatitis B and C virus infections: a global perspective. *Vaccine*, *17*(13-14), 1730-1733.

Mangia, A., Minerva, N., Bacca, D., Cozzolongo, R., Ricci, G. L., Carretta, V., ... & Cristofaro, G. (2008). Individualized treatment duration for hepatitis C genotype 1 patients: a randomized controlled trial. *Hepatology*, *47*(1), 43-50.

Strader, D. B., Wright, T., Thomas, D. L., & Seeff, L. B. (2004). Diagnosis, management, and treatment of hepatitis C. *Hepatology*, *39*(4), 1147-1171.

Backus, L. I., Boothroyd, D. B., Phillips, B. R., & Mole, L. A. (2007). Predictors of response of US veterans