



Incidence and mortality of liver cancer and their relationship with the human development index in the world

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Abstract— Background: Information on the incidence and mortality of liver cancer can be useful for health programs and research activities, and with regard to the possible role of the HDI and liver cancer, this study aimed to investigate incidence and mortality from the cancer and their relationship with the indicator and its components in 2012 in world. **Methods:** In this ecologic study, data were extracted from GLOBOCAN in 2012. Data on HDI and its components were extracted from the World Bank. The number and standardized incidence and mortality rates of liver cancer were reported by regions in the world. Data were analyzed by SPSS software and Correlation coefficient test. **Results:** There was a total of 782,451 incidence cases. Of these patients, 228, 082 cases (29.15 %) were women and 554, 369 cases (70.85 %) men, and there were 745,533 deaths. Of the deaths, 224, 492 cases (30.11 %) occurred in women and 521, 041 cases (69.89 %) men were recorded in the world in 2012. Results showed that there was a significant inverse correlation between age-specific incidence rate (ASIR) and HDI ($r=-0.345$, $p\leq 0.001$), as well significant inverse correlation was seen between age-specific mortality rate (ASMR), and HDI and its components. **Conclusion:** Liver cancer incidence and mortality are higher in the medium HDI countries. The relationship between the standardized incidence and mortality of liver cancer with HDI and its components, including life expectancy at birth, mean years of schooling and income level per person was significantly negative.

Keywords: Incidence, Mortality, Liver Cancer, Human Development Index, World

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the main causes of mortality worldwide and most cases occur in Asia and Africa. It is the fifth and seventh cause of death from cancer in men and women, respectively (Shen et al., 2012).

The cancer is classified into three types of intrahepatic cholangiocarcinoma (ICC), HCC and the combination of the two classifications (Ikai et al., 2004; Tang et al., 2006). HCC, as main form of primary cancer, is an

aggressive malignancy and more than 50% of cases died within the first year after diagnosis (Altekruse et al., 2009; Jemal et al., 2012). Evidence suggests that HCC incidence is still increasing (Kim et al., 2014). Increased trends in rates of PLC for both sexes have been observed in many populations, for example: Europe, America, Oceania, the United Kingdom, France, Germany, Netherlands, Italy, Canada and Colombia (Zhang et al., 2015).

The highest increasing trend of DALY was attributed to pancreatic and liver cancers between 1990 and 2010 (Murray et al., 2013). In 2013, among US adults, 22720 men and 7920 women were diagnosed with primary liver cancer, which is increasing (Siegel et al., 2013). There is a high prevalence of liver cancer in 22 countries, mainly in East Africa and Southeast Asia, as a result of risk factors in these areas (Bray et al., 2012). It was seen that 25% of cancers related to infectious agents (liver, stomach and cervix cancers) occur in sub-Saharan Africa while 27% of cases were seen in East Asia, and incidence of liver cancer in Asian countries is increasing almost two times (Soerjomataram et al., 2012). International trends in primary liver cancer incidence rates during 1973 to 2007 revealed that most ESR for primary liver cancer was a range from 19 to 26.7 per 100,000 men and from 4.8 to 8.7 per 100,000 women in some Asian populations (Zhang et al., 2015). HCG differences in the incidence rates in different geographical areas are correlated with hepatitis B and C rates because chronic viral hepatitis has been reported as an important risk factor for HCC in endemic areas (Chisari et al., 1989; Colombo et al., 1989; Idilman et al., 1998). This is despite the fact that approximately 45 million and 15 million people worldwide suffer from chronic hepatitis B and C (Kar, 2014). Another reason for the difference in incidence in different regions was Human papillomavirus (HPV), which is responsible for stomach, liver and cervical cancers (Vineis and Wild, 2014). Other etiologies for liver cancer are modifiable risk factors, such as smoking, alcohol, contaminated injections in health care centers, immigration and obesity (Chuang et al., 2009; Ezzati and Riboli, 2013; Franceschi and Wild, 2013; Shih et al., 2012). The relative risk associated with family history of liver cancer is 2.6 and the cancer is also significantly more common in men (Huang et al., 2011; Yang et al., 2014).

The difference in the incidence of deaths from cancer between different countries can be caused by differences in development of countries. Some studies have confirmed the relationship between human development indicators (HDI) with the incidence and mortality of cancer (Bray et al., 2012; Rafiemanesh et al., 2016).

In countries with a low HDI, incidence and mortality rates from cervical, liver, esophagus and stomach cancers are higher than countries with high HDI (Franceschi and Bray, 2014; Humans, 2011; Pakzad et

al., 2016). Also, studies showed that some of cancer is related to the HDI (Ghoncheh et al., 2015; Pakzad et al., 2015a, b). Chronic diseases, including liver cancer, have multiple causes, and one of the possible causes could be development. Therefore, having information on the incidence and mortality of liver cancer can be useful for health programs and research activities and with regard to the possible role of the HDI, this study aimed to investigate incidence and mortality from the cancer and their relationship with the indicator and its components in 2012 in world.

METHODS

In this ecologic study, data about the age-specific incidence and mortality rate (ASR) for every country in 2012 were get from the global cancer project that available in (<http://globocan.iarc.fr/Default.aspx>) (Ferlay J et al., 2016) and HDI from Human Development Report 2013 (Malik, 2013), that includes information about HDI and its details for every country in the word in 2012. More details about data collection were previously published (Ferlay J et al., 2016; Ferlay et al., 2015).

Method for estimating the age-specific incidence and mortality rates in global cancer project by international agency for research on cancer

Age-specific incidence rate estimate

The methods of estimation are country specific, and the quality of the estimation depends upon the quality and on the amount of the information available for each country. In theory, there are as many methods as countries, and because of the variety and the complexity of these methods, an overall quality score for the incidence and mortality estimates combined is almost impossible to establish. However, an alphanumeric scoring system which independently describes the availability of incidence and mortality data has been established at the country level. The combined score is presented together with the estimates for each country with an aim of providing a broad indication of the robustness of the estimation. The methods to estimate the sex- and age-specific incidence rates of cancer for a specific country fall into one of the following broad categories, in priority order:

- 1-Rates projected to 2012 (38 countries)
- 2-Most recent rates applied to population in 2012 (20 countries)
- 3-Estimated from national mortality by modelling, using incidence mortality ratios derived from recorded data in country-specific cancer registries (13 countries)
- 4-Estimated from national mortality estimates by modelling, using incidence mortality ratios derived from recorded data in local cancer registries in neighboring countries (9 European countries)
- 5-Estimated from national mortality estimates using modelled survival (32 countries)
- 6-Estimated as the weighted average of the local rates (16 countries)
- 7-One cancer registry covering a part of a country is used as representative of the country profile (11 countries)
- 8-Age/sex specific rates for "all cancers" were partitioned using data on relative frequency of different cancers (by age and sex) (12 countries)
- 9-The rates are those of neighboring countries or registries in the same area (33 countries) (Ferlay J et al., 2016).

Age-specific mortality rate estimate

Depending on the degree of detail and accuracy of the national mortality data, six methods have been utilized in the following order of priority:

- 1-Rates projected to 2012 (69 countries)
- 2-Most recent rates applied to population in 2012 (26 countries)
- 3-Estimated as the weighted average of regional rates (1 country)
- 4-Estimated from national incidence estimates by modelling, using country-specific survival (2 countries)
- 5-Estimated from national incidence estimates using modelled survival (83 countries)
- 6-The rates are those of neighboring countries or registries in the same area (3 countries) (Ferlay J et al., 2016; Ferlay et al., 2015).

For assessment of the correlation between age-specific incidence and mortality rate (ASR) with HDI and its details, which include life expectancy at birth, mean years of schooling and gross national income (GNI) per capita, we used correlation bivariate method. Statistical significance was assumed if $P < 0.05$. Statistical analyses were performed using SPSS (Version 15.0, SPSS Inc.).

RESULTS

Incidence rate

In 2012, 782,451 new patients suffered from the cancer were diagnosed; so that the patients included 5.6% of all cancers. Of these patients, 228, 082 cases (29.15 %) were women and 554, 369 cases (70.85 %) men. According to the estimates of GLOBOCAN, the cancer with ASIR equal to 10.1 per 100,000 is known as the seventh common cancer in the world. The cancer is the ninth and fifth common cancer in women and men with the incidence of 5.3 and 15.3, respectively. Of the six WHO regions, the highest incidence rate was seen in the region WPRO (20.4) and the lowest incidence rate was 4.3 for the region EUROP. Considering the regions in terms of development (HDI), the highest incidence rate (14.6) belonged to Medium Human Development and the lowest incidence rate (3.8) to High Human Development. Among the countries in the world, the highest and lowest incidence rates were related to the countries MONGOLIA and NEPAL, 78.1 and 0.9 respectively. According to the division of the continent, the highest incidence rate was taken in account to Eastern Asia and Northern Europe, 20.9 and 3.1 respectively (**Fig. 1**).

Mortality rate

It was estimated that there were 745,533 deaths from the cancer in 2012. Of the deaths, 224, 492 cases (30.11 %) occurred in women and 521, 041 cases (69.89 %) men. The cancer with ASMR equal to 9.5 per 100,000 is the third cause of death worldwide. Liver cancer in women with mortality rate of 5.1 was the sixth cause of cancer death after breast, lung, and cervix uteri cancers and in men with mortality rate of 14.3 was second common and fatal cancer after lung cancer. Of the six WHO regions, the highest mortality rate was seen in the region WPRO (19.1) and the lowest

mortality rate was 4 for the region EUROP. Considering the regions in terms of development (HDI), the highest mortality rate (14.1) was observed in Medium Human Development and the lowest incidence rate (4.1) in High Human Development. According to the division of the continent, the highest mortality rates were related to Eastern Asia and Northern Europe, 19.6 and 2.8 respectively (Fig. 2).

HDI

The ratio of mortality to incidence (MIR) was estimated about 0.95 in the world for the cancer. This ratio for the six WHO regions was different from 1.07 for EUROP and WPRO to 1.13 for PAHO and 1.04 for AFRO, SEARO and EMRO. Considering the regions in terms of development (HDI), the highest ASMR (69%) was observed in Medium Human Development and the lowest ASMR (6.9%) in High Human Development.

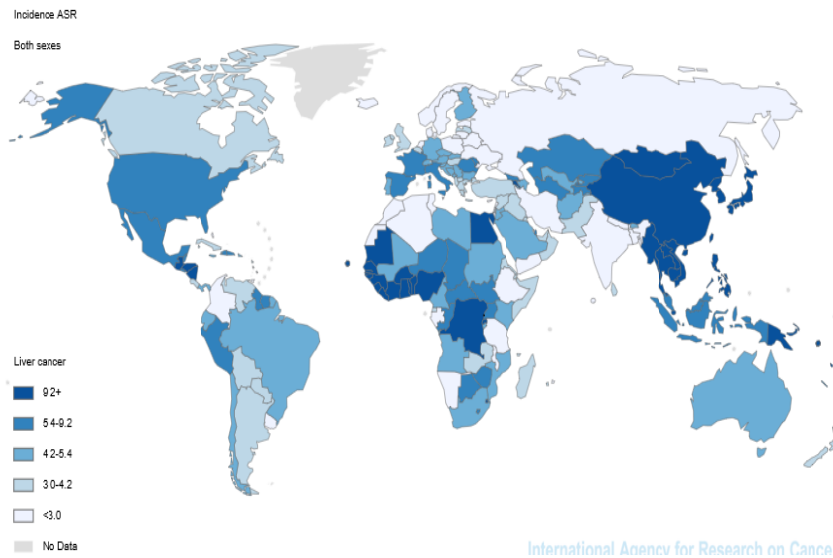


Figure 1. Distribution of the standardized incidence rate of Liver cancer in the World in 2012.

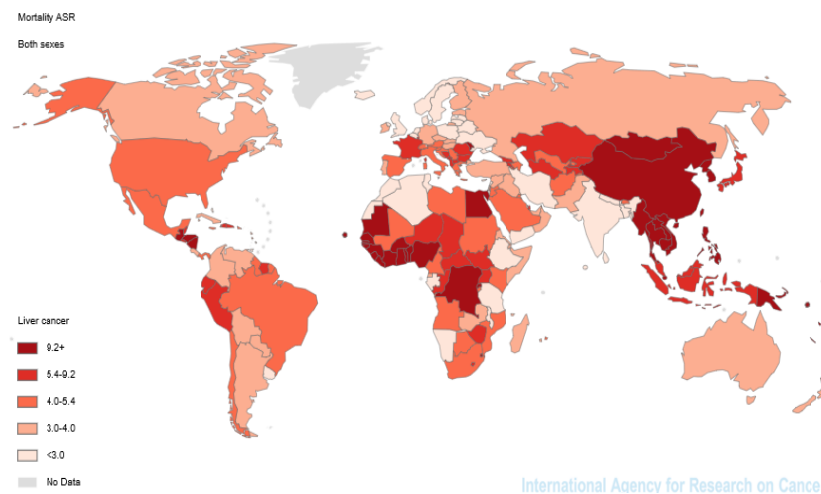


Figure 2. Distribution of standardized Liver cancer mortality rates in World in 2012.

Table 1. Pearson correlation between HDI component and dependent variable

Variable	ASIR		ASMR	
	r	p-value	r	p-value
life expectancy	-0.274	<0.001	-0.297	0.001
Mean schooling	-0.288	<0.001	-0.322	<0.001
GNI	-0.329	<0.001	-0.349	<0.001

Dependent variables: ASIR and ASMR

Results showed that there was a significant inverse correlation between ASIR and HDI ($r=-0.345$, $p\leq 0.001$). Pearson correlation test revealed significant correlation between ASIR and components of the HDI, including life expectancy at birth, mean years of schooling and Gross national product (GNI) (**Table 1**). Significant inverse correlation was seen between ASMR and HDI and its components (**Table 1**).

DISCUSSION

Liver cancer was the fifth common cancer in the world with 437,000 new cases in 1990 and the incidence rate was 2 to 3 times higher in developing countries than in developed countries (El-Serag, 2012). However, in 2014 the cancer was dropped to seventh common cancer in the world with 782,451 new cases and more than 85% of cases of primary liver cancer are diagnosed in developing countries. Highest incidence rate is attributed to regions of Southeast Asia and Sub-Saharan Africa (El-Serag, 2012; El-Serag and Rudolph, 2007).

Based on the results of this study, the highest and lowest rates of cancer incidence and mortality were seen in the West Pacific, East Asia and North Europe, respectively; but both of these rates are negatively correlated with the development index and its components. Polk DB in 2010 and Perz JF in 2006 found that stomach cancer and liver cancer are common in areas with medium HDI (Perz et al., 2006; Polk and Peek, 2010). Milena Maule (2012) indicated that although absolute risk of cancer is down in countries with low HDI, some cancers, such as cervical, stomach, liver and Kaposi's sarcoma, have the highest incidence and mortality rates in these areas (Franceschi and Wild, 2013; Maule and Merletti, 2012). Etiology of these cancers is resulting from infectious agents. In a study by El-Serag HB in 2004, it was

found that liver cancer in Asian countries is on the rise 2 times (El-Serag, 2004). Freddie Bray in 2012 also indicated that there is a high prevalence of liver cancer in 22 countries, mainly in East Africa and Southeast Asia (Bray et al., 2012). An investigation on all cancers registered between 2008 and 2013 in regions with different HDI showed that the annual incidence increased to 75 % (Bray et al., 2012). Increasing trend from 1990 to 2014 revealed that the incidence is higher in developing countries and is consistent with the results of this study. Yue Zhang in 2015 did not confirm the result of this study and showed that there were the declining trend in Asian populations and the increasing trend in some European and Pacific populations between 1973 and 2007 (Zhang et al., 2015). According to final results of HCC in the United States during 2007 to 2010, there was no significant increase in incidence, but mortality rate has increased (Altekruse et al., 2014). A study by Silvia Franceschi in 2015 it was shown that an epidemiological transition towards patterns of cancers associated with infectious agents in countries with a high HDI (Franceschi and Wild, 2013). Although the reasons for this trend are completely not clear, it seems that public health measures in Asia and HCV transmission in Europe, America, and Oceania contributed to the formation of these patterns (Zhang et al., 2015). The stunning result of this study was that the maximum and minimum MIR by the division of the continent was 1.25 and 0.76 for Central America and Northern America. Qi-Da Hu in 2013 indicated that an inverse relationship between HDI and MIR, which is contrary to findings of the present study (Altekruse et al., 2009). This difference may be due to registration of the death rates in many countries and diagnostic accuracy of liver cancer cases in health care systems. F. Vostakolaei (2010) confirmed the reasons. On the other hand, the prognosis for primary liver cancer is poor, and the cancer is typically diagnosed in advanced stages (Vostakolaei et al., 2011). Therefore, the difference in reporting can have remarkable impact on MIR.

In this study, sex ratio of ASIR (male to female) was 2.89 around the world. Bosch FX in 1999 the sex ratio of ASIR was 1.5 to 3, which is consistent with the present study (Bosch et al., 1999). Of the cancers related to infectious agents, about half of the burden of cervical cancer was seen in women, while more than 80 % of liver cancer and stomach occurred in men (Vineis and Wild, 2014). The high incidence of liver cancer in men can be at higher risk of the most

important factors such as smoking, alcohol, and infected injection (Franceschi and Wild, 2013; Kar, 2014). In examining the relationship between the life expectancy of the HDI, an inverse relationship was observed between the component with rates of incidence and mortality. Given that the age is a firm prognosis in many cancers, age may have a paradoxical role in relation to cancer prognosis (Chen et al., 2006). Liver cancer is one of cancers that influenced by the paradoxical role of age because about 30 % of cancers related to infection agents occur in people younger than 50 years (Vineis and Wild, 2014). Although liver cancer is more common in people 65 years, the incidence and mortality of the cancer are higher in younger age because the main risk factors for liver cancer, such as viral hepatitis and alcohol abuse, affect people in early middle age (Blachier et al., 2013; Starr and Raines, 2011).

In this study, an inverse and significant relationship was observed between national income with rates of incidence and mortality from the cancer. Ahmedin Jemal confirmed that HCC cases in each ethnic group had the lowest socio-economic status compared with their reference population (Jemal et al., 2013). Other studies have shown an inverse relationship between low socioeconomic and the incidence of HCC (Karlamañgla et al., 2010). HB antigen prevalence and alcohol abuse and finally liver cancer are higher in people who have low socioeconomic status because the persons more exposed to risk factors and have poor access to health care system. As a result, higher incidence and mortality rates were observed among them (Akil and Ahmad, 2011; Joshi et al., 2008; Karlamañgla et al., 2010; Khan et al., 2002; Loucks et al., 2007; Roblin et al., 2010).

In examining the relationship between education level of HDI with the incidence and mortality of the cancer, significantly negative correlation was seen. Ahmedin Jemal revealed that an increase in death rates for liver cancer is common in people with lower degrees of education (Jemal et al., 2013). In Flores YN's study, it was found that if the level of education is lower, viral load of hepatitis infection and the incidence of HCC will be more (Flores et al., 2008). Kyunghye Jung-Choi indicated that mortality from the cancer is higher in population groups with lower education than population groups with higher education (Jung-Choi et al., 2014). Li-Yen GOH also confirmed that drinking alcohol is effective in increased risk of incidence and mortality from liver cancer in men with lower levels of

education. Therefore, the low education level is associated with increased risk factors for the cancer (GOH et al., 2014).

CONCLUSION

Liver cancer incidence and mortality are higher in the medium HDI countries. Therefore, it seems that health policy makers should make serious decisions in this area to deal with the increase in the incidence and mortality of Liver cancer. The relationship between the standardized incidence and mortality of liver cancer with HDI and its components, including life expectancy at birth, mean years of schooling and income level per person, was significantly negative.

Plans for the control and prevention of this cancer must be a high priority for health policy makers; also, it is necessary to increase awareness of risk factors and early detection in all countries, also it is necessary to investigate the related risk factors in medium HDI countries and less developed countries.

Competing Interests

The authors declare they have no competing interests.

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