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Liver cancer incidence and mortality: Disparities based on age, ethnicity, health and nutrition, molecular factors, and geography

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ABSTRACT

Liver cancer (LCa) is the fifth and eighth leading cause of cancer death for men and women, respectively. However, despite improvements in treatment strategies and options, it has limited therapeutic options. Worldwide, the prevalence of LCa varies widely. Various factors are associated with the development of LCa, and its incidence, morbidity, and mortality rates differ due to disparities that are multifactorial and complex, including genetic and geographic factors. The frequency of LCa varies by race/ethnicity, age and sex and relates to viral infections, lifestyle, nutrition, obesity, and health. In addition, various molecular factors, including cytokines, hormones, apoptosis, and mutations, are involved in disparities in the progression and mortality of LCa. Here, we provide an overall perspective on LCa by presenting available information on these associated factors and discussing their importance in its disproportionate incidences and clinical outcomes.

KEYWORDS: Liver cancer, health disparity, nutrition and health, morbidity

Citation: SK Singh and R Singh (2019) Liver cancer incidence and mortality: Disparities based on age, ethnicity, health and nutrition, molecular factors, and geography. Cancer Health Disparities 4: e1-e10. doi:10.9777/chd.2019.1014

Introduction

In the United States, liver cancer (LCa), including intrahepatic bile duct cancer, is the fifth and eighth leading cause of cancer for men and women, respectively (Chen, 2018). For the United States, 42,030 cases are expected to be diagnosed in 2019, and 31,780 deaths are predicted (Siegel et al., 2019). The death rates for LCa are increasing at a faster pace than those for other cancers (Islami et al., 2017; Jemal et al., 2017). In the United States, the incidence of liver cancer is projected to rise continuously from the mid-1970s through 2030. A factor contributing to this increase is the hepatitis C virus (HCV) infections in those called "baby boomers," who were born during 1945 to 1965 (Geboy et al., 2016).

A decline in overall cancer mortality rates in the United States was evident in the 1990's, due to widespread cancer screening, improvements in treatments, and reductions in cancer risk factors such as tobacco smoking (Jemal et al., 2017; O'Keefe et al., 2015). However, the mortality rate for LCa increased, with an unequal distribution throughout the population. Additionally, hepatocellular carcinoma (HCC), reported more often in Asia than in the United States, is the third leading cause of cancer mortality worldwide (Altekruse et al., 2009). Thus, HCC is one of the most fatal cancers, with only a 7% 5-year survival (Ruggieri et al., 2010). Moreover, in the United States, geographical and biological factors are associated with racial disparities. In the development of HCC, exposure to hepatitis B virus (HBV) and HCV infections, alcoholic liver disease, hemochromatosis, and non-alcoholic steatohepatitis are involved; there are also genetic and environmental contributions (Ruggieri et al., 2010). Furthermore, some racial groups are more affected, as shown by data on cancer incidence and mortality (Deshmukh et al., 2017). In the United States, the mortality for African Americans (AA) with HCC is worse than for any other racial group. In addition, in Eastern and Southern Asia, Middle and Western Africa, Melanesia, and Micronesia/Polynesia, the incidence of HCC is higher for males than females (Ferlay et al., 2010). According to the NIH Surveillance, Epidemiology, and End Results (SEER) database, the annual incidence of HCC has tripled between 1975 and 2005 (Altekruse et al., 2009). The statistical data of the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) show a difference in the LCa-based mortality rates by race/ethnicity. A schematic presentation of liver cancer disparity associated factors are shown in Figure 1. In the present review, our focus was to estimate the worldwide burden of LCa disparities based on race/ethnicity, health and nutrition, and molecular and geographical factors.

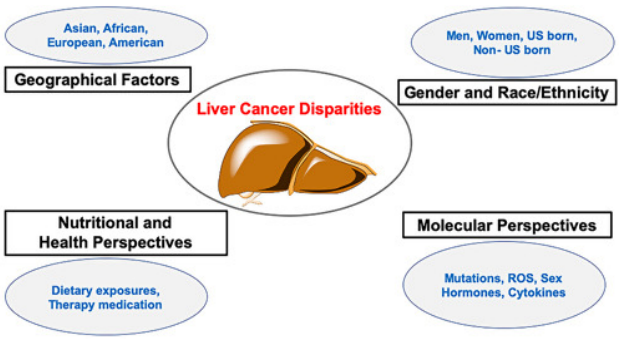

Figure 1. Schematic presentation of liver cancer disparity associated factors

Factors associated with LCa

Disparities of LCa occurrence by sex and race/ethnicity

The incidence of LCa varies by race/ethnicity due to differences in the prevalence of risk factors and, to some extent, disparities in access to high-quality care. Recently, an annual report on cancer

incidences from 1975-2012 and/or 2014 (Islami et al., 2017; Ryerson et al., 2016), showed lower rates of overall cancer incidences among both men and women but increased rates of LCa-related deaths for both sexes. From 2003 through 2012, the mortality rates were higher among men (Ryerson et al., 2016). Early 2000 estimates indicated that LCa incidence was the fifth most common cancer in men and eighth for women worldwide, with male/female ratios regularly averaging between 2:1 and 4:1. (Montalto et al., 2002). However, for countries with low incidences of LCa, the age distribution for males and females was rare before the age of 50. Among high-risk countries such as those in Southeast Asia and West and Coastal Africa, the occurrence of LCa was evident before the age of 20; gender ratios were higher, and the male excess was greater for those less than 50 years of age. In addition, clinical observations and death statistics showed that LCa due to hepatitis infections appeared to progress more in males than females and that cirrhosis was largely a disease of men and postmenopausal women (Giannitrapani et al., 2006; Ruggieri et al., 2010).

In the United States, there were disparities in the rates and survival for various races/ethnicities and between states; the relative risk of death for all cancers combined was 33% higher for non-Hispanic (NH) blacks and 51% higher for NH Indian/Alaska Natives compared to NH whites (Islami et al., 2017). However, there was a disparity in LCa incidence in that it was higher among NH whites, NH blacks, and Hispanic men and women born after 1938-1947; it was minimal for NH Asian and Pacific Islanders (Ryerson et al., 2016). Among Hispanics, the disparities in LCa incidence and mortality were related to their nativity. The HCC incidence was twice as high for US-born Hispanic men compared to the foreign-born Hispanic men (Setiawan et al., 2016). The risk factors of smoking status, hepatitis B/C infection, and diabetes accounted for HCC among US-born Hispanics. An overview of the disparities of LCa incidence according to race and ethnicity is presented in table 1.

Table 1. Disparities of LCa incidences according to race and ethnicity.

Region born	Ethnicity/ Gender	Incidence (per 100,000)	Severity	Causes	Mortality (per 100,000)	Reference
US born	Men (overall)	21-35		----		(Altekruse et al., 2009)
	Women (overall)	3.8-13.6		----		(Altekruse et al., 2009)
	Hispanic (men/women)	1.8-60.2/1.2-48	Localized to advanced and unknown	Chronic hepatitis/fibrosis/ alcohol-related/other	63/42	(Setiawan et al., 2016)
	Asian (men/women)	35-83/5.9-37.9	Localized to advanced	HCV/HBV infection		(Altekruse et al., 2009)
	African (men/women)	37-40/6.9-13.6	Localized to advanced	HCV/HBV infection/other		(Altekruse et al., 2009)
	White	16.5-28/3-10.2	Localized to advanced	HCV/HBV infection/obesity/0ther		(Altekruse et al., 2009)

Non-US born	Men	75.9		-----		(Njei et al., 2015)
	Women	24.5		-----		(Njei et al., 2015)
	Hispanic (men/women)	0-44/0-50	Localized to advance and Unknown	Chronic hepatitis/Fibrosis/Alcohol related/Other	35/19	(Setiawan et al., 2016)
	Asian	18.9-24	Localized to advanced	HCV/HBV infection		(Njei et al., 2015)
	African	10.9-12.5	Localized to advanced	HCV/HBV infection/other		(Njei et al., 2015)
	White	67	Localized to advanced	HCV/HBV infection/obesity/other		(Njei et al., 2015)

Geographical factors associated with disparities in LCa

HCC is the dominant histologic type of LCa, accounting for approximately 80% of total cases globally (Petrick et al., 2016). HCC poses a prominent disease burden throughout the world and particularly in Africa and Asia where HBV is the principal cause (Bosch et al., 2005). In Western countries, chronic alcohol abuse is the primary factor associated with HCC. High disease levels in Northern Thailand are due to chronic infections with the liver fluke, *Opisthorchis viverrini*, which is ingested through infected raw fish (Petrick et al., 2016; Sripa et al., 2012).

In countries undergoing socio-economic development, such as some in Asia, HCC cases account for nearly 75% of all LCas, and China accounts for 56% of the world's burden. The highest incidence of HCC occurs in Mongolia; the lowest incidence is in Nepal (Baatarkhuu et al., 2017; Shrestha, 2018). However, HCC incidence has been increasing in several other countries, but there have been declines in some Asian countries (McGlynn and London, 2011; McGlynn et al., 2015; McGlynn et al., 2001; Zhang et al., 2015). However, the rates of HCC remain highest in Asian counties (Petrick et al., 2016). Although there was a decrease in HCC burden in these high-risk countries, there was a rise in India as well as in low-risk countries of Africa, Europe, the Americans, and Oceania; in Thailand, France, and Italy, there was a decline. The decreased incidence in high-risk countries was likely due to a lower prevalence of HBV infections. Particularly in low-risk countries, a reduction in HCC burden will be seen when incidences of HCV, diabetes, and obesity are lowered.

Disparities of LCa from the nutritional and health perspective

"Food insecurity" refers to a lack of access to sufficient, safe, and nutritious food that fulfils the dietary needs and food preferences for living a healthy life. There is evidence suggesting a relationship between specific dietary components and risk of cancers at various anatomic sites (Schutte et al., 2016). The nutritional status of patients is related to their performance status and to their tolerance for cancer therapy (Schutte et al., 2016).

Few studies are investigating the role of diet in hepatocarcinogenesis. Risk factors for the occurrence of LCa include chronic viral infections (hepatitis B and C), excess alcohol consumption,

non-alcoholic fatty liver disease, dietary exposure to aflatoxin, obesity, smoking, and diabetes mellitus (El-Serag and Rudolph, 2007). However, a substantial portion of LCa occurs in patients without exposure to these risk factors, suggesting a role of additional factors. Observational studies indicate a protective role of a diet containing vegetables, fruits, and cereals (Koumbi, 2017) in preventing cancer. Although various studies have presented conflicting results, high intakes of red meat, fish, and dietary sugars are associated with a high risk for Western Europeans (Fedirko et al., 2013). Among Japanese, Italians, and Europeans, high intakes of vegetables, fruits, cereals, eggs, milk, and yogurt are associated with a lower occurrence of LCa (Kurozawa et al., 2004; Negri et al., 1991; Talamini et al., 2006). These results are supported by findings of a study of Chinese men and women, which showed that a vegetable-based diet is associated with reduced risk of LCa (Zhang et al., 2013).

For Japanese individuals, overweight or obesity moderately increases the risk of LCa (Tanaka et al., 2014). Obesity among Americans has reached an epidemic proportion (Vastag, 2004), and 64% of the adult population is overweight or obese. There is a positive association between obesity and high death rates for liver and other cancers (Calle et al., 2003). It was estimated that more than 90,000 cancer deaths per year could be avoided with the maintenance of normal weight, and obesity was a major risk factor for cancer (Donaldson, 2004). Among Americans, obesity, nutrient-sparse foods such as concentrated sugars and refined flour products that contribute to reduced glucose metabolism, low fiber intake, consumption of red meat, and an imbalance of omega 3 and omega 6 fats contribute to excess risk of LCa (Donaldson, 2004).

A study focused on the type of therapy and patients with diagnosed stages shows that for LCa stage A patients, liver transplants, radiofrequency ablation (RFA), and embolization were utilized less often for Hispanics, NH blacks, patients with Medicaid, and patients in the highest income quartile. Stage D patients were less likely to receive cancer therapy if they had Medicaid insurance (Harlan et al., 2015). Additionally, 26.8% of patients diagnosed with stage B received surgery, followed by 12.4% of those with stage 0. For younger patients, those diagnosed and treated at earlier stages were more likely to receive surgery than NH black Medicaid patients. Furthermore, transplants were more frequent for stage 0 (36.5%) and stage A disease (48.1%) than for patients aged 50 or older, NH blacks, Hispanic patients, and stage B-D Medicaid patients (Harlan et al., 2015). In addition to surgery and transplantation, RFA was more often used for stage 0 (3.7%) and stage A (3.9%); for stage B disease, tumor embolization was most often performed in combination with systemic chemotherapy (15.3%) (Harlan et al., 2015).

Molecular perspectives related to disparities in LCa

Morphologically, liver tumors are heterogeneous within the same tumor and for different tumors. Some subtypes of LCa have stem cell features; others have a phenotype intermediate between hepatocytes and cholangiocytes (Sia et al., 2017). These observations have raised the possibility of disparities in the origin of LCa. Hepatic precursor cells might generate primary liver tumors as, during development, hepatocytes and cholangiocytes can arise from a common precursor cell. However, tumors developing from mature hepatocytes and cholangiocytes could be different. Moreover, hepatocytes could be a source of LCa as these cells can undergo mutations in their genes, dedifferentiate into

precursor cells, and ultimately transform into LCa cells with precursor cell markers (Chen et al., 2012; Sia et al., 2017; Tanimizu et al., 2013).

The liver is a sexually dimorphic organ. For males and females, there are differences in gene expression, mitochondrial function and enzyme activity, lipids composition of cell membranes, and immune responses (Dhir et al., 2006). The differentiation of liver gender is maximum at puberty, with the elevation of testosterone in males associated with the tyrosine phosphorylation cascade of Jak2/Stat5, which is involved in the transcription of masculine genes that repress feminine genes. However, for females, secretion of growth hormone continues, but at a lower rate, with unphosphorylated Stat5 associated with gene transcription. Such differences could account for the disparity in the development of LCa between the two sexes (Dhir et al., 2006; Waxman and Holloway, 2009). Molecular factors involved in the disparities of incidence and mortality of LCa are shown in table 2. A separate study of HCC showed that inhabitants of Asian and African countries were more likely to have chronic HBV infections, whereas those in Japan and the United States were more likely to have HCV infections (El-Serag and Rudolph, 2007). In addition, about half of the cancers are activated due to TP53 mutations; in a clinical study of Chinese patients, nearly half had a point mutation at codon 249 (Aravalli et al., 2008). Thus, understanding the molecular mechanism of HCC is a promising strategy for dealing with cancer disparities.

Table 2. Molecular factors involved in disparities in incidence and mortality of LCa.

Cellular and Molecular factors/mechanisms	Dysregulation	Associated with	Reference
Cytokines			
IL-6	Overexpression	HCV	(Rogers et al., 2007); (Nakagawa et al., 2009); (Wong et al., 2009)
IL-10	Polymorphism in promoter	HCV	(Paladino et al., 2006); (Persico et al., 2006)
Interferon	Overexpression	HCV	(Rogers et al., 2007)
Sex hormones			
Androgen, estrogen, and progesterone	Differential expression	Regulation of transcriptional factors NFkB and C/EBPβ, immune response, and cell proliferation	(Naugler et al., 2007); (Ohnishi et al., 1986)
Reactive oxygen species	Production	Depletion of antioxidant defences; changes in key organelles, including mitochondria	(Tien Kuo and Savaraj, 2006)
Mutations	Hypermethylation of genes	LZTR1, EEF1A1, SF3B1, and SMARCA4, CCR5 32 delta	(et.al., 2017)

Chemokines are the low molecular weight proteins that function in leukocyte trafficking and other biological activities. They belong to the G-protein coupled receptor family, bind to their cognate receptors, and determine the metastatic destination of tumor cells (Singh et al., 2018). Chemokines are involved in liver inflammation, which regulates activities of circulating immune cells, endothelial cells, and hepatocytes. Moreover, they contribute to cell proliferation, pathogenesis,

angiogenesis, and the inflammatory microenvironment of HCCs (Abdolmohammadi et al., 2016). Therefore, we reviewed the role of chemokines and their receptors in the regulation of LCa disparities. Chemokine receptor 5 (CCR5) delta 32 alleles may predispose patients to chronic HBV infections. A total of 812 Iranian individuals, grouped into HBV-infected and healthy controls, demonstrated that CCR5 delta 32 was more frequent in healthy controls than in HBV-infected individuals (Abdolmohammadi et al., 2016). In addition, the CCR5 receptor is a coreceptor for the HIV gp120 protein (Wilkin et al., 2010). A CCR5 delta 32 mutation is present in 10-15% of Caucasians. Those who have a copy of the gene encoding CCR5 delta 32 have a greater probability of recovery from HBV infection (Thio et al., 2007). Indians having CCR5 delta 32 heterozygosity are more susceptible to HBV-related liver disease (Suneetha et al., 2006). This shows that, due to differences in genetic background, those with CCR5 delta 32 are resistant to HBV infection. The CCR5 delta 32 allele is not present in residents of Southeast Asian countries, and, in a study of CCR5 delta 32 polymorphism in China, no mutated allele was detected.

Conclusions

In the future, the burden of LCa in the United States and worldwide is expected to increase. Despite improvements in LCa treatments and survival rates, the overall prognosis for LCa remains poor. Wide disparities in LCa rates by sex, age, gender, and ethnicity reflect differences in the major risk factors and inequalities in access to high-quality care. The increase in obesity in the general population, lack of healthy nutrition, inappropriate lifestyles, and limited understanding of the molecular aspects and origin of LCa are impediments in preventing and treating these cancers. To curb the rising problem of LCa and its disparities, interventions should include the application of existing knowledge in prevention, early detection, and treatment, maintaining healthy body weight, providing access to high-quality diabetes care, preventing excessive alcohol drinking, and controlling tobacco consumption.

Acknowledgements

This study was supported in part by the National Institutes of Health under Award Number SC1CA193758 and U54CA118638, and by the Department of Defence, Award Number W81XWH1810429.

Conflict of interest

All authors declare no potential conflicts of interest.

Authors' contributions

SKS was involved in data collection and drafting of the article. RS designed the concept, critically reviewed and editing of the final version of the manuscript. All authors read and approved the final manuscript.

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