International Journal of Life Science Research Archive

ISSN: 0799-6640 (Online)

Journal homepage: https://sciresjournals.com/ijlsra/

(RESEARCH ARTICLE)

Check for updates

Molecular epidemiology of liver cancer: Liver cancer incidence and mortality pattern worldwide

Nasrin Jafari [1] and Roya Dolatkhah [2,*]

[1] *Department of Statistics and Epidemiology, Faculty of health, Tabriz University of Medical Sciences, Golgasht St. Attar e Neshabouri St., Tabriz, 5166614711, Iran.*
[2] *Hematology and Oncology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.*

International Journal of Life Science Research Archive, 2021, 01(01), 018–023

Publication history: Received on 12 June 2021; revised on 15 July 2021; accepted on 17 July 2021

Article DOI: https://doi.org/10.53771/ijlsra.2021.1.1.0046

Abstract

Primary liver cancer was the sixth most prevalent cancer and third leading cause of cancer mortality worldwide. The highest rates of incidence and mortality were reported in Eastern Asia and it was 2 to 3 times more common than females in most regions. The summary estimates of the global trends in incidence rates of liver cancer indicated decreasing trends in many Asian high-risk countries, however increasing trends for North American and European countries. Understanding the several involved cells signaling pathways in liver cancer pathogenesis provide an opportunity to identify novel targets that can be utilized for therapeutic and diagnostic modalities.

At this time there are only a few effective strategies to prevent or treat liver cancer, and, therefore, a great deal of research is being conducted on liver cancer early detection and prevention. There are no widely recommended screening tests for liver cancer in people who are at average risk at this time. But, testing might be recommended for some people at higher risk. However researchers are studying ways to prevent or treat hepatitis infections before they cause liver cancers. Research into developing a vaccine to prevent hepatitis C is ongoing. Since population-based methods for screening the disease have not been introduced, the greatest focus should be placed on the predominant risk factors for the disease in older men, further studies should be conducted and high-risk provinces should be spotlighted.

Keywords: Hepatocellular Carcinoma; Incidence; Mortality; Early Diagnosis; Survival

1. Background

1.1. Global Incidence and Mortality Pattern of Liver Cancer

In 2020, Primary liver cancer was the sixth most prevalent cancer and third leading cause of cancer mortality worldwide, with approximately 906,000 new cases and 830,000 deaths (1). In males, liver cancer ranked fifth in incidence and second in mortality, and it was 2 to 3 times more common than females. Based on estimates from 2020, the highest rates of incidence and mortality were reported in Eastern Asia, and according to the human developing index (HDI) index, areas with high HDI index reported the highest rates of incidence, and mortality (1). Liver cancer was the most prevalent cancer among 11 geographically diverse countries in Eastern Asia, while Mongolia had the highest age standardized incidence rate (ASIR=85.6) and age standardized mortality rate (ASMR=80.6) (1).

* Corresponding author: Roya Dolatkhah
Hematology and Oncology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.

The Global Burden of Disease (GBD) study is uniquely poised to provide these crucial data to describe the cancer burden for 29 cancer groups in 195 countries from 1990 to 2017 and also provide necessary data for cancer control planning. The results of this systematic analysis revealed that between 2007 and 2017, there has been a 35% increase in liver cancer incidence, of which 17% and 13% have been attributed to population aging and growth, respectively, and an increase of 6% in age-specific incidence rates was estimated (2). Also between 2006 and 2016, in the high, high-middle, and middle socio-demographic index (SDI) countries, ASIRs increased for both genders whereas it decreased for the low-middle and low SDI countries. ASMRs in all countries decreased except those with low SDI, where they increased by 3% (3). However, the summary estimates from a Systematic Review and Meta-Analysis of the global trends in incidence rates of liver cancer indicated decreasing trends in many high-risk countries in Asia by an annual percentage change (APC) -1.7 , stable trends for African and South American countries, and increasing trends for North American and European countries (APC +3.2) (4). Vaccination and preventive disciplines against hepatitis infections, likely reflect declines in the population seroprevalence, as well as a reduction in aflatoxin exposure, reduced the prevalence of hepatitis B (HBV) infection and the incidence of hepatocellular carcinoma (HCC) in high-risk countries (4).

Based on the results of a meta-analysis study, survival rates of liver cancer in Asian countries were estimated, and the one-year survival rate was 34.8 % (95 % CI; 30.3- 39.3). Based on the HDI index, the highest (46 %, 95 % CI; 38-54) and the lowest (25.6 %, 95 % CI; 8.2-43.6) one-year survival rates were reported from countries with a very high and medium HDI level, respectively. The three-year survival rate was estimated at 19 %, (95 % CI; 16.2-21.8), based on the HDI index, the highest (26.9 %, 95 % CI; 32.3-21.5) and the lowest 14 % (95 % CI; 18.2-12.29) the three-year survival rates were reported from countries with a high and medium HDI level, respectively. The five-year survival rate was estimated at 18.1 % (95 % CI, 16.2-20.1), based on the HDI index, the highest (20.7 %, 95 % CI; 18.2-23.2) and the lowest 8 %, 95 % CI; 5.3-10.7) five-year survival rates were reported from countries with a very high and medium HDI levels, respectively. The ten-year survival rate was estimated at 4.1 % (95 % CI; 1.5-6.7), there were no sufficient studies available to scrutinize the maximum and minimum rates of survival (5).

The incidence and mortality rates of liver cancer rank tenth and fifth in Iran, respectively (3). Iran is one of the five countries with the lowest standardized incidence and mortality rates of liver cancer (6). According to the results of a meta-analysis study between 1996 to 2016 the age-standardized rate (ASR) of liver cancer was 1.66 (95% CI 1.49–1.83) for males and 1.25 (95%CI1.12–1.38) for females (7), and the incidence rate of liver cancer among Iranian men is lower than those in other Asian countries (7). Between 1990 to 2015, the age-standardized mortality rate of liver cancer increased from 1.18 (95% CI: 0.86 to 1.61) deaths to 5.66 (4.20 to 7.63) deaths per 100,000 persons in Iran, respectively (8). The highest mortality rate has been recorded in the age group over 85 years, which has increased at an increasing trend between 1990 to 2015, between 1990 to 2015 it has increased from 22.41(95% CI: 16.48 to 30.49) to 158.15 (95% CI: 118.3 to 211.31) per 100,000 persons, respectively (8). On the other hand with aging, the mortality rate from liver cancer increases, and this trend is more common in men than women (9).

Over 12 years, an increasing trend for the incidence of liver cancer in East Azerbaijan has been recorded, and annual percent changes (APC) for men and women were 21.3% and 16.3%, respectively (10). Also, between 2001 to 2008, a 3.7-fold increase has been recorded in ASR of liver cancer in Fars province (11). Between 1999 and 2006, the annual incidence rates of HCC in Kerman was 0.7 (95% CI = 0.4 to 1.1) and between 2005 and 2006, it was estimated 0.2 (95% CI = 0.2 to 0.3) per 100,000 persons across Iran ($P < 0.01$) (12). There has been an increasing trend in liver cancer mortality in all provinces between 1990 and 2015 (8). Generally, the pattern of liver cancer mortality in Iran has been changing over time.

1.2. The Molecular Pathways Involved in the Pathogenesis of Primary Liver Cancer

Hepatocarcinogenesis is a multistep process that may last for decades and involves the progressive accumulation of different genetic and epigenetic alterations ultimately leading to malignant transformation (13). At least four pathways have been studied, that regulate either cell proliferation or cell death (i.e., the phospho-retinoblastoma (pRb), transforming growth factor-b (TGF-b), p53, and b-catenin pathways are affected in HCCs. However, numerous signaling pathways have been observed to be dysregulated, either in response to viral infection or by exposure to toxic agents in HCC .Receptors that activate multiple downstream signals in the receptor tyrosine kinase pathway include the Vascular Endothelial Growth Factor (VEGF) receptor ,Fibroblast Growth Factor (FGF) receptor ,Platelet-Derived Growth Factor (PDGF) receptor ,Epidermal Growth Factor (EGF) receptor, and Insulin-like Growth Factor (IGFR) receptor. Also, the hepatocyte growth factor (HGF/ c-MET) and Wnt signaling pathways are a group of signal transduction pathways that begin with proteins that pass signals into a cell through cell surface receptors (14, 15). Although liver cancer patients at the early stage of the disease may benefit from some current treatment options including liver transplantation and/or surgical resections, response to treatment options are not effective in most advanced HCCs. Understanding the several

involved cells signaling pathways in liver cancer pathogenesis provide an opportunity to identify novel targets that can be utilized for therapeutic and diagnostic modalities (13, 14, 16, 17).

Three main subtypes of VEGF receptors are VEGF 1, 2, and 3. Among the three VEGF subtypes, VEGFR-2 appears to mediate most of the known cellular responses to VEGFs. VEGF interacts with receptors (VEGFR 1,2,3) present on the endothelial cell surface, which leads to auto-phosphorylation of intracellular receptor tyrosine kinase, and a cascade of downstream proteins is activated (18). PDGF has its receptor on the surface of capillary endothelial cells. The binding of PDGF to the receptors has several effects on endothelial cell motility and apoptosis. Moreover, it has demonstrated significant activity against several receptor tyrosine kinases involved in neovascularization and tumor progression (19).

Targeted therapies act specifically on tumorigenesis regulating components, unlike broad-spectrum, conventional cytotoxic agents. Currently, the only approved drug for advanced HCC is Sorafenib, which partially targets the multi-kinases involved in advanced liver cancer. At ASCO 2007, results from the SHARP trial were presented, which showed the efficacy of Sorafenib in hepatocellular carcinoma. The primary endpoint was median overall survival, which showed a 44% improvement in patients who received Sorafenib compared to placebo. Because of this trial, Sorafenib obtained FDA approval for the treatment of advanced hepatocellular carcinoma in November 2007 (20). Sorafenib is a protein kinase inhibitor with activity against many protein kinases involved in both tumor cell proliferation (tumor growth) and angiogenesis. Also, Sorafenib inhibits the action of tyrosine kinase Raf and other factors involved in vasculogenesis, which in turn inhibits the activation of other downstream multikinases that are normally essential for cell growth, angiogenesis, proliferation, and metastasis of HCC cells (21).

1.3. The Risk Factors of Primary Liver Cancer

The main risk factors for HCC are chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), aflatoxin-contaminated foods, heavy alcohol intake, excess body weight, type 2 diabetes, and smoking (22). However, major risk factors vary from region to region. In most high-risk HCC areas (China, the Republic of Korea, and sub-Saharan Africa), the key determinants are chronic HBV infection, aflatoxin exposure, or both; whereas, in other countries (Japan, Italy, and Egypt), HCV infection is likely the predominant cause. In Mongolia with the highest incidence and mortality rates for liver cancer, HBV and HCV and co-infections of HBV carriers with HCV or hepatitis delta viruses, as well as alcohol consumption, all contribute to the high burden of the disease (23). Meanwhile chronic hepatitis B and C and associated liver cirrhosis represent major risk factors for HCC development, being implicated in more than 70% of HCC cases worldwide. Additional etiological factors, which often represent co-factors of an underlying HBV- or HCV-related chronic liver disease, include alcohol, aflatoxins, Diabetes, metabolic liver diseases (e.g., hereditary hemochromatosis, a1-antitrypsin deficiency), steatosis, non-alcoholic fatty liver diseases, and diabetes (24).

1.4. Prevention and Screening of Primary Liver Cancer

Some scientists believe that vaccinations and improved treatments for hepatitis could prevent about half of liver cancer cases worldwide. However researchers are studying ways to prevent or treat hepatitis infections before they cause liver cancers. Research into developing a vaccine to prevent hepatitis C is ongoing. Progress is also being made in treating chronic hepatitis (25, 26). HBV infection and HCV infection account for 56% and 20% of liver cancer deaths worldwide, respectively. By the end of 2019, countries had introduced the HBV vaccine into their national infant immunization programs, and global coverage with 3 doses of hepatitis B vaccine was estimated at 85%. Currently, there is no vaccine available to prevent HCV infection, therefore, antiviral treatment options are the only way to control the disease. Although an 8-week to 12-week course of orally administered, direct-acting antiviral agents appears to cure HCV infection in most instances (25, 26), as of 2020, Inovio Pharmaceuticals is developing a synthetic multi-antigen DNA vaccine covering HCV genotypes 1a and 1b and targeting the HCV antigens' nonstructural proteins (27, 28).

At this time there are only a few effective strategies to prevent or treat liver cancer, and, therefore, a great deal of research is being conducted on liver cancer early detection and prevention. Scientists are constantly seeking out the causes of liver cancer and ways to prevent it, as well as ways to improve treatment. However, the main concern/question now is: “Can liver cancer be detected early?”

A liver cancer diagnosis is often hard to make early on, because signs and symptoms typically do not emerge until it is in its later stages. Small liver tumors are hard to detect on a physical examination and even during Ultrasound and by the time a tumor can be felt, it might already be quite large. According to the last guidelines provided by the American Cancer Society (ACS), there are no widely recommended screening tests for liver cancer in people who are at average risk at this time. But, testing might be recommended for some people at higher risk (29). However, according to the last updated guidelines of the National Comprehensive Cancer Network (NCCN) for Hepatocellular Carcinoma Screening,

patients at risk for HCC should be screened (30). For people at higher risk of liver cancer, screening should be performed with alpha-fetoprotein (AFP) blood test and ultrasound exams every 3-6 months, because they have cirrhosis (because of Hepatitis B and C, Alcohol, Genetic hemochromatosis, Non-alcoholic fatty liver disease, Stage 4 primary biliary cholangitis, Alpha 1 antitrypsin deficiency, and other causes of cirrhosis), and chronic hepatitis B infection (even without cirrhosis). However, CT scans and MRI scans are also being studied as different imaging tests to screen for liver cancer instead of ultrasound. But, AFP level is not a perfect test for liver cancer. Many patients with early liver cancer have normal AFP levels. Also, AFP levels can be increased from other kinds of cancer as well as some non-cancerous conditions. Several new blood tests are being studied to determine whether liver cancer can be detected earlier rather than using AFP and ultrasound. The New biomarkers being studied, include Des-gamma-carboxy prothrombin (DCP), Glypican-3, lens culinaris agglutinin-reactive AFP, Midkine (MDK), Osteopontin, Golgi protein-73, and Genomic markers including miRNA. However, screening is always linked to improved survival in most cancers (31-33). In recent years, despite signs of progress made in liver cancer early diagnosis and provisional programs, only 20 percent of liver cancer patients survive five years after diagnosis. However, about 43% of liver cancer patients may be diagnosed at the early stages of disease, and then their 5-year survival rate will be 31%. If cancer spreads to nearby organs or lymph nodes, the 5-year survival rate will be 11% and will be reduced by just 3% in distant metastatic liver cancers (34).

2. Conclusion

Numerous factors make liver cancer more serious, including its poor prognosis, direct association with aging, and the high mortality and prevalence of liver cancer in men than women. Furthermore, based on information from the American Cancer Society, since population-based methods for screening the disease have not been introduced, the greatest focus should be placed on the predominant risk factors for the disease in older men, further studies should be conducted and high-risk provinces should be spotlighted.

Compliance with ethical standards

Acknowledgments

NJ and RD: Participated in the topic selection and design of the article. NJ and RD: Drafted and modified the key theory of the article. RD: Can follow the revision of the editorial department to revise the article, answer the academic questions, and finally agree to the publication of the article. NJ and RD: Agreed to be accountable for all aspects of the work.

Availability of data and material

Data are openly available in a public repository that issues datasets with the responsibility of the corresponding author.

Disclosure of conflict of interest

The author reports no conflicts of interest in this work.

Statement of informed consent

This study didn't involve information about any individual e.g. case studies, survey, interview etc., so statement of informed consent was not applicate.

References

[1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021; 71(3): 209-49.

[2] Global Burden of Disease Cancer C, Fitzmaurice C, Abate D, Abbasi N, Abbastabar H, Abd-Allah F et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-Years for 29 Cancer Groups, 1990 to 2017: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol. 2019; 5(12): 1749-68.

[3] Fitzmaurice C, Dicker D, Pain A, Hamavid H, Moradi-Lakeh M, MacIntyre MF et al. The global burden of cancer 2013. JAMA oncology. 2015; 1(4): 505-27.

[4] Dasgupta P, Henshaw C, Youlden DR, Clark PJ, Aitken JF, Baade PD. Global Trends in Incidence Rates of Primary Adult Liver Cancers: A Systematic Review and Meta-Analysis. Front Oncol. 2020; 10: 171.

[5] Hassanipour S, Vali M, Gaffari-Fam S, Nikbakht H-A, Abdzadeh E, Joukar F et al. The survival rate of hepatocellular carcinoma in Asian countries: a systematic review and meta-analysis. EXCLI journal. 2020; 19: 108.

[6] Mohammadian M, Soroush A, Mohammadian-Hafshejani A, Towhidi F, Hadadian F, Salehiniya H. Incidence and mortality of liver cancer and their relationship with development in Asia. Asian Pacific Journal of Cancer Prevention. 2016; 17(4): 2041-7.

[7] Hassanipour S, Mohammadzadeh M, Mansour-Ghanaei F, Fathalipour M, Joukar F, Salehiniya H et al. The incidence of hepatocellular carcinoma in iran from 1996 to 2016: A systematic review and meta-analysis. Journal of gastrointestinal cancer. 2019; 50(2): 193-200.

[8] Rezaei N, Far FF, Khademiureh S, Sheidaei A, Gohari K, Delavari F, et al. Liver cancer mortality at national and provincial levels in Iran between 1990 and 2015: A meta regression analysis. Hepatitis Monthly. 2018; 18(1).

[9] Mahdavi S, Amoori N, Salehiniya H, Enayatrad M. Epidemiology and trends in mortality from liver cancer in Iran. International Journal of Epidemiologic Research. 2015; 2(4): 239-40.

[10] Somi MH, Dolatkhah R, Sepahi S, Belalzadeh M, Naghashi S, Jafarabadi MA. A 12-year trend analysis of the incidence of gastrointestinal cancers in East Azerbaijan: last updated results of an ongoing population-based cancer registry. BMC cancer. 2019; 19(1): 782.

[11] Farahmand M, Almasi-Hashiani A, Fallahzade MH, Deputy H, Rate S, Rate C. Epidemiology of Cancer of Liver and Intrahepatic Bile Ducts Based on Fars Province Cancer Registry's Data,(2001-08). Zahedan Journal of Research in Medical Sciences. 2013; 15(2): 86-9.

[12] Moghaddam SD, Haghdoost AA, Hoseini SH, Ramazani R, Rezazadehkermani M. Incidence of hepatocellular carcinoma in southeast iran. Hepatitis monthly. 2010; 10(4): 270.

[13] Dimri M, Satyanarayana A. Molecular Signaling Pathways and Therapeutic Targets in Hepatocellular Carcinoma. Cancers (Basel). 2020; 12(2).

[14] Tripathy A, Thakurela S, Sahu MK, Uthanasingh K, Behera M, Ajay AK et al. The molecular connection of histopathological heterogeneity in hepatocellular carcinoma: A role of Wnt and Hedgehog signaling pathways. PLoS One. 2018; 13(12): e0208194.

[15] Singh G, Hossain MM, Bhat AQ, Ayaz MO, Bano N, Eachkoti R et al. Identification of a cross-talk between EGFR and Wnt/beta-catenin signaling pathways in HepG2 liver cancer cells. Cell Signal. 2021; 79: 109885.

[16] Akhtar B, Muhammad F, Sharif A, Akhtar MF, Majeed W. Diverse Signaling Pathways and Current Status of Molecular Targeted Treatments for Hepatocellular Carcinoma. Crit Rev Eukaryot Gene Expr. 2017; 27(4): 373-85.

[17] Jayachandran M. An Updated Portrait of Pathogenesis, Molecular Markers and Signaling Pathways of Hepatocellular Carcinoma. Curr Pharm Des. 2017; 23(16): 2356-65.

[18] Wang Y, He F, Zhang H, Cao Y, Zhang Y, Ling Y et al. Preparation and identification of an anti-idiotypic antibody antagonist (FG8) for EGFR that shows potential activity against liver cancer cells. Biotechnol Lett. 2021; 43(2): 369-82.

[19] Yuge R, Kitadai Y, Shinagawa K, Onoyama M, Tanaka S, Yasui W et al. mTOR and PDGF pathway blockade inhibits liver metastasis of colorectal cancer by modulating the tumor microenvironment. Am J Pathol. 2015; 185(2): 399-408.

[20] Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008; 359(4): 378-90.

[21] Liu M, Zhou R, Liang X, Su M, Li R, Yang B. Antineoplastic effects of sorafenib on primary liver cancer: a systematic review and meta-analysis. Int J Clin Exp Pathol. 2019; 12(7): 2389-97.

[22] Borena W, Strohmaier S, Lukanova A, Bjorge T, Lindkvist B, Hallmans G, et al. Metabolic risk factors and primary liver cancer in a prospective study of 578,700 adults. Int J Cancer. 2012; 131(1): 193-200.

[23] Barsouk A, Thandra KC, Saginala K, Rawla P, Barsouk A. Chemical Risk Factors of Primary Liver Cancer: An Update. Hepat Med. 2020; 12: 179-88.

[24] Campbell C, Wang T, McNaughton AL, Barnes E, Matthews PC. Risk factors for the development of hepatocellular carcinoma (HCC) in chronic hepatitis B virus (HBV) infection: a systematic review and meta-analysis. J Viral Hepat. 2021; 28(3): 493-507.

[25] Chang MH. Prevention of Hepatitis B Virus Infection and Liver Cancer. Recent Results Cancer Res. 2021; 217: 71-90.

[26] Lim EJ, Torresi J. Prevention of Hepatitis C Virus Infection and Liver Cancer. Recent Results Cancer Res. 2021; 217: 107-40.

[27] Laidlaw SM, Dustin LB. An HCV Vaccine on the Fly. J Infect Dis. 2020; 221(8): 1216-8.

[28] Stroh LJ, Krey T. HCV Glycoprotein Structure and Implications for B-Cell Vaccine Development. Int J Mol Sci. 2020; 21(18).

[29] Can Liver Cancer Be Found Early? https://www.cancer.org/cancer/liver-cancer/detection-diagnosis-staging/detection.html. American Cancer Society. 2021.

[30] NCCN Clinical Practice Guidelines in Oncology , Hepatobiliary Cancers, Version 2.2021-April 16, 2021 [database on the Internet]. National Comprehensive Cancer Network (NCCN). 2021.

[31] Beudeker BJB, Boonstra A. Circulating biomarkers for early detection of hepatocellular carcinoma. Therap Adv Gastroenterol. 2020; 13: 1756284820931734.

[32] Parikh ND, Mehta AS, Singal AG, Block T, Marrero JA, Lok AS. Biomarkers for the Early Detection of Hepatocellular Carcinoma. Cancer Epidemiol Biomarkers Prev. 2020; 29(12): 2495-503.

[33] Wang K, Li M, Qin J, Sun G, Dai L, Wang P et al. Serological Biomarkers for Early Detection of Hepatocellular Carcinoma: A Focus on Autoantibodies against Tumor-Associated Antigens Encoded by Cancer Driver Genes. Cancers (Basel). 2020; 12(5).

[34] Wang T, Zhang KH. New Blood Biomarkers for the Diagnosis of AFP-Negative Hepatocellular Carcinoma. Front Oncol. 2020; 10: 1316.