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# LIVER CANCER IN THE WORLD: EPIDEMIOLOGY, INCIDENCE, MORTALITY AND RISK FACTORS

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**Abstract – *Objective:*** *Liver cancer is the sixth common cancer and the second leading cause of death from cancer around the world. It is significantly more observable among male with its highest incidence in the age group of 45 to 60 years. The aim of this study was to investigate the incidence, mortality, and risk factors of liver cancer in the world.*

***Materials and Methods:*** *This review study was performed on published English studies by searching for databases PubMed, Scopus and web of science up to end of 2017. The strategy search includes key words of "Liver cancer", "Hepatocellular carcinoma (HCC)", "Epidemiology", "incidence", "mortality", "risk Factors", and "the world". We reviewed studies on the incidence, mortality, and risk factors of liver cancer.*

***Results:*** *Generally, liver cancer is more common in the East Asia with, the highest incidence rate in Mongolia. The standard incidence of liver cancer was 10.1 per 100,000 people (15.3 in males and 5.3 in females). The highest mortality rates occurred observed in the East Asian countries. The standardized mortality rate for liver cancer was 9.5 per 100,000 people (14.3 in males and 5.1 in females). The most important risk factors for liver cancer included the chronic infections with HBV and HCV, Aflatoxin, alcohol consumption and cigarette smoking.*

***Conclusions:*** *Liver cancer has a higher incidence rate in East Asian countries. Majority of the cases are detected mostly at the advanced level of disease. Then, an early diagnosis could be effective in reducing mortality rate of this cancer. Also, conparing HCV(hepatitis C virus) and HIV (human immunodeficiency virus) may lead to reducing risk factors of liver cancer.*

**KEYWORDS:** *Liver Cancer, Hepatocellular Carcinoma, Incidence, Mortality, Risk Factor, world.*

**LIST OF ABBREVIATIONS:** *LC: Liver Cancer, CI: Confidence Interval, NAFLD: Non-alcoholic fatty liver disease, HCC: Hepatocellular carcinoma, ASIR: Age-Standardized Incidence Rate, ASMR: Age-Standardized Mortality Rate, RR: Relative Risk.*

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## INTRODUCTION

Cancers are the main cause of mortality and health problem worldwide, and liver cancer (LC) is one of the most common[1-3]. It is considered as the sixth most common cancer and the second leading cause of cancer deaths around the world[4]. Liver cancer is divided into two types: primary and secondary LC. The primary LC starts in the liver, but the secondary LC begins in other organs of the body and spreads to the liver due to metastases of this cancer and creation of the most common cases including colorectal, breast, pancreatic, ovarian and lung cancers[5]. Primary liver tumors include Hepatocellular carcinoma, Cholangio carcinoma and Sarcoma which account for about 6% of the total cancer burden worldwide[6].

The incidence of primary LC is very diverse in different countries[7]. The highest incidence of this cancer can be seen in Eastern Asia, South-Eastern Asia, Northern Africa and Southern Africa[8]. In general, it has a high incidence in developing countries so that more than 85% of cases occur in these countries[9]. This cancer is significantly more common in men[10]. This difference is higher in regions with high incidence than areas with lower one[11]. The highest incidence of LC occurs in the age group of 45-60 years[12], and its treatment may be difficult because most cases, especially in developing countries, are diagnosed in advanced grade and does not potentially respond to drug therapy[13].

According to previous studies, there are widely various differences in estimating mortality and incidence rate of LC around the world yearly. It is true that multiple risk factors may lead to LC; however, there is no comprehensive literature about the incidence, mortality, and risk factors of LC. Turning to the fact that epidemiological aspects recognition and incidence and mortality awareness of this cancer may lead to diminish severity and incidence of LC, the aim of this study was to investigate the incidence, mortality, and risk factors of liver cancer in the world.

## MATERIALS AND METHODS

This investigation was performed on published English studies by searching on PubMed, Scopus and web of science up to end of 2017. The search strategy included key words “Liver cancer”, “Hepatocellular carcinoma (HCC)”, “Epidemiology”, “incidence”, “mortality” and “risk factors”. We investigated the relevant studies on the incidence, mortality and risk factors of LC. which addressed the therapeutic and surgical aspects of liver cancer were excluded. A total of 90 full papers were reviewed. In this study, the incidence and mortality rates are considered per 100,000 people at risk of disease.

## INCIDENCE RATE

In total, there were 782,451 cases of LC worldwide in 2012. Among this, 554369 cases occurred in males and 228082 in females. The Age-Standardized Incidence Rate (ASIR) of LC was 10.1 (in males were15.3 and in females were 5.3). Based on the continental division, the highest and lowest ASIR of LC was 20.9 and 3.1 for Eastern Asia and Northern Europe respectively[14].

The highest and lowest ASIR worldwide were 78.1 and 0.9 in Mongolia and Nepal, respectively. In Mongolia, LC with 6408 cases in 2003-2007, was reported as the most common cancer in both men and women[15]. However, more than a half of new cases and deaths from LC occur in China[16]; and a major portion of this‒rising in cancer burden can be attributed to population growth, aging and socio-demographic changes[17]. South Korea is another country with a high incidence of LC. In this country, the incidence of LC was soaring from 1999 to 2011, while declined during the period from 2011 to 2014, probably due to the significant advances in the treatment of viral hepatitis, despite the fact that the obesity and uncontrolled liver disease were also the main causes of LC[18]. In general, the global trend for the incidence of this cancer is widely variable in the world. For instance, despite the reducing incidence of LC in China, Philippines and Singapore, its incidence was increasing in the United States, Britain, Canada, Australia, Germany and Switzerland[19]. The geographical model for incidence of this cancer is dependent on etiological viral factors[20]

## MORTALITY RATE

In 2012, there were 745,533 deaths from LC of which 52,104 (69.89%) were in males and 224,492 cases (30.11%) in females worldwide and the Age-Standardized Mortality Rate (ASMR) for LC was 9.5 (in males were 14.3 and in females were 5.1). Based on the continental division, the highest and lowest ASMR of LC were 19.6 and 2.8 for Eastern Asia and Northern Europe[14].

In general, the mortality from LC has decreased in countries with previously high mortality rates and increased in areas with the previous low mortality in recent years[21]. In South Korea, the survival of LC has increased over the past two decades, so that five-year survival rate of LC increased from 10.7% in the period of between 1993 and 1995 to 32.8 in 2010-2014[18]. While the death from more types of cancer dropped sharply in the United States, the mortality rate from LC had a growing trend from 2003 to 2012 with the highest mortality rate among male patients in the United States in 2012[22,23]. Such

changes were probably due to changes in the risk factors for this cancer in different regions[24]. For instance, an increase in the prevalence of overweight, obesity, and diabetes may play an important role in the recent unfavorable trend in some regions especially North America[25].

## RISK FACTORS FOR LC

### Hepatitis B (HBV) and Hepatitis C (HCV) viruses

Chronic infections with HBV and HCV are the main causes of HCC worldwide[26,27] accounting for three quarters of all cases of LC worldwide[28]. HBV in East Asia and HCV in the Mediterranean countries are more observable[29]. There is a strong geographical correlation between the incidence of chronic infection with HBV and the incidence of HCC. It is estimated that 54% of LCs can be attributed to infection of HBV[30]. Despite the fact that most LC cases associated with HBV occur in low and middle-income countries[29], the estimated risk of developing HCC among patients infected by HCV compared to uninfected ones ranges between 20 and 30 in most epidemiological studies[25]. However, studies carried out in the United States also indicated the association between the LC and HBV[30]. In addition, about 33% of LC was due to HCV worldwide. This rate was higher in low and middle-income countries than the high-income countries[31].

### Alcohol drinking

Results of previous studies showed that heavy drinking increases the incidence of primary LC[32,33]. More than one daily drinking in women and twice a day in men are usually considered as the high alcohol consumption[32], so that the Relative Risk (RR) of LC in people who drink 3 times or more alcohol per day is 1.16 and the RR for those who consume 6 times or more alcohol per day is 1.22 higher than those who do not drink alcohol[34]. A prospective Cohort study in 8 European countries also attributed 33% and 18% of LC cases to the past and current history of alcohol consumption[35].

### Cigarette and tobacco

Many studies have reported a significant association between cigarette and tobacco smoking with LC. It has been found that the relative risk of LC is higher in people who are currently smoking than those who have a history of smoking[36,37]. A meta-analysis investigation on this field, which included 38 cohort studies and 58 case-control studies, revealed a relative risk of LC equal to 1.51 and 1.12 in current smokers and those with a history of smoking compared to those who never smoked[38]. Interestingly, the model of relationship between smoking and the risk of LC is dose-response, that is, the number of cigarettes per day and the duration of smoking, significantly increases the risk of LC[37].

### Aflatoxin

Food contamination with aflatoxin is one of the major risk factors for hepatocellular carcinoma (HCC)[39,40]. Aflatoxin is a toxic and carcinogenic chemical produced by Aspergillus fungus and it contaminates food products such as maize, peanuts and nuts[41,42]. The highest level of exposure to this risk factor belongs to Sub-Saharan Africa and East Asia especially South China[41,43]. In areas with high exposure to aflatoxin, it has multiplying interaction with HBV, and thus the presence of these two factors together increases the risk of HCC in an exponential fashion[44].

### Dietary factors

Evidence suggests that the dietary composition plays an important role in the risk of developing HCC and may act as a protective agent. Compared to other types of cancer, there are few studies on the role of diet supplement in development of HCC[45]. Reporting data indicates that the high consumption of red meat and sugar has a positive relationship with susceptibility to HCC, but the high consumption of white meat or fish[46,47], vegetables[48,49], fruits[50], cereals, eggs[51], milk[50] and yogurt[48] has reverse relationship with HCC. An increase of 100 g of daily intake of vegetables reduces the risk of HCC by 8%, and the consumption of 20 g of fish instead of red meat per day reduced its risk by 16%[52,53]. However, some other studies[54-56] did not indicate any significant relationship between the consumption of fruits and the risk of LC. Coffee consumption also has a reverse relationship with susceptibility to LC as the coffee contains various types of chemicals such as antioxidants, minerals and many phenolic compounds that have favorable potential effects on the liver and reduce the risk of LC[57-60]. The results of a meta-analysis in 2012 indicated that the RR of LC was 0.66 in people who consumed coffee, compared to those who didn't[61].

### Non-alcoholic fatty liver disease (NAFLD)

Non-alcoholic fatty liver disease (NAFLD) with an estimated prevalence of 25.2% is one of the most common chronic liver diseases worldwide[62]. It may progress to non-alcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma (HCC)[62]. Recent data indicate that this disease is the leading cause of HCC[63-65], so that the number of HCC cases related to the NAFLD had 9% of increase in the United States from 2004 to 2009[63], and the incidence of HCC was reported equal to 44 per 100000 people per year among patients with NAFLD[62].

### Obesity and diabetes

Studies have found that the overweight and obesity are associated with the increased risk for some malignancies including HCC[66]. The risk of LC in those with overweight and obesity is respectively 17% and 89% higher than those who have normal weight. The relationship between LC and obesity appears to be stronger in men than women[67]. The effect of obesity on LC can be due to the effect on insulin-resistant genes, the NAFLD and also type 2 diabetes[68], so that several epidemiological studies have found that type 2 diabetes is associated with an increased risk of HCC[69,70].

### Oral contraceptives

The consumption of combined estrogen-progestogen OCs may affect the females' susceptibility to HCC[71]. There is biological and experimental rationale for a possible risk factor of oral contraceptives (OC) in liver neoplasia[71]. Some studies have found that the consumption of OCs raises the risk of LC[72,73], but other studies have not found this relationship[74-77]. The results of a meta-analysis in this field also reported the RR of LC equal to 1.57 (95% Confidence Interval (CI), 0.96-2.54)[78].

### Arsenic

Many studies have found the association between human exposure to arsenic and LC[79,80]. For instance, in regions of Taiwan and Japan, where drinking water contains a significant amount of arsenic, there is an increased risk of LC in residents[81,82]. Undoubtedly, environmental exposure to arsenic is unavoidable, as recently arsenic compounds have been used for the treatment of some cancers[83].

### Hemochromatosis (Excessive iron in the liver)

The liver is the main site for maintaining iron in the body. Accumulation of excessive iron in the liver due to the hereditary hemochromatosis[84,85] or dietary iron overload in the African indicate a causal relationship with susceptibility to HCC[86-88]. Excessive iron intake can be seen in rural areas of several sub-Saharan African countries because in these regions, two thirds of adult males consume traditional beverages that contain large amounts of iron compared to commercial beverages (46-82 mg/L compared with <0.5 mg/L in commercial beers)[89].

### Familial and genetic susceptibility

Studies have reported the familial LC accumulation. A part of this accumulation is due to the transfer of HBV and HCV in the family, and to have inappropriate lifestyles and habits such as exposure to environmental factors including smoking and alcohol consumption[90,91], and another issues which is related to genetic sensitivity and some hereditary disorders associated with HCC such as hemochromatosis[92]. In general, the risk of LC in those with a familial history is twice more than those without the familial history[93].

### Age and sex

In most high-risk areas, the incidence of this cancer increases after the age of 20 and peaks at the age of 50 and above. In these areas, the incidence of LC may be also seen before the age of 20. The second model can be seen in low-risk areas where the incidence of LC steadily increases by age. Its incidence rises after the age of 45 to 50, and becomes almost constant after 65. LC is usually 2 to 4 times higher in men than women[94,95] due to the more exposure of men to important risk factors of this cancer such as alcohol, smoking, and the infected injection[96].

### Socioeconomic status

Studies have found that the incidence and mortality of LC have different models in countries with multitude geographical, cultural, social and economic backgrounds[97], so that more LC cases are annually diagnosed in less developed countries, since people who are living in lower socioeconomic areas are more exposed to risk factors such as HBV, alcohol and tobacco consumption and their access to health systems is lower, thus making higher the incidence and mortality of LC[98-102].

## CONCLUSIONS

The present study aimed to investigate the incidence and mortality of LC in the world and the association between different risk factors of LC. Findings of the present study indicated that the ASIR of LC was 10.1 per 100,000 people and the ASMR for LC was 9.5 per 100,000 people worldwide. The most important risk factors of LC included the chronic infections with HBV and HCV, aflatoxin, alcohol drinking and smoking. Excessive consumption of white meat or fish, vegetables, fruits, cereals, eggs, milk and yogurt was known as a protective agent for this cancer. However, this is not a systematic review and only English studies were included.

### Conflict of Interest:

The Authors declare that they have no conflict of interests.

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