Hepatocellular Carcinoma in the World and the Middle East

H Poustchi[1*], SG Sepanlou[1], S Esmaili[1], N Mehrabi[1], A Ansarymoghadam[2]

1. Digestive Disease Research Center, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran
2. Health Promotion Research Center, Zahedan University of Medical Sciences, Zahedan, Iran

[*]**Corresponding Author:**
Hossein Poustchi MD, PhD
Assistant Professor, Digestive Diseases Research Center, Shariati Hospital, North Kargar Ave., Tehran, 14117-13135, Iran
Tel: +98 21 82415300
Fax: +98 21 82415400
E-mail: Poustchi@ams.ac.ir
Received: 3 October 2009
Accepted: 26 December 2009

ABSTRACT

Hepatocellular carcinoma (HCC) is a major worldwide public health concern. Despite recent advances, there has been little success in improving the survival of HCC patients. Due to advances in diagnostic modalities and the increasing incidence of chronic viral hepatitis and nonalcoholic fatty liver disease (NAFLD), both of which are well known risk factors of HCC, the prevalence of HCC is increasing in developed countries and it is expected that this trend will continue in the future.

In Middle Eastern countries the prevalence of this cancer is lower compared to sub-Saharan Africa and some Far East countries; however it is documented that the prevalence of this cancer in some parts of the Middle East is also increasing. In the current review, the prevalence and burden of this disease worldwide, particularly in Middle Eastern countries, and risk factors for HCC are discussed.

KEYWORDS
Hepatocellular Carcinoma; Prevalence; Viral Hepatitis; Chronic Hepatitis

Introduction and Global Importance

Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer accounting for 7.5% and 3.5% of all cancers among men and women, respectively[1] and accounts for half a million deaths per year.[2,3] The distribution of HCC varies widely.

In terms of global prevalence, HCC ranks as the eighth most common cancer, sixth among men and eleventh among women.[4] In some countries, such as China, HCC ranks as the second most common internal malignancy.[5,6]

Primary liver cancer is more prevalent among men than women. The gender-specific age-adjusted incident rate (AAIR) ratio ranges from 1.3 to 3.6 worldwide.[1]

In high risk areas, liver cancer incidence rates increase after 20 years of age and peak at about age 50. In most European countries and America, HCC incidence peaks at 75 years of age.[7]

The global difference in AAIR reflects differences in the natural history of the hepatitis B virus (HBV), the most common cause of liver cancer in Asian and African countries and the hepatitis C virus (HCV), the most common cause of HCC in regions with a low prevalence of HBV (e.g., America, Northern Europe and Australia).

Although HCC is more prevalent in Asian and African nations, there is evidence to conclude that the incidence of HCC is rising in developed countries. During the last two decades, an increase in HCC incidence has been reported from Australia,[8] France,[9] the United Kingdom,[10] Japan[11] and North America.[7] Evidence suggests that the increased incidence of HCC in developed countries is not solely attributable to more accurate and earlier diagnosis or to an increase in immigration from high prevalence regions.

HCC is a disease that is relatively insensitive to chemotherapy and/or radiotherapy. Further, given that the liver is usually compromised in the majority of persons who develop the tumor, it is associated with an extremely poor prognosis. For this reason, mortality from HCC almost equals its incidence.

There were an estimated 383,593 deaths among men and 164,961 deaths among women attributable to HCC for the year 2000, which is quite close to the HCC incidence during the same time period.[7]

An increase in the mortality rate of liver cancer among men has recently been reported in some developed countries including the United States, Japan, Scotland, France and Italy.[12,13]

The mortality rate among women however was unchanged.[7] These data suggest that primary liver cancer is an important global public health problem. In spite of vaccination programs against HBV in many countries, the incidence and mortality from HCC is increasing, particularly in western countries where the prevalence of HBV is low.

Burden of Liver Cancer in the Middle East

In Middle Eastern countries, liver cancer is a major concern among men, especially in certain countries such as Egypt and Saudi Arabia, and to a lesser extent in other countries of this region.

Recent reports demonstrate that the incidence of HCC has increased sharply in the last 5–10 years,[14-16] with an especially high incidence in Egypt.[17]

However, in general, HCC is less prevalent in the Middle East compared to high incidence countries.[18] The incidence varies significantly among different districts and countries[18,19] (Table 1).

Table 1: Population-based Cancer Registry Data for Middle Eastern countries.[18]

Country	Annual incidence of liver cancer per 100,000	
	Males	Females
Egypt	21.9	4.5
Kuwait	8.1	3.6
Oman	7.4	3.2
Saudi Arabia	5.9	2.2
Bahrain	5.3	3.1
Lebanon[23]	3.5	2.2
Qatar	3.4	1.8
Palestine	2.6	0.7
Tunisia	2.2	0.7
Jordan	1.9	1.3
Iran	1.4	1.9

The prevalence of HCC is high in the Nile Delta area. HCC is also more common among males, rural residents and farmers which it is believed that pollution due to insecticides might be one of the risk factors.[20] In Iran, HCC is the 16th most prevalent cancer.[21,22]

Risk Factors for HCC

HCC is one of the few cancers with clearly defined major risk factors. These include chronic viral hepatitis, alcohol consumption, NAFLD, aflatoxin ingestion, exposure to inorganic arsenic through drinking water,[23,24] exposure to cigarette smoke, oral contraceptives,[25,26] iron overload,[27] advanced hepatic fibrosis, exogenous (oral contraceptive pill) and endogenous (androgens) hormones, male gender and a familial tendency to HCC. The population attributable risk estimates for liver cancer for each of these risk factors varies among countries, but chronic infection with HBV and HCV are the most important precursors for HCC development on a global scale, together accounting for over 80% of liver cancer cases worldwide.[28] Due to the more important roles of HBV and HCV infection in the incidence of HCC, minor risk factors are not discussed in this review.

Chronic Hepattis B

HBV infection can cause acute or chronic hepatitis. Chronic hepatitis B (CHB) is defined by the presence of hepatitis B surface antigen (HBsAg) for

more than six months after infection. Worldwide, the 350 million people diagnosed with CHB have a 15-25% risk of dying from HBV-related liver disease, including cirrhosis and HCC. Each year, acute and chronic HBV infection causes approximately one million deaths.[29]

HBV is a DNA virus which has eight different genotypes (A-H). A distinct pattern of geographic distribution of the HBV genotypes is evident and is reinforced by recent findings (Table 2). Indeed, genotyping can help trace the migration patterns of ancestors as well as the routes of transmission following accidental exposure to HBV.

Epidemiologic studies have demonstrated a strong association between CHB and HCC. Thus, the incidence of HCC increases parallel the prevalence of HBsAg in all geographic areas.[30] Generally, in patients who are infected in the first year or two year of life, the interval between initiation of chronic infection and the peak incidence of HCC is 30-50 years.[31,32]

The relative risk for the development of HCC in cohort studies in which HBV infected patients were followed until HCC developed has been reported to be 7-100 times higher than in those without infection.[33-35]

The exact level of risk depends on the severity and activity of the resultant liver disease as well as the presence or absence of other pro-oncogenic risk factors.

There are two possible pathways for the involvement of HBV in the development of liver cancer. In the first, the HBV genome may directly participate in causing genetic changes in the host genome that lead to hepatocarcinogenesis. In the second, HCC develops in HBV-related cirrhosis.

Mutations in the HBV genotype are also found to be associated with HCC occurrence. Two important groups of predisposing mutations have been described: those occurring in the pre-core region and those occurring in the basal core promoter (BCP).

The dominant pre-core variant is a point mutation from G to A at nucleotide (nt) 1896 (G1896A). This terminates translation of the pre-core/core protein and interrupts HBeAg synthesis.[36,37] The most common BCP variants are at nucleotide 1762 (A1762T) and 1764 (G1764A).

Table 2: Geographic distribution of HBV genotypes.

Genotype	Geographic distribution
A	Northwest Europe, sub-Saharan Africa, North, Central and South America
B	Southeast Asia, China, Japan, Oceania
C	Southeast Asia, China, Japan, Korea Oceania
D	Middle East, Mediterranean basin, India, Central Asia and South America
E	West and Central Africa
F	Central and South America, Alaska
G	France, USA
H	Central America, Mexico, South USA

These variants reduce the pre-core RNA level and consequently reduces HBeAg production at a transcriptional level.[36,37] Core promoter and BCP mutants are associated with severe and advanced liver disease.[37-41]

PreS deletion of HBV has recently been shown to be associated with liver disease progression and HCC development in HBV carriers. PreS mutant viruses lack potent B- and T cell epitopes which normally exist in the preS region. This variant could escape from immune system surveillance.

These preS protein mutants accumulate in the endoplasmic reticulum (ER), resulting in ER stress.

Subsequently, ER stress not only can induce oxidative DNA damage and genomic instability, but also can induce proliferation-related signal pathways in the hepatocytes which may progress to tumor formation.[42]

Thus, the observed difference in fraction of HCC that is attributable to HBV in different regions may be due to difference in the influence of the HBV genotype on the outcome of CHB.

HBV in the Middle East

In Middle Eastern countries, the prevalence of HBV varies according to geographic region. Similar to the world distribution of HBV, countries of this region fall within all three groups of low, intermediate and high endemic areas of HBV.

The HBV prevalence ranges from 0.8 to 7% in Iran, 2 to 5% in the UAE, 2.3 to 10% in Oman, 2.6 to 10% in Jordan, 2 to 6% in Libyan Arab Jamahiriya, 4 to 5% in Iraq, 5 to 6% in Palestine, 6.5% in Tunisia, 5 to 10% in Turkey, 7.4 to 17% in Saudi Arabia, 12.7 to 18.5% in Yemen and 16 to 20% in Sudan.[43-46]

In Lebanon, the prevalence of HBV in blood donors is 1-2%.[47,48] In Turkey, HBV is endemic. The seropositivity rate for HBsAg in the general population in Turkey is 5-10%.

Studies from Iran, Pakistan, Turkey, Egypt, Saudi Arabia, Jordan and Yemen provide evidence to show that the dominant genotype of HBV in most Middle Eastern countries is genotype D.[49-54]

It seems that certain mutations in the genome of HBV are associated with the severity of hepatitis B chronic infections and the natural history of HCC. In Iran, a country with intermediate endemicity for HBV infection, approximately 35% of the population have been exposed to the virus while about 3% have chronic infection.[55,56]

Although HBV is the most common etiological agent for cirrhosis in Iran with evidence of previous exposure in up to 30% of cases,[57] HCC is only the 16th most prevalent cancer.[21,22] This contrasts markedly with other regions with a similar prevalence of CHB where HCC is among the top seven cancers in incidence and prevalence.[58] Studies of the molecular aspects of HBV infection in Iran have demonstrated that genotype D with ayw2 is predominant in Iranian strains and these are closely interrelated, which support earlier reports.[59,60] Bahramali et al. have also demonstrated that genotype D1 is predominant in Iran and mutations in BCP and precore regions influence the disease outcome in HBeAg-negative patients.[51] In our previous study among 110 Iranian patients with HBV genotype D, we were able to demonstrate a strong relationship between this part of the HBV genome with clinical aspects of the disease.

The results of this study showed that the prevalence of A1762T-G1764A mutation was higher in patients with advanced liver disease (cirrhosis and HCC) and was also associated with higher ALT level and viral load.[49] On the other hand, we have found the G1757A substitution in this part of HBV gene which seems to be protective, being 90% less frequent among patients with cirrhosis and HCC (p=0.001).

In addition, other factors might be responsible for a low prevalence of HCC in Iran and other Middle Eastern countries. These include very low consumption of alcohol, lower pathologic-based diagnosis of HCC and perhaps lower survival of cirrhotic patients.

In conclusion, HBV genotype may influence the severity of CHB disease and development of HCC. Further research however is required to clarify the role of virus genotype and the associated mutations to the progression of liver disease and HCC.

Chronic Hepattis C

HCV infects about 170 million people worldwide[61] and plays an important role in HCC development in regions where CHB is less common. In Japan, Egypt, Saudi Arabia, southern Europe and the USA, HCV is the main risk factor for HCC. Serological markers of HCV infection (positive anti-HCV) are thus found in 71%, 80% and 73% of HCC cases from Egypt,[62] Japan[63] and the USA[64], respectively.

With the implementation of vaccination programs against HBV, the importance and the prevalence of HCV as an etiological factor for HCC is increasing as demonstrated by data from the United State,[65] Germany,[66] Japan,[11] France[67] and Australia.[68] Before the introduction of screening tests, blood transfusion and injection drug use (IDU) were the main risk factors for HCV acquisition, being identified in 60–80% of cases. After the implementation of routine blood donor screening however, injection drug use is the main risk factor.[69]

Phylogenetic analysis of the nucleotide sequences derived from HCV has identified six major genotypes of the virus. Table 3 demonstrates the global distribution pattern of HCV infection by genotype.[70]

HCV infection causes acute and chronic liver disease. Unlike CHB, the majority (70%) of

patients infected with HCV, irrespective of their age of acquisition, will progress to chronic disease.[70]

Table 3: Global distribution pattern by HCV genotype.

Genotype		Geographic distribution
1	1a	North and South America, Australia
	1b	North America, Europe, Japan
2	B	USA, Northern Europe
	C	Western and Southern Europe
3a		Australia, Southern Asia
4	4a	Egypt
	4c	Central Africa
5		South Africa
6		Asia

The exact pathogenesis of hepatic injury is not well understood in chronic HCV. It has been suggested that HCV is not cytopathic to hepatocytes and that the immune response, especially cytotoxic T cell responses against HCV-infected hepatocytes, is the main cause of liver cell injury, fibrosis, cirrhosis and eventually HCC. Cytokines such as interferon gamma and tumor necrosis factor alpha released from activated lymphocytes may play important roles in the pathogenesis of liver injury associated with chronic HCV infection (CHC).[71]

Cirrhosis and HCC are the most serious complications of CHC.[72] Donato et al.[73] noted that the risk of HCC increased 17-fold among HCV-infected patients compared with anti-HCV negative controls. Unlike CHB, HCV-related HCC always occurs in older persons, and nearly all cases are associated with advanced hepatic fibrosis or cirrhosis.[74]

The incidence of liver cancer in HCV patients with cirrhosis is 3 to 10% per annum. The incidence in Western countries is 3-5% per year, but higher in Asian nations.[75]

Results of a study in Japan revealed that the incidence of HCC among those with CHC and cirrhosis was approximately 10%, which was higher than seen for CHB infection (4%).[76] Shiratori et al.[77] analyzed the characteristics of 205 HCC cases from Japan and noted that CHC-associated HCC occurred in the presence of more severe liver disease than in CHB-associated HCC.

These data suggest that HBV is more oncogenic than HCV with the latter being associated with the development of HCC usually only in the presence of advanced liver disease.

HCV in the Middle East

The World Health Organization estimates that there are at least 21.3 million HCV carriers in the Eastern Mediterranean countries, which is close to the number of carriers estimated in the Americas and Europe combined.[78]

The prevalence of HCV infection in Middle Eastern countries varies geographically. This prevalence is 0.5-1% in Iran, 6.8% in Saudi Arabia, 4.2% in Yemen, 4.4% in Sudan, 5% in Pakistan, 0.1-0.6% in Lebanon, and 1.5% in Turkey.[6,47,48,79-84] The highest prevalence belongs to Egypt with 22%.[82,85] In a population-based study in Iran done by Merat et al., the prevalence of HCV in Iran was 0.3%, 1.6% and 1.0% in Tehran, Hormozgan, and Golestan provinces, respectively.[86] It has been well documented that the prevalence rate of HCV infection in Egypt is among the highest in the world [87] in which various strains are involved.[88] The distribution of HCV genotypes and subtypes in the Middle East[79,89-102] are shown in Table 4.[103]

The accumulated data show that there are two main patterns for the distribution of HCV genotypes: one is peculiar to the Arab countries (with the exception of Jordan) where genotype 4 predominates, while the other pattern is characteristic of the non-Arab countries (Turkey, Pakistan and Iran) where genotype 1 predominates. Although varying prevalence of genotype 4 have been reported from Arab countries, it is noteworthy that genotype 4 is quasi-exclusive (91%) in Egypt which is also a North African country.[79,94,97] Based on only one known study in Jordan, 1a is the dominant subtype (40%) followed by 1b (33.3%) and genotype 4 (26.6%).[91]

In Turkey[92,93] subtype 1b is the dominant subtype (>70%) followed by 1a, which is similar to the

pattern seen in Eastern and Southern Europe.[104,105] Subtype 3a is the most common subtype in Iran followed by 1a, 1b and 4.[98]

Table 4: Distribution of hepatitis C virus genotypes and subtypes in the Middle East.[103]

Region	Genotype/subtype	
	Most common	Less common
Arab countries		
Egypt	4	1a, 1b, 2a
Gaza Strip	4	1, 3a
Jordan	1a	1b, 4
Kuwait	4	1
Lebanon	4	1a, 1b
Saudi Arabia	4	1a, 1b, 3a
Syria	4	1b, 1a
Non-Arab countries		
Iran	3a	1a
South	1a	1b
Northwest	3a	4
Tunisia	1b	3a
Pakistan[80]	3a	3b, 1a
Turkey	1b	1a

Results from the limited number of clinical trials on the treatment of chronic HCV genotype 4 using peginterferon alfa-2b in combination with ribavirin are encouraging.[106-110] However, efforts to develop more effective antiviral therapies and the establishment of an effective HCV vaccine remain the largest challenges for the near future.

HBV and HCV Co-infection

Co-infection with HBV and HCV is associated with a higher risk for developing HCC than either infection alone. In an Australian case-control study, Dutta et al.[111] have demonstrated that the risk of developing HCC in HCV-infected patients was 5.5-fold higher if a patient was anti-HBc positive.

Likewise, in a meta-analysis of 32 case-control studies, the odds ratio for the development to HCC was 165 for the co-infection with HBV and HCV (versus no infection), 23 for isolated infection with HBV, and 17 for isolated infection with HCV (both versus no infection).[73]

Attribution of HCC to HBV or HCV in the Middle East

Understanding the risk factors for HCC and predictors of poor survival are important in prevention and treatment. Studies from Middle Eastern countries have shown wide variation in the etiology of HCC. We have reviewed the attribution of HCC to HBV or HCV in Middle Eastern countries as follows (Table 5).

Table 5: Common causes of HCC in Middle East countries.

Region	Cause of HCC	
	Most common	Less common
Egypt	HCV	HBV
Palestine - Gaza Strip	HBV	HCV
Jordan	HBV/HDV	HCV
Kuwait	HBV	HCV
Lebanon[112]	HBV	HCV
Saudi Arabia	HCV	HBV
Syria	HBV	HCV
Iran	HBV	HCV
Turkey	HBV	HCV

In Lebanon, HCC is a relatively rare cancer, ranking 14th among both males and females with an age standardized rate of 3.5 and 2.2 per 100 000, respectively.[23] Results of studies in this country reveal that most HCC patients in Lebanon have HBV-related liver cirrhosis, accounting for nearly two thirds of the subjects followed by HCV, and alcohol abuse.

Interestingly, there were no cases of non-alcoholic steatohepatitis- or cryptogenic cirrhosis-related HCC in this study population.[112] Of note, the HBV and HCV carrier state in Lebanese blood donors is 1%-2% and 0.1%-0.6%, respectively.[47]

In Jordan, an association between hepatitis D virus (HDV)-positive status and HBsAg positive primary HCC was found. The prevalence of HDV infection in Jordan was 23% in patients with chronic liver disease and in 67% of patients with HCC. In contrast, none of HCC patients in Iran were positive for HDV infection.[49]

In Turkey, HBV infection was found to be the leading cause of HCC, followed by HCV infection and alcoholic liver disease.[45] Hepatitis B, hepatitis C and

excessive alcohol intake were detected in 56%, 23.2% and 15.9% of Turkish HCC patients, respectively.[45]

In Saudi Arabia, a study by Altaf et al. has demonstrated that HBsAg and HCVAb were positive in 23% and 53% of chronic liver disease cases, respectively.[113] HCV plays a major role in the epidemiology of HCC in Saudi Arabia where 39.5% of patients are anti-HCV antibody positive.[79] This is in contrast to an overall HCV seroprevalence of 1.1% to 2.9% among Saudi- blood donors.[79]

This might be attributed to some factors related to either the virus or host in the Saudi population.

In Iran, a study by Fani et al. has shown the prevalence of HCC to be approximately 3.1% in HBV and HCV chronic carriers combined, and the estimated annual incidence of HCC is 1.02 (95% CI: 0.5-1.8). The authors have found no association between viral type and HCC.[114]

Lastly, recent studies have demonstrated that unlike other countries of the Middle East, the attributable fraction of HCC due to HCV is quite high in Egypt and Saudi Arabia, and HBV and environmental risk factors play a minor role in the incidence of HCC.[82,85]

In spite of vaccination against HBV, this virus will remain one the major etiologies for HCC in next 40 years. However the role of HBV infection as an etiology of HCC would become negligible during the second half of the 21st century.

As no vaccination is available for HCV, further investigation of the risk factors and modes of transmission of HCV are required to reduce infection rates and to prevent future cases of HCC. Sampling of markers of HBV and HCV exposure through population-based studies can provide useful data in designing cost-effective and country-specific intervention strategies to reduce HCC.

Further, the development of early detection markers is a vital missing component in strategies to reduce HCC mortality.[115] Molecular epidemiology studies may provide a better understanding of the temporal occurrence of genetic and epigenetic alterations in the natural history of liver carcinogenesis.[116-118]

In conclusion HCC is not as common in the Middle East as it is in East Asia. The rising incidence of HCV infection along with the pandemic of obesity and diabetes mellitus will become major risk factors for HCC in the future. Further studies to develop an evidence-based strategy to prevent HCC in Middle Eastern countries are necessary.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Ferlay J BF, Pisani P. Globocan 2000: Cancer incidence, mortality and prevalence worldwide. IARC Cancer Base No. 5, IARC Nonserial Publication, 2001.
2. Kirk GD, Bah E, Montesano R. Molecular epidemiology of human liver cancer: insights into etiology, pathogenesis and prevention from The Gambia, West Africa. *Carcinogenesis* 2006;**27**:2070-82.
3. Parkin DM, Bray FI, Devesa SS. Cancer burden in the year 2000. The global picture. *Eur J Cancer* 2001;**37**:S4-66.
4. Okuda K, Tabor G. Liver Cancer. New York: Churchill Livingstone; 1997.
5. Parkin DM. Global cancer statistics in the year 2000. *Lancet Oncol* 2001;**2**:533-43.
6. Tang ZY. Hepatocellular carcinoma. *J Gastroenterol Hepatol* 2000;**15**:G1-7.
7. Bosch FX, Ribes J, Cleries R, Diaz M. Epidemiology of hepatocellular carcinoma. *Clin Liver Dis* 2005;**9**:191-211.
8. Law MG, Roberts SK, Dore GJ, Kaldor JM. Primary hepatocellular carcinoma in Australia, 1978-1997: Increasing incidence and mortality. *Med J Aust* 2000;**173**:403-5.
9. Benhamiche AM, Faivre C, Minello A, Clinard F, Mitry E, Hillon P, et al. Time trends and age-period-cohort effects on the incidence of primary liver cancer in a well-defined French population: 1976-1995. *J Hepatol* 1998;**29**:802-6.
10. Taylor-Robinson SD, Foster GR, Arora S, Hargreaves S, Thomas HC. Increase in primary liver cancer in the UK, 1979-94. *Lancet* 1997;**350**:1142-3.
11. Okuda K, Fujimoto I, Hanai A, Urano Y. Changing incidence of hepatocellular carcinoma in Japan. *Cancer Res* 1987;**47**:4967-72.
12. Khan SA, Taylor-Robinson SD, Toledano MB, Beck A, Elliott P, Thomas HC. Changing international trends in mortality rates for liver, biliary and pancreatic tumours. *J Hepatol* 2002;**37**:806-13.
13. Levi F, Lucchini F, Negri E, Boyle P, La Vecchia C. Cancer mortality in Europe, 1995-1999, and an overview of trends since 1960. *Int J Cancer* 2004;**110**:155-69.
14. Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, et al. Clinical management of hepato-

cellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. *J Hepatol* 2001;**35**:421-30.

15. El-Serag HB. Hepatocellular carcinoma: An epidemiologic view. *J Clin Gastroenterol* 2002;**35**:S72-8.
16. Velazquez RF, Rodriguez M, Navascues CA, Linares A, Perez R, Sotorrios NG, et al. Prospective analysis of risk factors for hepatocellular carcinoma in patients with liver cirrhosis. *Hepatology* 2003;**37**:520-7.
17. Elattar I. Website of the National Cancer Institute, Egypt: http://www.nci.edu.eg. 2003. data accessded 2010.
18. Salim EI, Moore MA, Al-Lawati JA, Al-Sayyad J, Bazawir A, Bener A, et al. Cancer epidemiology and control in the arab world - past, present and future. *Asian Pac J Cancer Prev* 2009;**10**:3-16.
19. Lehman EM, Soliman AS, Ismail K, Hablas A, Seifeldin IA, Ramadan M, et al. Patterns of hepatocellular carcinoma incidence in Egypt from a population-based cancer registry. *Hepatol Res* 2008;**38**:465-73.
20. Abdel-Wahab M, El-Ghawalby N, Mostafa M, Sultan A, El-Sadany M, Fathy O, et al. Epidemiology of hepatocellular carcinoma in lower Egypt, Mansoura Gastroenterology Center. *Hepatogastroenterology* 2007;**54**:157-62.
21. Sadjadi A, Malekzadeh R, Derakhshan MH, Sepehr A, Nouraie M, Sotoudeh M, et al. Cancer occurrence in Ardabil: Results of a population-based cancer registry from Iran. *Int J Cancer* 2003;**107**:113-8.
22. Sadjadi A, Nouraie M, Mohagheghi MA, Mousavi-Jarrahi A, Malekezadeh R, Parkin DM. Cancer occurrence in Iran in 2002, an international perspective. *Asian Pac J Cancer Prev* 2005;**6**:359-63.
23. Shamseddine A, Sibai AM, Gehchan N, Rahal B, El-Saghir N, Ghosn M, et al. Cancer incidence in postwar Lebanon: findings from the first national population-based registry, 1998. *Ann Epidemiol* 2004;**14**:663-8.
24. Chen CJ, Chen CW, Wu MM, Kuo TL. Cancer potential in liver, lung, bladder and kidney due to ingested inorganic arsenic in drinking water. *Br J Cancer* 1992;**66**:888-92.
25. Neuberger J, Forman D, Doll R, Williams R. Oral contraceptives and hepatocellular carcinoma. *Br Med J (Clin Res Ed)* 1986;**292**:1355-7.
26. Palmer JR, Rosenberg L, Kaufman DW, Warshauer ME, Stolley P, Shapiro S. Oral contraceptive use and liver cancer. *Am J Epidemiol* 1989;**130**:878-82.
27. Mandishona E, MacPhail AP, Gordeuk VR, Kedda MA, Paterson AC, Rouault TA, et al. Dietary iron overload as a risk factor for hepatocellular carcinoma in Black Africans. *Hepatology* 1998;**27**:1563-6.
28. Bosch FX, Ribes J, Borras J. Epidemiology of primary liver cancer. *Semin Liver Dis* 1999;**19**:271-85.
29. Kane M. Global programme for control of hepatitis B infection. *Vaccine* 1995;**13**:S47-9.
30. Simonetti RG, Camma C, Fiorello F, Politi F, D'Amico G, Pagliaro L. Hepatocellular carcinoma. A worldwide problem and the major risk factors. *Dig Dis Sci* 1991;**36**:962-72.
31. Beasley RP. Hepatitis B virus as the etiologic agent in hepatocellular carcinoma:epidemiologic consideration. *Hepatology* 1982;**2**:21S-6S.
32. Beasley RP, Hwang LY. Overview on the epidemiology of the hepatocellular carcinoma. In: F.B.Hollinger. Baltimore: Lemon and Wilkins *Co*; 1991.p.532-5.
33. Oshima A, Tsukuma H, Hiyama T, Fujimoto I, Yamano H, Tanaka M. Follow-up study of HBs Ag-positive blood donors with special reference to effect of drinking and smoking on development of liver cancer. *Int J Cancer* 1984;**34**:775-9.
34. Tagger A, Donato F, Ribero ML, Chiesa R, Portera G, Gelatti U, et al. Case-control study on hepatitis C virus (HCV) as a risk factor for hepatocellular carcinoma: The role of HCV genotypes and the synergism with hepatitis B virus and alcohol. Brescia HCC Study. *Int J Cancer* 1999;**81**:695-9.
35. Beasley RP. Hepatitis B virus. The major etiology of hepatocellular carcinoma. *Cancer* 1988;**61**:1942-56.
36. Buckwold VE, Xu Z, Chen M, Yen TS, Ou JH. Effects of a naturally occurring mutation in the hepatitis B virus basal core promoter on precore gene expression and viral replication. *J Virol* 1996;**70**:5845-51.
37. Takahashi K, Aoyama K, Ohno N, Iwata K, Akahane Y, Baba K, et al. The precore/core promoter mutant (T1762A1764) of hepatitis B virus: Clinical significance and an easy method for detection. *J Gen Virol* 1995;**76**:3159-64.
38. Raimondo G, Schneider R, Stemler M, Smedile V, Rodino G, Will H. A new hepatitis B virus variant in a chronic carrier with multiple episodes of viral reactivation and acute hepatitis. *Virology* 1990;**179**:64-8.
39. Orito E, Mizokami M, Sakugawa H, Michitaka K, Ishikawa K, Ichida T, et al. A case-control study for clinical and molecular biological differences between hepatitis B viruses of genotypes B and C. Japan HBV Genotype Research Group. *Hepatology* 2001;**33**:218-23.
40. Baptista M, Kramvis A, Kew MC. High prevalence of 1762(T) 1764(A) mutations in the basic core promoter of hepatitis B virus isolated from black Africans with hepatocellular carcinoma compared with asymptomatic carriers. *Hepatology* 1999;**29**:946-53.
41. Brunetto MR, Stemler M, Bonino F, Schodel F, Oliveri F, Rizzetto M, et al. A new hepatitis B virus strain in patients with severe anti-HBe positive chronic hepatitis B. *J Hepatol* 1990;**10**:258-61.
42. Goodarzi Z, Jazayeri SM. Hepatitis B virus preS variant and hepatocellular carcinoma. *Hepatitis Monthly* 2008;**8**:129-33.
43. Pourshams A, Malekzadeh R, Monavvari A, Akbari MR, Mohamadkhani A, Yarahmadi S, et al. Prevalence and etiology of persistently elevated alanine aminotransferase levels in healthy Iranian blood donors. *J Gastroenterol Hepatol* 2005;**20**:229-33.

44. Jahani MR, Motevalian SA, Mahmoodi M. Hepatitis B carriers in large vehicle drivers of Iran. *Vaccine* 2003;**21**:1948-51.

45. Uzunalimoglu O, Yurdaydin C, Cetinkaya H, Bozkaya H, Sahin T, Colakoglu S, et al. Risk factors for hepatocellular carcinoma in Turkey. *Dig Dis Sci* 2001;**46**:1022-28.

46. Qirbi N, Hall AJ. Epidemiology of hepatitis B virus infection in the Middle East. *East Mediterr Health J* 2001;**7**:1034-45.

47. Irani-Hakime N, Tamim H, Samaha H, Almawi WY. Prevalence of antibodies against hepatitis C virus among blood donors in Lebanon, 1997-2000. *Clin Lab Haematol* 2001;**23**:317-23.

48. Araj GF, Kfoury-Baz EE, Barada KA, Nassif RE, Alami SY. Hepatitis C virus: prevalence in Lebanese blood donors and brief overview of the disease. *J Med Liban* 1995;**43**:11-6.

49. Poustchi H, Mohamadkhani A, Bowden S, Montazeri G, Ayres A, Revill P, et al. Clinical significance of precore and core promoter mutations in genotype D hepatitis B-related chronic liver disease. *J Viral Hepat* 2008;**15**:753-60.

50. Aghakhani A, Hamkar R, Zamani N, Eslamifar A, Banifazl M, Saadat A, et al. Hepatitis B virus genotype in Iranian patients with hepatocellular carcinoma. *Int J Infect Dis* 2009;**13**:685-689.

51. Bahramali G, Sadeghizadeh M, Amini-Bavil-Olyaee S, Alavian SM, Behzad-Behbahani A, Adeli A, et al. Clinical, virologic and phylogenetic features of hepatitis B infection in Iranian patients. *World J Gastroenterol* 2008;**14**:5448-53.

52. Baig S, Siddiqui AA, Ahmed W, Qureshi H, Arif A. The association of complex liver disorders with HBV genotypes prevalent in Pakistan. *Virol J* 2007;**4**:128.

53. Abdo AA, Al-Jarallah BM, Sanai FM, Hersi AS, Al-Swat K, Azzam NA, et al. Hepatitis B genotypes: Relation to clinical outcome in patients with chronic hepatitis B in Saudi Arabia. *World J Gastroenterol* 2006;**12**:7019-24.

54. Goodarzi Z, Malekzadeh R, Montazeri G, Alavian SM, Qurbanalizadegan M, Daram M, et al. Phylogenetic analysis of HBV based on preS region in Iranian fepatocellular carcinoma patients. *Hepatitis Monthly* 2007;**7**:201-5.

55. Merat S, Malekzadeh R, Rezvan H, Khatibian M. Hepatitis B in Iran. *Arch Iran Med* 2000;**3**:192-201.

56. Merat S, Rezvan H, Nouraie M, Jamali A, Assari S, Abolghasemi H, et al. The prevalence of hepatitis B surface antigen and anti-hepatitis B core antibody in Iran: A population-based study. *Arch Iran Med* 2009;**12**:225-31.

57. Bagheri Lankarani K, Saberi Firoozi M, Nabipoor I, Fattahi F. Reassessment of the role of hepatitis B and C viruses in postnecrotic cirrhosis and chronic hepatitis in southern Iran. *Irn J Med Sci* 1999;**24**:117-21.

58. International Agency for Research on Cancer: http://www.iarc.fr/en/publications/index.php. 2008

59. Amini-Bavil-Olyaee S, Sarrami-Forooshani R, Adeli A, Sabahi F, Abachi M, Azizi M, et al. Complete genomic sequence and phylogenetic relatedness of hepatitis B virus isolates from Iran. *J Med Virol* 2005;**76**:318-26.

60. Amini-Bavil-Olyaee S, Sarrami-Forooshani R, Mahboudi F, Sabahi F, Adeli A, Noorinayer B, et al. Genotype characterization and phylogenetic analysis of hepatitis B virus isolates from Iranian patients. *J Med Virol* 2005;**75**:227-34.

61. Feinstone SM, Kapikian AZ, Purcell RH, Alter HJ, Holland PV. Transfusion-associated hepatitis not due to viral hepatitis type A or B. *N Engl J Med* 1975;**292**:767-70.

62. Rahman El-Zayadi A, Abaza H, Shawky S, Mohamed MK, Selim OE, Badran HM. Prevalence and epidemiological features of hepatocellular carcinoma in Egypt-a single center experience. *Hepatol Res* 2001;**19**:170-9.

63. Miyakawa Y, Iino S. Toward prevention of hepatocellular carcinoma developing in chronic hepatitis C. *J Gastroenterol Hepatol* 2001;**16**:711-4.

64. El-Serag HB. Hepatocellular carcinoma and hepatitis C in the United States. *Hepatology* 2002;**36**:S74-83.

65. Davila JA, Morgan RO, Shaib Y, McGlynn KA, El-Serag HB. Hepatitis C infection and the increasing incidence of hepatocellular carcinoma: a population-based study. *Gastroenterology* 2004;**127**:1372-80.

66. Erhardt A, Theobald I, Petry W, Rohrborn A, Heintges T, Wettstein M, et al. Hepatocellular carcinoma: rising incidence of hepatitis C virus-associated cases at a university clinic in Germany. *Dtsch Med Wochenschr* 2002;**127**:2665-8.

67. Deuffic S, Buffat L, Poynard T, Valleron AJ. Modeling the hepatitis C virus epidemic in France. *Hepatology* 1999;**29**:1596-601.

68. Law MG. Modeling the hepatitis C virus epidemic in Australia. Hepatitis C Virus Projections Working Group. *J Gastroenterol Hepatol* 1999;**14**:1100-07.

69. Touzet S, Kraemer L, Colin C, Pradat P, Lanoir D, Bailly F, et al. Epidemiology of hepatitis C virus infection in seven European Union countries: a critical analysis of the literature. HENCORE Group. (Hepatitis C European Network for Co-operative Research). *Eur J Gastroenterol Hepatol* 2000;**12**:667-78.

70. Ramadori G, Meier V. Hepatitis C virus infection: 10 years after the discovery of the virus. *Eur J Gastroenterol Hepatol* 2001;**13**:465-71.

71. Huang L, Koziel MJ. Immunology of hepatitis C virus infection. *Curr Opin Gastroenterol* 2000;**16**:558-64.

72. Higuchi M, Tanaka E, Kiyosawa K. Epidemiology and clinical aspects on hepatitis C. *Jpn J Infect Dis* 2002;**55**:69-77.

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

74. Llovet JM, Beaugrand M. Hepatocellular carcinoma: Present status and future prospects. *J Hepatol* 2003;**38**:S136-49.

75. Di Bisceglie AM. Hepatitis C and hepatocellular carcinoma. *Semin Liver Dis* 1995;**15**:64-9.

76. Takano S, Yokosuka O, Imazeki F, Tagawa M, Omata M. Incidence of hepatocellular carcinoma in chronic hepatitis B and C: A prospective study of 251 patients. *Hepatology* 1995;**21**:650-5.

77. Shiratori Y, Shiina S, Imamura M, Kato N, Kanai F, Okudaira T, et al. Characteristic difference of hepatocellular carcinoma between hepatitis B- and C- viral infection in Japan. *Hepatology* 1995;**22**:1027-33.

78. Hepatitis C--global prevalence (update). *Wkly Epidemiol Rec* 1999;**74**:425-7.

79. Fakeeh M, Zaki AM. Hepatitis C: prevalence and common genotypes among ethnic groups in Jeddah, Saudi Arabia. *Am J Trop Med Hyg* 1999;**61**:889-92.

80. Waheed Y, Shafi T, Safi SZ, Qadri I. Hepatitis C virus in Pakistan: a systematic review of prevalence, genotypes and risk factors. *World J Gastroenterol* 2009;**15**:5647-53.

81. el Guneid AM, Gunaid AA, O'Neill AM, Zureikat NI, Coleman JC, Murray-Lyon IM. Prevalence of hepatitis B, C, and D virus markers in Yemeni patients with chronic liver disease. *J Med Virol* 1993;**40**:330-3.

82. Ezzat S, Abdel-Hamid M, Eissa SA, Mokhtar N, Labib NA, El-Ghorory L, et al.. Associations of pesticides, HCV, HBV, and hepatocellular carcinoma in Egypt. *Int J Hyg Environ Health* 2005;**208**:329-39.

83. Ghavanini AA, Sabri MR. Hepatitis B surface antigen and anti-hepatitis C antibodies among blood donors in the Islamic Republic of Iran. *East Mediterr Health J* 2000;**6**:1114-6.

84. Alavian SM, Gholami B, Masarrat S. Hepatitis C risk factors in Iranian volunteer blood donors: a case-control study. *J Gastroenterol Hepatol* 2002;**17**:1092-7.

85. Hassan MM, Zaghloul AS, El-Serag HB, Soliman O, Patt YZ, Chappell CL, et al.The role of hepatitis C in hepatocellular carcinoma: A case control study among Egyptian patients. *J Clin Gastroenterol* 2001;**33**:123-6.

86. Merat S, Rezvan H, Nouraie M, Jafari E, Abolghasemi H, Radmard AR, et al.. Seroprevalence of hepatitis C virus: The first population-based study from Iran. *Int J Infect Dis* 2010 Mar 31.

87. Global surveillance and control of hepatitis C. Report of a WHO Consultation organized in collaboration with the Viral Hepatitis Prevention Board, Antwerp, Belgium. *J Viral Hepat* 1999;**6**:35-47.

88. Abdel-Hamid M, El-Daly M, Molnegren V, El-Kafrawy S, Abdel-Latif S, Esmat G, et al. Genetic diversity in hepatitis C virus in Egypt and possible association with hepatocellular carcinoma. *J Gen Virol* 2007;**88**:1526-31.

89. Abdulkarim AS, Zein NN, Germer JJ, Kolbert CP, Kabbani L, Krajnik KL, et al. Hepatitis C virus genotypes and hepatitis G virus in hemodialysis patients from Syria: identification of two novel hepatitis C virus subtypes. *Am J Trop Med Hyg* 1998;**59**:571-6.

90. Al-Ahdal MN, Rezeig MA, Kessie G. Genotyping of hepatitis C virus isolates from Saudi patients by analysis of sequences from PCR-amplified core region of the virus genome. *Ann Saudi Med* 1997;**17**:601-4.

91. Bdour S. Hepatitis C virus infection in Jordanian haemodialysis units: Serological diagnosis and genotyping. *J Med Microbiol* 2002;**51**:700-4.

92. Bozdayi AM, Aslan N, Bozdayi G, Turkyilmaz AR, Sengezer T, Wend U, et al. Molecular epidemiology of hepatitis B, C and D viruses in Turkish patients. *Arch Virol* 2004;**149**:2115-29.

93. Bozdayi G, Rota S, Verdi H, Derici U, Sindel S, Bali M, et al. The presence of hepatitis C virus (HCV) infection in hemodialysis patients and determination of HCV genotype distribution. *Mikrobiyol Bul* 2002;**36**:291-300.

94. Chamberlain RW, Adams N, Saeed AA, Simmonds P, Elliott RM. Complete nucleotide sequence of a type 4 hepatitis C virus variant, the predominant genotype in the Middle East. *J Gen Virol* 1997;**78**:1341-7.

95. Osoba AO. Hepatitis C virus genotypes in Saudi Arabia. *Saudi Med J* 2002;**23**:7-12.

96. Ramia S, Koussa S, Taher A, Haraki S, Klayme S, Sarkis D, et al. Hepatitis-C-virus genotypes and hepatitis-G-virus infection in Lebanese thalassaemics. *Ann Trop Med Parasitol* 2002;**96**:197-202.

97. Ray SC, Arthur RR, Carella A, Bukh J, Thomas DL. Genetic epidemiology of hepatitis C virus throughout Egypt. *J Infect Dis* 2000;**182**:698-707.

98. Samimi-Rad K, Nategh R, Malekzadeh R, Norder H, Magnius L. Molecular epidemiology of hepatitis C virus in Iran as reflected by phylogenetic analysis of the NS5B region. *J Med Virol* 2004;**74**:246-52.

99. Sharara AI, Ramia S, Ramlawi F, Fares JE, Klayme S, Naman R. Genotypes of hepatitis C virus (HCV) among positive Lebanese patients: comparison of data with that from other Middle Eastern countries. *Epidemiol Infect* 2007;**135**:427-32.

100. Shobokshi OA, Serebour FE, Skakni L. Chronic hepatitis C treatment: a review. *Ann Saudi Med* 2000;**20**:402-8.

101. Shobokshi OA, Serebour FE, Skakni L, Al-Saffy YH, Ahdal MN. Hepatitis C genotypes and subtypes in Saudi Arabia. *J Med Virol* 1999;**58**:44-8.

102. Shobokshi OA, Serebour FE, Skakni LI. Hepatitis C genotypes/subtypes among chronic hepatitis patients in Saudi Arabia. *Saudi Med J* 2003;**24**:S87-91.

103. Ramia S, Eid-Fares J. Distribution of hepatitis C virus genotypes in the Middle East. *Int J Infect Dis* 2006;**10**:272-7.

104. Nousbaum JB, Pol S, Nalpas B, Landais P, Berthelot P, Brechot C. Hepatitis C virus type 1b (II) infection in France and Italy. Collaborative Study Group. *Ann Intern Med* 1995;**122**:161-8.

105. Viazov S, Kuzin S, Paladi N, Tchernovetsky M, Isaeva E, Mazhul L, et al. Hepatitis C virus genotypes in different regions of the former Soviet Union (Russia, Belarus, Mol-

dova, and Uzbekistan). *J Med Virol* 1997;**53**:36-40.

106. Diago M, Hassanein T, Rodes J, Ackrill AM, Sedarati F. Optimized virologic response in hepatitis C virus genotype 4 with peginterferon-alpha2a and ribavirin. *Ann Intern Med* 2004;**140**:72-3.
107. Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncales FL Jr, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002;**347**:975-82.
108. Hadziyannis SJ, Sette H Jr, Morgan TR, Balan V, Diago M, Marcellin P, et al. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med* 2004;**140**:346-55.
109. Hasan F, Asker H, Al-Khaldi J, Siddique I, Al-Ajmi M, Owaid S, et al. Peginterferon alfa-2b plus ribavirin for the treatment of chronic hepatitis C genotype 4. *Am J Gastroenterol* 2004;**99**:1733-7.
110. Khuroo MS, Dahab ST. Meta-analysis: A randomized trial of peginterferon plus ribavirin for the initial treatment of chronic hepatitis C genotype 4. *Aliment Pharmacol Ther* 2004;**20**:931-8.
111. Dutta U, Byth K, Kench J, Khan MH, Coverdale SA, Weltman M, et al. Risk factors for development of hepatocellular carcinoma among Australians with hepatitis C: a case-control study. *Aust N Z J Med* 1999;**29**:300-7.
112. Yaghi C, Sharara AI, Rassam P, Moucari R, Honein K, BouJaoude J, et al. Hepatocellular carcinoma in Lebanon: Etiology and prognostic factors associated with short-term survival. *World J Gastroenterol* 2006;**12**:3575-80.
113. Altaf FJ. Hepatocellular carcinoma. *Saudi Med J* 2001;**22**:416-8.
114. Fani A, Fani I, Eshrati B, Samadian P, Fani P, Gorishi Y, et al. Screening for hepatocellular carcinoma in chronic carriers of hepatitis B and C in Markazi Province, Iran. *Hep Mon* 2007;**7**:149-52.
115. Anwar WA, Khaled HM, Amra HA, El-Nezami H, Loffredo CA. Changing pattern of hepatocellular carcinoma (HCC) and its risk factors in Egypt: Possibilities for prevention. *Mutat Res* 2008;**659**:176-84.
116. Hussain SP, Harris CC. Molecular epidemiology of human cancer. *Toxicol Lett* 1998;**102-103**:219-25.
117. Montesano R, Hainaut P, Wild CP. Hepatocellular carcinoma: From gene to public health. *J Natl Cancer Inst* 1997;**89**:1844-51.
118. Wild CP, Law GR, Roman E. Molecular epidemiology and cancer: promising areas for future research in the post-genomic era. *Mutat Res* 2002;**499**:3-12.