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Epidemiology and viral risk factors for hepatocellular carcinoma in the Eastern Mediterranean countries

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Abstract

Given the high prevalence of viral hepatitis in the Eastern Mediterranean countries, hepatitis B and C infections are the major causes of hepatocellular carcinoma (HCC) in the region. Most cases are associated with cirrhosis related to hepatitis B or C infection. Environmental, host genetic and viral factors can affect the risk of HCC in patients with hepatitis B and C infection. Understanding the epidemiology and viral risk factors in the region provides the implementation of strategies for prevention and treatment of viral hepatitis. Herein, we reviewed the epidemiology, burden of disease and viral risk factors for HCC.

Keywords: Viral hepatitis, Eastern Mediterranean countries, hepatocellular carcinoma, epidemiology, risk factors, burden

INTRODUCTION

Hepatocellular cancer (HCC) is the fifth most common cancer in men and the seventh most common cancer in women worldwide accounting for 90% of all primary liver cancers. Furthermore, HCC is the third leading cause of cancer-related death[1-3]. Because of the low resectability rate, high recurrence rate after resection and poor response to the conservative treatment, the prognosis of HCC is poor with a 5-year survival rate of 6.9%[1-3]. The burden of HCC is higher in developing countries and varies markedly by age, gender, race and exposure to risk factors in different geographic regions. In the Eastern Mediterranean countries, HCC has a lower prevalence compared to the highly prevalent regions like Eastern Asia and sub-Saharan Africa. However, HCC remains to be a major concern for countries like Egypt and Saudi Arabia. This article reviews the epidemiology and viral risk factors of HCC in Eastern Mediterranean countries.

Table 1. ASIR with 95% UI and male to female ratio by region, by sex in 2015

	ASIR 2015 (95% UI): male	ASIR 2015 (95% UI): female	ASIR ratio: male/female
HCC	8.1 (7.1-9.1)	4.7 (3.7-5.4)	1.7
HCC due to alcohol	1.4 (1.0-1.8)	0.3 (0.2-0.6)	4.7
HCC due to HBV	2.2 (1.7-2.6)	1 (0.7-1.2)	2.2
HCC due to HCV	3.5 (3.0-4.1)	2.4 (1.9-2.9)	1.5

Adapted from reference[8]. ASIR: age-standardized incidence rates; UI: uncertainty interval; HCC: hepatocellular carcinoma; HBV: hepatitis B virus; HCV: hepatitis C virus

GLOBAL EPIDEMIOLOGY AND BURDEN OF HCC

High-incidence regions of HCC are sub-Saharan Africa and Eastern Asia with 25 and 35 cases per 100,000 population/year, respectively. In these regions, high incidence rate of HCC is associated with high hepatitis B virus (HBV) prevalence. China has the highest incidence of HCC in the world, accounting for more than 40% of all HCC cases and 55% of liver cancer deaths[3,4]. Southern European countries have an intermediate-incidence (10-20 cases per 100,000 population/year); while North America, South America, Northern Europe, and parts of Middle East have low-incidence rates (< 5 cases per 100,000 population/year)[3-5]. The incidence in Asian countries tends to decline in the past 2 decades whilst it increased in United States and Canada because of high rate of chronic hepatitis C virus (HCV)-related cirrhosis, nonalcoholic fatty liver disease and immigrants from HBV endemic regions[4].

Hepatitis B and hepatitis C infections are the most important risk factors for HCC. Geographic distribution of HBV and HCV infections is the major factor, which determines the incidence of HCC. Owing to the high hepatitis B surface antigen (HBsAg) seroprevalance rates, HCC incidence is highest in East Asia and Africa. On the other hand, HCV is the etiological factor in approximately 20% of all HCC cases, particularly in the low-incidence regions such as Western Europe and North America[3,6].

The mean age of HCC diagnosis was 55-59 years in China and 63-65 years in Europe and North America[7]. Men were found to have 2-4 fold increased incidence of HCC than women. The results of the global burden of disease (GBD) study for 195 countries or territories from 1990 to 2015 showed that HCC was more common in men with 591,000 incident cases compared to women with 264,000 cases[8]. Similarly, mortality rates were higher among men. The gender disparity was also notable for high rates of HBV-related and alcohol-related HCC in men[8]. The variations in hepatitis carrier state, sex steroid hormones, immune responses and epigenetics were linked to higher HCC incidence rates among men[7].

EPIDEMIOLOGY AND BURDEN OF DISEASE IN THE EASTERN MEDITERRANEAN COUNTRIES

According to GBD study 2015 report, in the Eastern Mediterranean countries age-standardized incidence rate (ASIR) of HCC was 8.1 per 100,000 in men, and 4.7 per 100,000 in women [Table 1][8]. HCC is a major health problem especially in certain countries such as Egypt and Saudi Arabia. In Egypt, HCC is the fourth most common cancer and is the second cause of cancer mortality in both sexes[8]. In the last decades, a twofold increase of HCC was reported among chronic liver disease patients in Egypt with a significant decline of HBV and slight increase of HCV as risk factors[9]. HCV is an important risk factor for HCC in Egypt where 71% of HCC cases were positive for anti-HCV antibodies[10]. Likewise, in the Nile delta, hepatitis C rather than hepatitis B was linked to the development of HCC[11]. In Saudi Arabia, and according to the National Cancer Registry, HCC is ranked the sixth most common cancer in males and thirteenth in females with a male to female ratio of 2.6:1. The overall age-standardized rate (ASR) is 3.5/100,000. ASR is 4.9/100,000 for males and 1.8/100,000 for females. The median age of diagnosis is 66 years[12]. The results of a tertiary center in Saudi Arabia showed that most of the patients diagnosed with HCC presented at late tumor stages with advanced liver disease and had poor prognosis with an average of 33-month survival[12]. This prompts the implementation of HCC surveillance strategies in this geographic region.

Table 2. Etiology of HCC in Eastern Mediterranean countries

Location	Alcohol	HBV	HCV	Other
Afghanistan	11%	36%	32%	21%
Bahrain	17%	39%	28%	16%
Cyprus	32%	19%	39%	14%
Dijibouti	13%	33%	36%	18%
Egypt	12%	13%	63%	12%
Iran	6%	44%	24%	26%
Iraq	12%	37%	32%	19%
Israel	15%	20%	49%	17%
Jordan	15%	35%	31%	19%
Kuwait	15%	37%	31%	18%
Lebanon	17%	28%	40%	15%
Libya	15%	33%	34%	18%
Morocco	14%	31%	36%	19%
Oman	17%	39%	28%	16%
Pakistan	7%	16%	54%	23%
Qatar	18%	38%	28%	15%
Saudi Arabia	17%	41%	17%	25%
Somalia	15%	36%	30%	18%
Sudan	18%	35%	30%	16%
Syria	14%	32%	34%	19%
Tunisia	18%	20%	44%	18%
Turkey	19%	26%	44%	11%
United Arab Emirates	21%	44%	22%	13%
Yemen	8%	44%	35%	12%

Adapted from reference[8]. HCC: hepatocellular carcinoma; HBV: hepatitis B virus; HCV: hepatitis C virus

RISK FACTORS FOR HCC

The major risk factors for HCC are the presence of cirrhosis, and HBV/HCV infection. Other factors, such as aflatoxin B exposure and nonalcoholic steatohepatitis (NASH) are important in certain regions of the world. In the high-incidence countries of Asia and Africa, chronic HBV infection and aflatoxin B exposure are the major risk factors. Exceptionally, in Japan and Egypt the most common risk factor is HCV infection. On the contrary, excessive alcohol consumption and metabolic syndrome play more important roles in the low-incidence regions. In addition, inherited metabolic disorders such as hemochromatosis, A1AT deficiency, tyrosinemia, several porphyrias also increase the risk of HCC[13].

The distribution of viral and other risk factors of HCC in the Eastern Mediterranean countries are summarized in Table 2.

Chronic hepatitis B

Countries with HBV prevalence of greater than 2% have increased incidence and mortality rates of HCC. The majority (70%-90%) of HBV-related HCC develops in patients with cirrhosis[14,15]. In persons chronically infected with HBV, the risk of HCC has been shown to increase up to 30-fold[14,15]. As a result of hepatic inflammation and liver damage, genetic and epigenetic defects lead to development of HCC[16-18]. However, in the absence of cirrhosis HCC can develop in 10%-20% of HBV-infected individuals as a result of integration of HBV into the host genome that induces chromosomal alterations and insertional mutagenesis of cancer genes[17-19]. The genetic instability of the hepatocyte triggers the clonal growth of hepatocytes before the liver damage occurs. HBV-encoded X protein (HBx) which is a multifunctional protein that regulates the expression of genes in the involved in the signal cascades, has a pivotal role in the pathogenesis of HBV-related HCC[17-19]. In addition to cirrhosis, other factors reported to increase HCC risk among patients with chronic HBV comprise; demographic (male sex, older age, Asian or African ancestry, family history of HCC), viral [higher levels of HBV replication, HBeAg positivity, HBV genotype, longer duration of infection, co-

infection with HCV, human immunodeficiency virus (HIV), or hepatitis D virus] and environment related factors (exposure to aflatoxin, excessive alcohol or tobacco consumption).

A population-based study of untreated chronic hepatitis B (CHB) patients from Taiwan named the risk evaluation of viral load elevation and associated liver disease/cancer-hepatitis B virus (REVAL-HBV), first reported that high baseline serum HBV DNA level was associated with the risk of cirrhosis and HCC[20]. The risk began to increase in a dose-response relationship from < 300 (undetectable) to ≥ 1,000,000 copies/mL. Furthermore, patients with persistently high HBV DNA levels had the highest risk of HCC. The role of viral load on HCC development was also confirmed in several cross-sectional and longitudinal cohort studies from Taiwan, Hong Kong, and China[21-23]. HBeAg-positivity, which shows active viral replication, is also associated with the development of HCC[24]. Although long-term suppression of viral replication can be achieved with the use of potent oral antiviral therapies, the risk of HCC is not eliminated. This was clearly demonstrated in a study of 1378 patients comparing the incidence of HCC between patients who received oral antiviral treatment and inactive carriers[25]. The study found a higher risk of HCC development in patients treated with oral antiviral drugs than those with inactive CHB and indicated that the risk of HCC is not eliminated in patients receiving oral antiviral treatment. These patients should continue to be screened for HCC.

HBV genotype is also important in determining the risk for HCC[26,27]. The risk is higher in patients with genotype C than patients with genotype B. High viral load and genotype C have an additive role in increasing the risk of HCC[28]. Genotype D patients carry a higher risk for HCC than patients with genotype A[28]. HBV genotype D was found to be the most prevalent genotype in studies reported from Turkey, Iran, Pakistan and Saudi Arabia[29-32]. There is rare evidence to show the association genotypes with the risk of HCC in the Middle Eastern countries. Studies from Iran have also demonstrated a strong relationship of genotype D and mutations in basal core promotor (BCP) and precore regions with the disease outcomes[33,34].

The prevalence of HBV infection is complex and a major public health problem in Eastern Mediterranean countries. In the early studies, reported HBV prevalence rates ranged from < 2% to 2%-8% in most countries, reaching up to ≥ 10% in Saudi Arabia, Yemen and Sudan[29,35-38]. In the latest report of World Health Organization (WHO), Eastern Mediterranean countries have a prevalence of chronic HBV infection ranging from low intermediate (2%-4%) in most countries to high intermediate (5%-7%) in Somalia and Sudan[39,40]. The WHO estimates that more than four million people are infected yearly with HBV in this region[41]. The lifetime risk of HBV infection in the pre-vaccination era ranged from 25% to > 75%, with continued transmission from the perinatal period throughout early children and adult life. It was estimated that around 100,000 persons from each birth cohort in the region would die from HBV-related liver disease and HCC during their lifetime. In these high-risk regions, the primary transmission routes are perinatal, child-to-child, sexual contact and percutaneous exposures (e.g., unsafe injections and blood transfusions).

Despite the introduction of hepatitis B vaccination programs, HBV continues to be transmitted among unvaccinated older children and adults. Therefore, in 2009 WHO Eastern Mediterranean regional committee implemented a regional target, to reduce the prevalence of CHB infection to less than 1% among children below 5 years of age by 2015[39]. The national health agencies in the region supported the program with hepatitis B vaccination of newborns. By the end of 2014, 68% of the countries achieved the target. The rate of hepatitis B birth dose vaccination coverage in the region increased to 24% in 2014 compared to 14% in 2000[39]. In 2014, 71% of newborns received a birth dose within 24 h in the countries, which had < 80% birth dose coverage[39].

A systematic review examining the viral etiologies of HCC in the Eastern Mediterranean countries indicated HBV as a major cause in 35%, 42.5%, 55% and 52% of HCC cases in Saudi Arabia, Yemen, Turkey and Iran,

respectively[42]. But the lack of high quality data and data registry systems represent a major challenge to determine the epidemiology of HCC in this region. Universal HBV vaccination is the most effective strategy to reduce the incidence of HCC. A 20-year follow-up report from Taiwan - an endemic region - clearly showed that HCC incidence among subjects 6-19 years of age decreased in the vaccinated cohort (64 HCC in 37,709,304 person-years), compared to the non-vaccinated cohort (444 HCC in 76,496,406 person-years), with the adjusted relative risk (RR) of 0.31[43].

The impact of vaccination programs on the incidence of HCC development in the Eastern Mediterranean countries needs to be clarified in future studies. However, many challenges remain. The war in this region leads to low or decreased coverage of vaccination programs. Furthermore, immigration after war is a major threat for the application of immunization programs, identification and treatment of CHB patients that will change the epidemiological trends for HBV and HBV-related HCC in the Eastern Mediterranean countries.

Chronic hepatitis C

HCV is one of the major global causes of liver-related death and morbidity. The risk of HCC is increased 15-20 fold in patients chronically infected with HCV infection. Over the last decade, HCV seroprevalence is estimated to increase by 2.8%, accounting for more than 185 million infections worldwide[44]. A systematic review analyzing the studies published between 2000 and 2015 from 138 countries (representing the 90% of the global population) estimated global HCV prevalence at 2.5%. Central Asia and Central Africa are estimated to have the highest prevalence (> 3.5%); East, South and Southeast Asia, West and East Africa, North Africa and Middle East, Southern and Tropical Latin America, Caribbean, Australasia, and Eastern Europe moderate prevalence (1.5%-3.5%); while Southern Africa, North America, Andean and Central Latin America, Pacific Asia and Western and Central Europe have low prevalence (< 1.5%). The global viremic rate was 67%, with HCV varying from 48.7% in Central Asia to 80.2% in Tropical Latin America[45]. HCV genotype 1 is the most frequent genotype followed by genotype 3 (17.9%), genotype 4 (16.8%), genotype 2 (11%), genotype 5 (2%) and genotype 6 (1.4%)[45]. The genotypes reported to be associated with high risk of HCC are genotype 1b and genotype 3[46-48].

Chronic HCV infection causes increased inflammation and cell-turnover leading to cirrhosis and development of dysplastic nodules and HCC[39]. Unlike HBV, HCV-associated hepatocarcinogenesis is more likely to be related to the indirect effects of the virus on the host cellular processes such as increased hepatocyte proliferation and steatosis, virus-induced inflammation and oxidative stress inducing genomic mutations and genome instability, mitochondrial damage and induction of reactive oxyen species, and virus-induced host immune responses[19]. In untreated patients, cirrhosis develops in 14%-45% of patients 20 years after transmission of HCV[49]. In patients with HCV-related cirrhosis, annual rate of HCC is 1%-4%, therefore patients with advanced fibrosis and cirrhosis should undergo HCC surveillance. The risk factors for HCC are older age, black race, HCV genotype 1b, co-infection with HBV or HIV, diabetes, obesity, steatosis, heavy alcohol consumption and low platelet levels in patients with cirrhosis[49-52].

The HCV prevalence in the Eastern Mediterranean region ranges from 1% to 2.5% in most countries, with higher prevalence reported in Egypt (> 10%), and in Libyan Arab Jamahiriya, Sudan and Yemen (2.5%-10%)[53]. In the Eastern Mediterranean region of WHO, it is estimated that at least 23 million people have HCV infection[53]. This represents almost the total of HCV patients in Europe and US. Regarding the parenteral spread by the previous use of intravenous anti-schistosomal treatment campaigns, HCV prevalence is very high in Egypt, particularly in the age group of 40-60 years[54-56]. A high prevalence of HCV among children born after these campaigns is explained by unsafe injections[54-56]. In Pakistan, the prevalence of HCV is variable from 2% to 14%, and HCV transmission in this region is due to unsafe injections[57].

HCV genotype is an important epidemiological determinant for the source and the possible mode of transmission. Furthermore, genotype has a substantial role in predicting the treatment response. Six major

genotypes of HCV were described. In the Eastern Mediterranean countries, there are 2 predominant genotypes; genotype 4 in the Arab countries (except Jordan) and genotype 1 in non-Arab countries (Islamic Republic of Iran, Israel and Turkey)[58]. Egypt is of particular importance with more than 90% of genotype 4 HCV infection[59]. The distribution of HCV genotype in Jordan differed from the other Arab countries, predominantly genotype 1a (40%), followed by genotype 1b (33%) and genotype 4 (33.3%)[60]. The most common genotype in Southern Israel was genotype 1b (62%) while genotype 4 (78%) was predominant in the Gaza Strip[61]. Turkey serves as a bridge between Europe and Asia, and HCV genotype pattern is similar to Eastern and Southern European countries, having genotype 1b as the most frequent genotype (> 70%) followed by genotype 1a[62]. HCV genotype 3a is the most common subtype in Iran followed by genotype 1a, 1b and 4[63]. The predominant genotypes (1a and 4) are the most difficult-to-treat groups. The association between the HCV genotype and the risk of HCC is based on the epidemiological data however one can speculate that the poor response to interferon (IFN)-based regimens in genotype 1 and 4 patients may explain the disease progression and high risk of HCC development.

Chronic HCV infection leads to HCC following a multistep carcinogenesis pathway. Interferon (IFN)-based regimens provided sustained virologic response (SVR) in 40%-50% of patients[64]. Recently developed direct-acting antivirals (DAAs), which directly target the viral protease, polymerase, or non-structural proteins, have achieved a revolutionary improvement of SVR rate over 90%[65].

In developing countries, less than 10% of HCV-infected patients can access to DAAs. Despite the high antiviral efficacy, high cost of the medications is a major barrier to the access to treatment of the sufferers[66,67]. In addition, more than 50% of infected individuals have unrecognized HCV infection[68]. These patients generally present with advanced liver disease. Each year approximately 3-4 million newly infected cases are expected, the burden of HCV-related liver disease will remain to be high, even in the developed countries.

A systematic review including 13 studies on 2386 patients in Egypt estimated the annual rates of death/transplantation, decompensation and HCC in patients with compensated HCV cirrhosis to be 4.58%, 6.37% and 3.36%, respectively[69]. In 2014, an estimated 125,000 viremic individuals/year were diagnosed with HCV infection. Of these 10% had chronic hepatitis, 30% had compensated cirrhosis, and the majority (60%) were diagnosed with decompensated cirrhosis or HCC[70,71]. The high prevalence of HCC in HCV patients was reported to be associated with decompensated cirrhosis in Egypt[72].

In the Eastern Mediterranean countries, treatment strategies are determined by the availability of resources, availability of medications and expected number of cases. In the countries, which have access to DAAs, treatment is prioritized for patients with advanced fibrosis and cirrhosis. In 2014, national committee for control of viral hepatitis (NCCVH) in Egypt negotiated with the industry to decrease the price of DAAs. Furthermore, local generic treatments were encouraged and decreased the cost of treatment. This program provided treatment of large number Egyptian genotype 4 HCV patients. This model needs to be reproduced in other developing countries to decrease the risk of cirrhosis and HCC in HCV-infected individuals. Elimination of HCV by 2030 is one of the major targets of WHO by implementing models to reduce the rate of new infections and provide treatment access in middle and low income countries. Many countries including Australia, Brazil, Egypt, Georgia, Germany, Iceland, Japan, the Netherlands and Qatar are on the track to eradicate hepatitis C by 2030.

Hepatitis D virus

The hepatitis D virus (HDV) is an incomplete RNA virus, which is dependent on HBsAg for transmission and replication[73,74]. HDV leads to fulminant hepatitis and further disease progression among hepatitis B infected patients. The long-term co-infection of HBV and HDV presents a worse prognosis than CHB

infection. Up to 80% of HBV and HDV co-infected patients progress to cirrhosis[73,74]. It has been estimated that almost 5% of HBV infected patients have HDV co-infection[73,74].

The epidemiologic distribution of HDV infection is variable throughout the world. HDV is highly endemic in the Eastern Mediterranean countries[75]. Two studies from Turkey show prevalence of anti-HDV in 18.8% to 23.0% of HBsAg positive HCC[37,76]. A Jordanian study reported the prevalence of anti-HDV in a small group of HBsAg positive HCC patients was 67%, but the sample size was very small[77]. The risk of HCC is increased in HDV infection compared to HBV monoinfection. HDV infection increases the risk for HCC threefold and for mortality two fold in patients with hepatitis B cirrhosis[78,79]. However, the pathogenetic mechanism of HDV in HCC development has not been clarified yet. Oxidative stress as a result of severe necroinflammation, epigenetic mechanisms like DNA methylation and histone modification are the proposed mechanisms[80].

The only available treatment for HDV is interferon with a very low efficacy[81]. Therefore, the spread of HDV can be prevented by effective HBV vaccination programs leading to a decrease in the incidence of HCC[82]. Health-care providers should be educated to check for HDV infection in chronic HBV carriers. In addition, patients should be informed about the risk of superinfection from carriers co-infected with HDV and educated about preventive practices.

SUMMARY

HBV and HCV infections are the most important etiologies for HCC in Eastern Mediterranean and Middle Eastern countries. Implementation of screening programs for individuals at high risk, maintaining HBV suppression in chronic hepatitis B and sustained viral response in CHC, surveillance of patients at high risk for developing HCC are recommended to prevent progression to cirrhosis and HCC development. The lack of data registry systems in the region resulted in limited understanding of the exact epidemiology of disease. Furthermore, the political and social unrest in the region and the immigrations after the wars may restrict the application of preventive programs and may lead to increased incidence of hepatitis. Public health policies should consider the future impact of the current situations.

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Authors' contributions

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Idea of the review, critical revision of the manuscript: Tozun N

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The authors declare that there are no conflicts of interest.

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