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Original Research Article

The changing patterns of liver cancer in Saudi Arabia over a 22-year period

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ABSTRACT

Background: Liver cancer is a major public health problem in the developing world. It is the sixth most common cancer in the developed world and the second leading cause of death among cancer patients, globally. This study evaluated the trends and geographical distributions of liver cancer in the Saudi Arabian population.
Methods: A secondary data analysis was performed on liver cancer cases registered in the Saudi Cancer registry for the period 1994 to 2015. In all, 8,785 liver cancer cases were included in the analysis, all of them Saudi nationals.
Results: There were significant decreases in the mean age-standardised rates of liver cancer over the study period. The incidence of liver cancer varied by region. A strong positive correlation was observed between liver cancer incidence and age. Hepatocellular carcinoma-NOS is the most common histopathology subtype among the Saudi population.
Conclusions: The overall trend of the liver cancer age-standardised rate for males and females decreased among the Saudi population. This rate varies by region. Studying this variation in more detail will help improve public health policy, optimise distribution of resources and allocation of funding for research on prevention and diagnosis and direct awareness programs to the regions that are most in need.

Keywords: Cancer epidemiology, Liver neoplasm, Hepatocellular carcinoma, Saudi cancer registry

INTRODUCTION

Liver cancer is an intractable global health problem. It is the sixth most common cancer in the developed world and the second leading cause of death worldwide.[1] Furthermore, liver cancer is a major public health problem in the developing world.[1] The highest incidence rates of liver cancer were recorded in Eastern Asia, South-eastern Asia, Northern Africa and Southern Africa. In 2018, the most recent year for which information from the International Agency for Research on Cancer (IARC) is available, approximately 18.1 million new cancer cases were diagnosed, and 9.5 million people died from cancer worldwide.[2] Of that number, 841,080 new cases of liver cancer were reported, representing 4.6% of all cancer cases.[2]

While liver cancer is relatively common across Arab Gulf countries, based on the latest the IARC data only a few studies have investigated liver cancer in the Saudi Arabian population.[2] The first study, published in 1980, used data of 54 consecutive patients diagnosed histologically.[3] A study published in 1996 used retrospective data compiled from 1987 to 1993 for 115 patients, who resided in the regions around Riyadh, that had undergone fine needle aspiration of liver masses.[4] The most recent paper, which was published in 2003, studied the risk of hepatocellular carcinoma (HCC) in non-alcoholic patients with chronic hepatitis viruses.[5] That study analysed the data of 118 patients who were admitted to a regional hospital in Saudi Arabia. Consequently, the idea emerged of investigating liver cancer trends in the Saudi population using recently updated national data.

Studying cancer rate reports has many benefits; it can ensure proper allocation of resources and implementation of education programs related to cancer factors, assist public health departments in formulating their executive plans related to the study of the types of cancer and the prevalence of cancer and, finally, help decision-makers direct funds for research on prevention and treatments. Therefore, this paper discusses the epidemiological parameters, geographic distribution and histopathological pattern of liver cancer trends in the Saudi population. It describes the burden of liver cancer among the Saudi population over a 22-year period from 1994 to 2015 by analysing a total of 172,424 cancer cases. It will also summarise the regional patterns and trends related to the age-standardised rate (ASR) of liver cancer cases among the Saudi population.

METHODS

Data

The dataset included 8,785 Saudi nationality registered cases of liver cancer over a 22-year period, from January 1994 through December 2015. The dataset was obtained from the Saudi Cancer Registry (SCR), a population-based registry established in 1994 by the Ministry of Health in the Kingdom of Saudi Arabia.

The SCR had full access to data from all hospitals covering all 13 administrative regions of Saudi Arabia. The data obtained from the SCR included demographics (sex, age, nationality), regional differences and tumour details, such as the primary site and histology of the malignancy that were noted and classified according to the International Classification of diseases, 10th revision (ICD-10). Data were collected for both Saudis and non-Saudis; however, the study discussed in this paper focused on the incidence of liver cancer in Saudi nationals. The data analysed in this study include cancers of the liver (ICD-10:C22).

Study design

A retrospective descriptive epidemiological study was conducted of liver cancer cases in the Saudi population diagnosed between January 1994 and December 2015. The analysis included all recorded cases for males and females without any exclusions.

Sample size

An entire population sampling method was performed in this study by involving all cancer cases within the Saudi population from 1994 to 2015.

Data analysis

This study's analysis method was similar to that used by Alshehr.6 GraphPad Prism 6.0 software was used to analyse the data. Descriptive analyses of the epidemiological data were conducted by calculating the mean and conducting a student t-test and simple linear regression. Data, such as the percentages of liver cancer and the ASR and age-specific incidence rates (ASIR) of liver cancer per 100,000 (stratified by age, sex, region and year of diagnosis) were obtained from the SCR reports.

RESULTS

Fluctuation in the number of liver cancer cases over the study period

The total number of cancer cases identified by the SCR from 1994 to 2015 was 172,424; of these 83,185 cases (48.2%) were male, 89,239 cases (51.7%) were female and 8,785 cases (7%) were liver cancer. The number of registered liver cancer cases fluctuated between 435 (315/120 M/F) in 1994 and 495 (339/156 M/F) in 2013. The lowest number of liver cancer cases (376) was reported in 2015 (274/102 M/F) (Table 1).

Table 1: Number and percent of liver cancer cases compared to all cancer types from 1994 to 2015.

Year	Number of male liver cancer cases	% of liver cancer male cases out of all cancer types	Number of female liver cancer cases	% of liver cancer female cases out of all cancer types
1994	315	10	120	4.7
1995	315	10.8	94	3.7
1996	276	10.1	96	4
1997	272	9.8	81	3.3
1998	294	9.8	112	4.1
1999	269	9.4	82	2.9
2000	243	8.6	102	3.6
2001	242	8.4	81	3
2002	243	8.2	89	3.1
2003	251	7.7	109	3.4
2004	231	6.6	93	2.7
2005	211	5.7	81	2.1

Continued.

Year	Number of male liver cancer cases	% of liver cancer male cases out of all cancer types	Number of female liver cancer cases	% of liver cancer female cases out of all cancer types
2006	291	7.5	125	3
2007	315	7.2	121	2.5
2008	303	7.2	115	2.5
2009	295	6.4	136	2.6
2010	329	7.2	154	2.9
2011	330	6.7	158	2.7
2012	344	6.8	130	2.2
2013	339	6.4	156	2.5
2014	310	5.9	156	2.5
2015	274	5	274	1.5
Mean	286	7.8	121	3

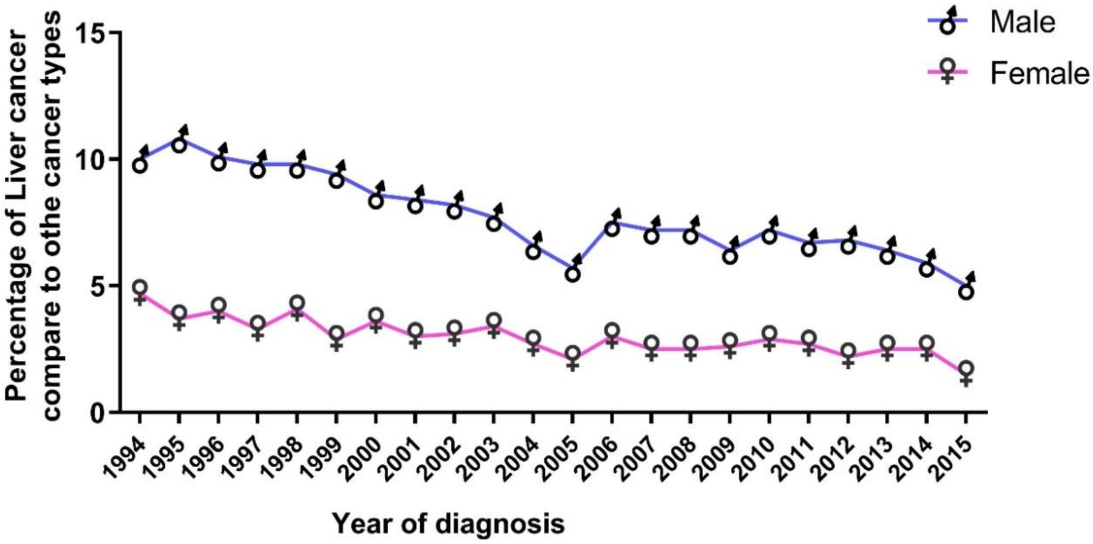

Figure 1: Decrease curve in the percentage of liver cancer cases out of all cancer types from 1994 to 2015. The percentage curve of liver cancer decreased out of all cancer types from 4.7% for females and 10.0% for males in 1994 to 1.5% for females and 5.0% for males in 2015.

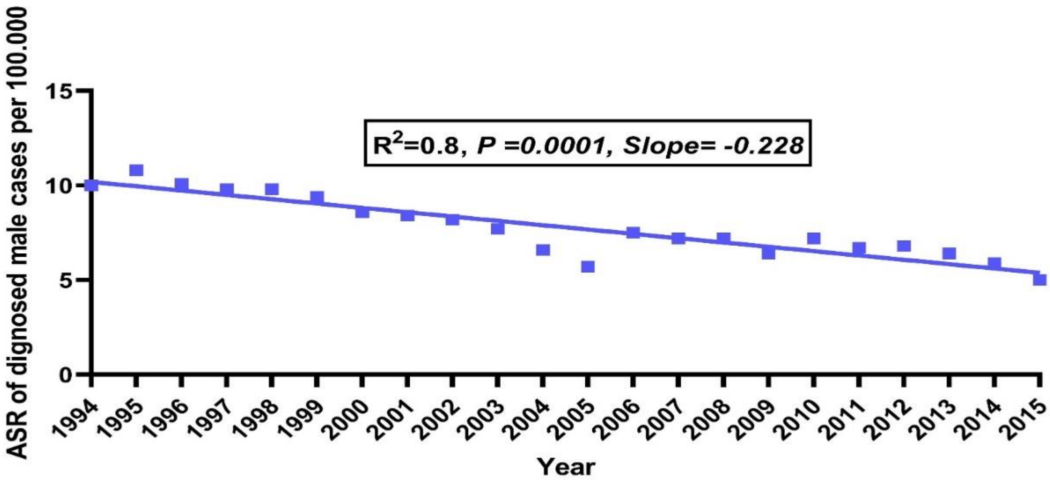

Figure 2: Male ASR of liver cancer decreased over the study period. Between 1994 and 2015, the male ASR was 9.1 per 100,000 in 1994 and dropped to 4.5 in 2015.

Decrease in the percentage of liver cancer in comparison to other cancer types over the study period

In 1994, the percentage of cases representing liver cancers was 4.7% for females and 10.0% for males (Figure 1). In 2015, that percentage decreased to 1.5% for females and 5.0% for males (Figure 1). The percentage curve for liver cancer out of all cancer types for males and females was correlated with the increases and decreases over the study period (Figure 1).

ASR of liver cancer decreased over the study period

The linear regression data from the study period (1994 to 2015) showed a significant negative association between the ASR of liver cancer and the year of diagnosis, with an R^2 of 0.8 and a p value of 0.0001 for males (Figure 2) and an R^2 of 0.7 and a p value of 0.0001 for females (Figure 3). The unpaired t-test analysis of the ASR data revealed that more males than females were diagnosed with liver cancer in Saudi Arabia from 1994 to 2015, with a p value of 0.0001 (Figure 4).

ASIR of liver cancer increased with age

The ASIR data from 1994 to 2015 showed a strong positive correlation between liver cancer incidence and age. The majority of cancer cases occurred in the older age groups. Figure 5 shows that the ASIR of liver cancer noticeably increased with age until age 75.

More than 85% of the cases were diagnosed after the age of 40 for both males and females (Figure 5). Therefore, linear regression analysis was performed for the data on cases in which the patients were older than 40. The analysis results indicated a strong positive correlation between liver cancer ASIR and age, with an R^2 of 0.96 and a p value of 0.0001 for males (Figure 6) and an R^2 of 0.98 and a P-value of 0.0001 for females (Figure 7).

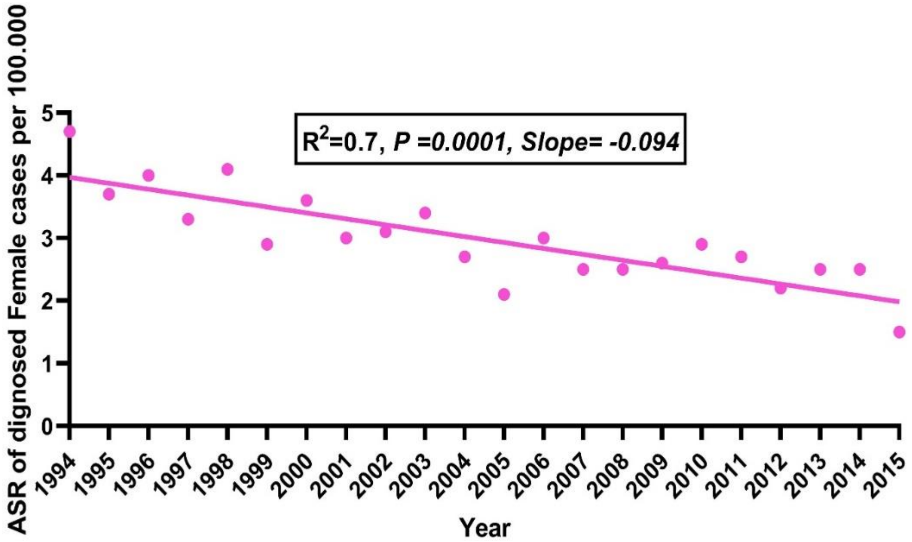

Figure 3: Female ASR of liver cancer decreased over the study period. Between 1994 and 2015, the female ASR deceased from 4.0 in 1994 to 1.5 per 100,000 in 2015.

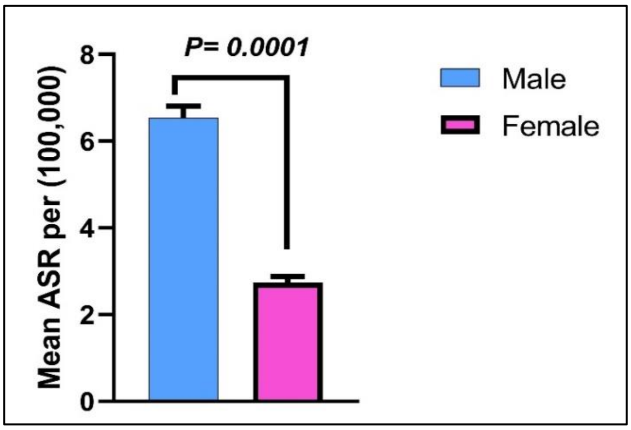

Figure 4: There are significant distinctions between ASIR and patient gender (P=0.0001).

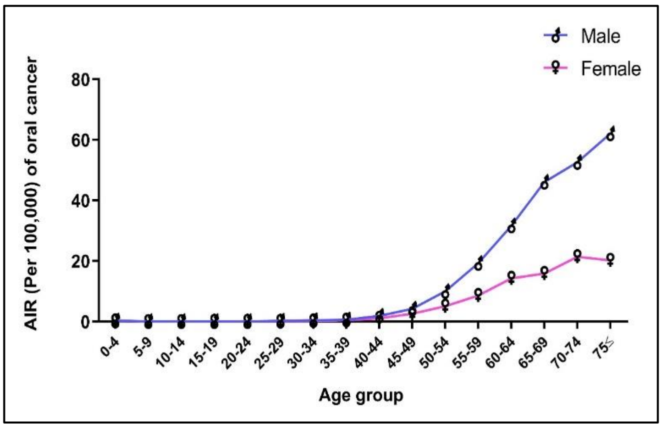

Figure 5: ASIR of liver cancer increase with age. More than 80% of the cases were diagnosed after the age of 40.

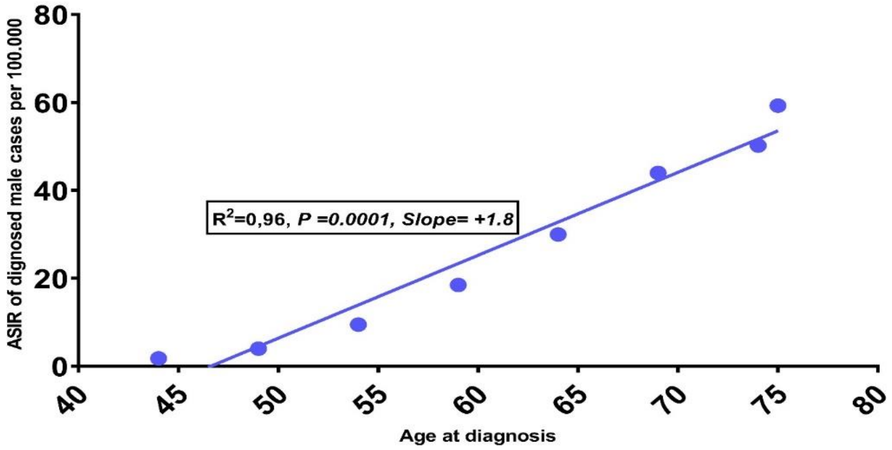

Figure 6: Linear regression correlation of the male ASIR reveals a strong uphill linear association between AISR and the age above 40 years (R^2=0.96; P=0.0001).

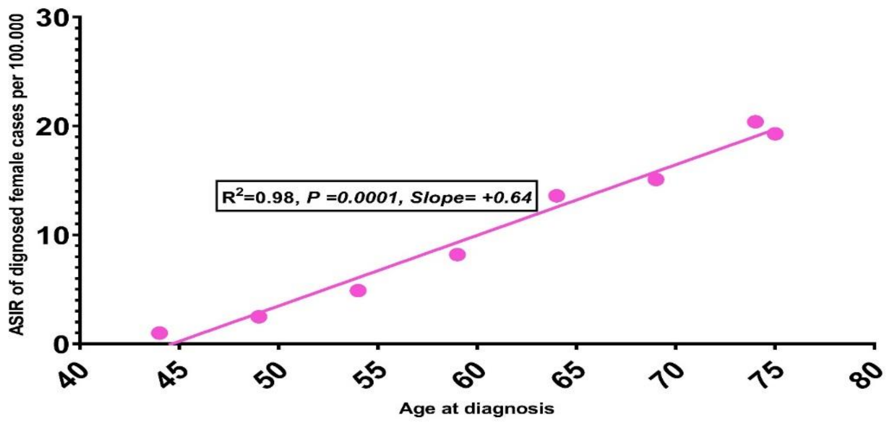

Figure 7: Linear regression correlation of the male ASIR reveals a strong uphill linear association between AISR and the age above 40 years (R^2=0.98; P=0.0001).

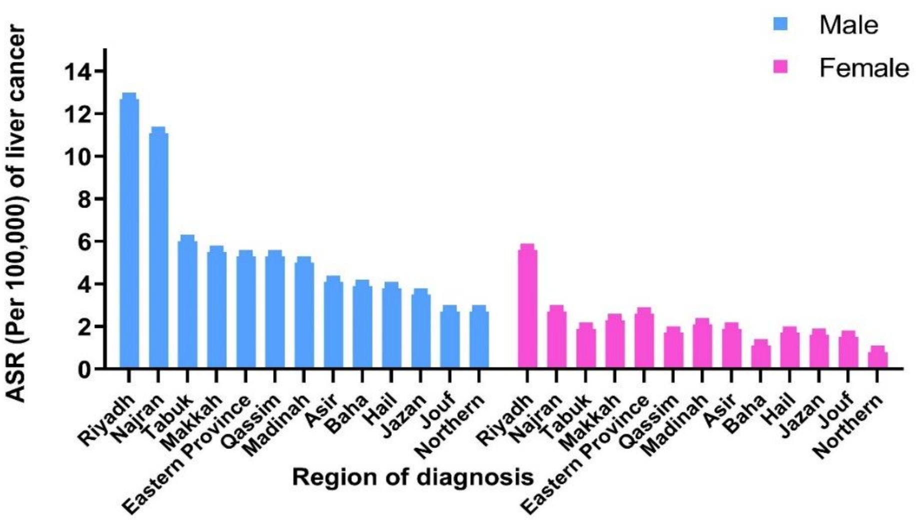

Figure 8: ASR of liver cancer varies by region in Saudi Arabia. The Riyadh and Najran regions display the highest ASR at 12.7, followed by the Najran at 11.1.

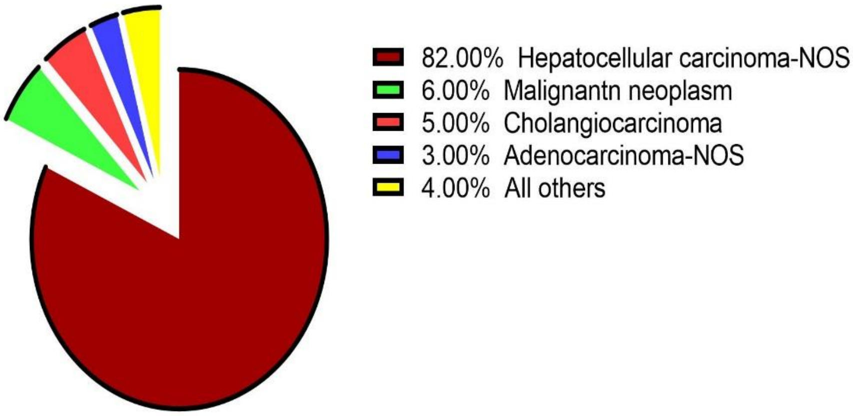

Figure 9: Hepatocellular carcinoma-NOS is the most common histopathology subtype among Saudis, constituting 82%. Malignant neoplasm is second at 6% among Saudi cancer cases. Around 5% of the liver cancer cases were cholangiocarcinoma.

The Riyadh and Najran regions recorded the highest ASR of liver cancer

The ASR data for all liver cancer cases demonstrated a wide variation across Saudi regions. The ASR means per 100,000 people for the period from 1994 to 2015 ranged from 3.2 in the Northern Province to 16.8 in Riyadh, with a national average of 6.9 per 100,000 (Figure 8).

The Riyadh region had the highest male ASR mean at 12.7, followed by Najran at 11.1 per 100,000. Conversely, the Northern Province and Jouf regions reported the lowest ASR averages at 2.7 per 100,000 (Figure 8).

The male and female ASR data were nearly equivalent in terms of region rankings, with the Riyadh region posting the highest overall ASR at an average of 5.6, followed by the Najran region at 2.7. The Northern Province, Baha and Jouf regions posted the lowest ASR averages at 0.8, 1.1 and 1.5, respectively (Figure 8).

Hepatocellular carcinoma-NOS is the most common form of histopathology liver cancer subtypes among Saudis

The proportion of histologic subtypes of liver cancer cases was calculated from the total number of cases in the 1994–2015 period (Figure 9). The most common liver cancer subtype was hepatocellular carcinoma- NOS (morphology code ICD-O-3-code 81703). This subtype is a tumour of the parenchymal cells of the liver; it constitutes 82% of all liver cancer cases (Figure 9). The malignant neoplasm subtype (morphology code ICD-O-3-code 80003) was reported in 6% of the liver cancer cases. Approximately 5% of the liver cancer cases were cholangiocarcinoma (morphology code ICD-O-3-code 81603); it arises in the cholangiocytes of the intrahepatic bile duct. Finally, adenocarcinoma NOS (morphology code ICD-O-3-code 81403), was the rarest liver cancer subtype, constituting about 3% of the liver cancer cases among the Saudi population (Figure 9).

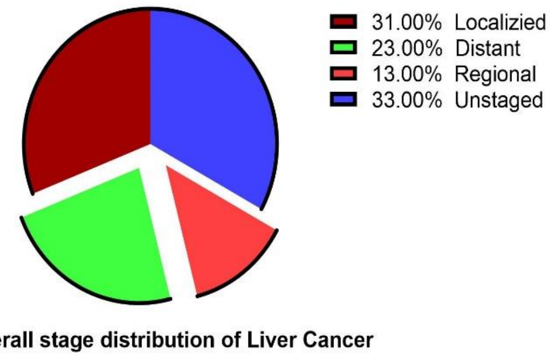

Figure 10: Stage Distribution of liver cancer in Saudi Arabia. Most liver cancer cases are diagnosed with an unknown stage.

Most liver cancer cases are diagnosed with an unknown stage

The SCR reports categorise liver cancer case distribution based on the stage at diagnosis and the calendar period of the diagnosis. From 1994 to 2015, the data on the stage distribution of liver cancer among Saudi nationals showed that 29% of the liver cancer cases were diagnosed at the localised stage and 21% were diagnosed at the distant stage. The rarest stage was regional cancer, which was diagnosed in 13% of patients. Finally, 33% of cases were diagnosed with an unknown stage (Figure 10).

DISCUSSION

This study of liver cancer cases in Saudi Arabia for the period ranging from 1994 to 2015 showed a significant decrease in the number of liver cancer patients and a decrease in the rate of ASR for both males and females. That reduction occurred despite substantial increases in the Saudi Arabian population, from 18.3 million in 1994 to 31.6 million in 2015.[7] This is considered to be great success in terms of health levels in Saudi Arabia, especially in comparison to data from the rest of the world. In Europe, for example, the ASR of liver cancer increased significantly from 8.6 in 1993 to 23.8 in 2016.8 Moreover, a report from the Arab Gulf region stated that Qatar had the highest incidence of liver cancer among men and women with an ASR of 13.9 and 7.6 for males and females, respectively.[9] Kuwait ranked second and Saudi Arabia ranked third.[9] Many factors may have contributed to the reduction in the ASR of liver cancer among Saudis. One important reason is increased accessibility to health services, which has contributed to the dissemination of early diagnostic techniques for liver diseases, such as imaging techniques and liver enzymes analyses. This has led to more frequent detection of pre-neoplastic cases and the prevention of their development into cancer. Furthermore, the introduction of immunisations for all new-born babies in 1989 was a remarkable development in the public health policies in Saudi Arabia this included immunisations against hepatitis viruses, which are the main causes of liver cancer and which are classified as carcinogenic by IARC.[10,11] Globally, 78% of HCC cases are attributable to either the hepatitis B virus (HBV) (53%) or the hepatitis C virus (HCV) (25%).[12] Thus, HCC is one of the types of cancer that can be prevented by eliminating hepatitis viruses.[5,13]

The SCR data reports also described the proportion of the stages of liver cancer. Because most of the liver cancer cases (33%) were diagnosed with an unknown stage, a comparison study of the proportions of the stages would be difficult and inaccurate.

Among the Saudi population, the rate of liver cancer is typically two-to-four times higher in men than women, with an ASR average over the period of study of 6.4 for males and 2.6 for females. This disparity in the incidence of liver cancer across genders is remarkable in almost all countries; the rates are two- to four-fold higher in males than females.[14] A study published in 2007 discussed the gender disparity in liver cancer.[15] It proposed that, in females, sex hormones (oestrogen-mediated) inhibited production of Interlukin-6 cytokines, which reduce the risk of liver cancer.[16] That study suggested that increased production of oestrogen might be used to prevent progression of liver cancer in males. More studies need to be conducted to explore the reason for the gender disparity in liver cancer.

Cancers are age-related diseases.[16] Therefore, the study discussed in this paper expected to find a strong direct positive correlation between age and liver cancer ASIR. About 85% of the liver cancer cases were diagnosed after the age of 40. Aging makes cells more susceptible to developing cancer, especially in the presence of cancer risk factors. Eliminating those factors will weaken the role that aging plays in cancer.

Another noteworthy part of this study’s results is the presence of variation in the ASR ratio of liver cancer between Saudi regions. Some regions, such as Riyadh and Najran, reported the highest ASR averages at 12.7 and 11.1, respectively. In contrast, other regions, such as the Northern Province and Jouf, reported the lowest ASR averages at 2.7 per 100,000. These rates vary between regions, even though the population is comprised of the same ethnic group, because the prevalence of risk factors varies between the regions in the Kingdom of Saudi Arabia. A more in-depth study of these regions and the risk factors of liver cancer in these areas will contribute to the prevention of liver cancer in Saudi Arabia.

Finally, the study showed that hepatocellular carcinoma-NOS (82%) is the most common of the histopathology subtypes among Saudis. These findings are consistent with the global finding that hepatocellular carcinoma-NOS (80%) is the predominant subtype of liver cancer.[14] Persistent infections by HBV and HCV are the main known risk factors for hepatocellular carcinoma-NOS. Aflatoxin exposure, produced by the fungi *Aspergillus flavus* and *Aspergillus parasiticus*, which contaminate food products, is also an important contributing factor for HCC development, especially in a poor and low-income population. However, in a high-income population, excessive consumption of alcohol, tobacco smoking, obesity, familial/genetic factors, diabetes and some dietary aspects play a relevant role in the development of hepatocellular carcinoma-NOS.[17]

CONCLUSION

this study found noticeable decreases in the liver cancer trends in the Saudi Arabian population for the period ranging between 1994 and 2015. Several etiological factors have been suggested for that decrease, mainly the introduction of hepatitis vaccines. The hepatocellular carcinoma-NOS subtype is the most common subtype in the Saudi population. In agreement with international data, males were more likely than females to be diagnosed with liver cancer in Saudi Arabia. Moreover, wide variation in the incidence rates among Saudi regions raises an important research question regarding the risk factors associated with those regions, which should be investigated further. As with the majority of studies, the findings of this study must be seen in light of a limitation. The SCR report did not contain the data of the original city in which the patient lived, as some patients from peripheral regions may have traveled to cities that contained central hospitals and then been diagnosed and calculated as residents of those central regions. This limitation may affect the accuracy of data related to the number of patients per region. A more in-depth analysis of that variation will help improve public health policy, thereby optimising distribution of resources and allocation of funding for research on prevention and diagnosis of liver cancer.

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