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Original Article

Patterns of hepatocellular carcinoma incidence in Egypt from a population-based cancer registry

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Aim: Hepatocellular carcinoma (HCC) is increasing worldwide, and is frequently attributed to rising rates of hepatitis C virus infection and interactions between viral and environmental risk factors. Because of Egypt's unique risk factor profile, we analyzed data from the Gharbiah Population-Based Cancer Registry for the period 1999–2003 to characterize demographic and geographic patterns of cases in this province.

Methods: We calculated age- and sex-specific and age- and sex-standardized HCC incidence rates for the eight districts in Gharbiah. We also compared rates from Gharbiah with the USA (US Surveillance Epidemiology and End Results [SEER] database).

Results: The analysis revealed a higher incidence in males than in females, significant geographic variations among

districts, and a higher incidence in Gharbiah than that reported by SEER.

Conclusion: The findings of this study document the heterogeneous distribution of HCC at regional and international levels. This population-based registry offers the opportunity for careful representative studies of various etiologies, particularly infectious and/or environmental factors that may contribute to risk.

Key words: age-specific rates, developing countries, geographic variation, liver cancer, USA

INTRODUCTION

LIVER CANCER RAPIDLY reduces quality of life and typically causes death 6 months–1 year from diagnosis.¹ Globally, it is the fifth leading cause of cancer and the third leading cause of cancer death.^{1,2} This cancer varies widely in incidence throughout the world, with rising incidence in Egypt. The primary risk factors for hepatocellular carcinoma (HCC) are hepatitis B virus (HBV), hepatitis C virus (HCV), dietary aflatoxin exposure, and chronic alcohol consumption.^{1,2}

Prior to the introduction of the HBV vaccine, chronic infection with HBV was generally high, with developing countries sharing the greatest burden.³ Consequently, HBV was the dominant etiologic factor in the develop-

ment of HCC. This is largely still true in Egypt, because vaccination programs were not started until the 1980s. More recently, HCV has begun to eclipse HBV in incidence in many countries throughout North America, Europe, and the Middle East.^{4,5} The rates of HCV in Egypt are among the highest in the world, with a prevalence rate of up to 20%.^{6,7} Although a HBV vaccine program has been successfully implemented, with childhood coverage estimated at 95%–100%, most people born 20 years ago or earlier in Egypt have not been vaccinated.^{8,9}

Hospital-based studies from Egypt have reported an overall increase in the relative frequency of all liver-related cancers in Egypt (>95% as HCC), from approximately 4% in 1993 to 7.3% in 2003.¹⁰ Recent investigations in Egypt have shown the increasing importance of HCV infection in the etiology of liver cancer, estimated to account for 40–50% of cases, and the declining influence of HBV and HBV/HCV infection (25% and 15%, respectively).^{10–12}

Few studies in Egypt have fully measured the presence of aflatoxins and their impact on liver disease there. A

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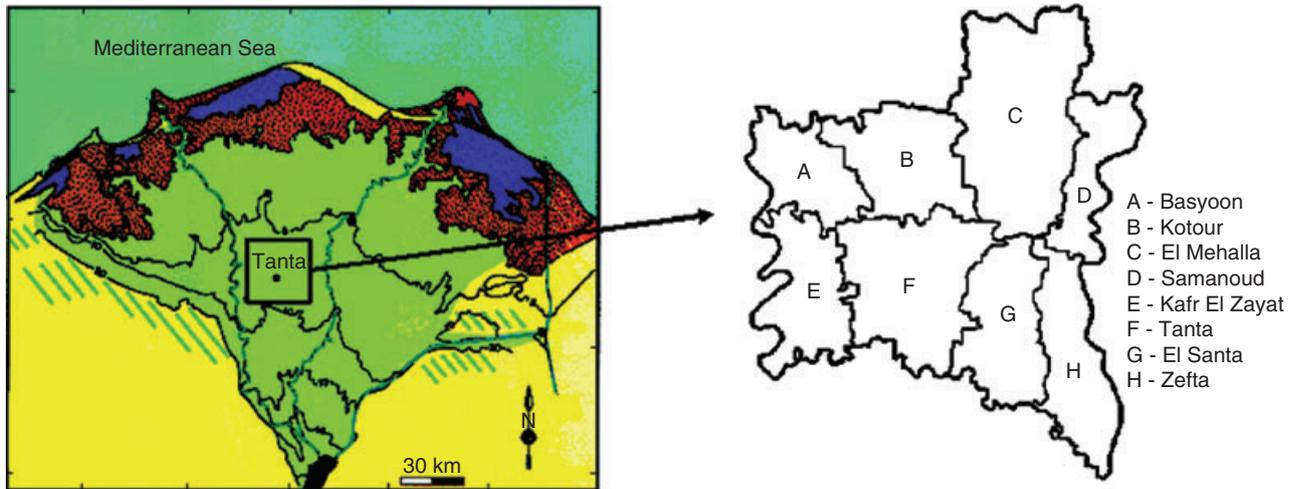


Figure 1 Northern Egypt (Nile Delta), Gharbiah Province, and its eight districts. (Map: <http://www.meccegypt.org>).

recent study by el-Zayadi *et al.*¹³ examined 200 HCC cases and 120 healthy controls and detected aflatoxin B(1) in 17% of the HCC cases compared to 9.4% of the healthy controls (risk ratio = 2). In 2005, Sayed *et al.*¹⁴ performed a cross-sectional analysis on risk factors for liver disease in a rural population south of Cairo to evaluate aflatoxin exposure in serum. They found aflatoxin B(1) to be associated with hepatitis B surface antigen seropositive patients (odds ratio = 6.2) and anti-HCV seropositive patients (odds ratio = 2.5).

In addition to HBV, HCV, and aflatoxins, other risk factors have been linked to HCC, including chronic alcohol consumption and hemochromatosis. Although alcohol plays a significant role in the etiology of HCC in many countries, it was not examined in this study because the prevalence of alcohol consumption in Egypt is extremely low.^{15,16} Hemochromatosis also was not investigated in this study, because in Egypt it is extremely rare.^{17,18}

With assistance and quality assurance from the US National Cancer Institute (NCI),¹⁹ Egypt successfully created a population-based cancer registry in Gharbiah province (Fig. 1) that has been successfully functional since 1999. The first year of the registry data (1999) showed that the age-standardized annual incidence rate of HCC was ~20.6/100 000 in males and ~5.2/100 000 in females. A comparison of data from the Gharbiah Population-based Cancer Registry (GPCR) for the period 1999–2001 with other countries in the Middle East Cancer Consortium showed that the liver cancer incidence rate was seven times greater than the next highest country rate, and more than three times the rate

reported by the US Surveillance Epidemiology and End Results (SEER).¹⁹ Our study was designed to characterize the demographic and geographic patterns of HCC cases in this region to lay the groundwork for future research directed at understanding the complex etiology of this disease. Accordingly, we retrieved and analyzed data of all HCC patients included in the GPCR from January 1 1999 to December 31 2003. We analyzed the demographic and geographic characteristics of HCC patients and compared patterns with those of HCC cases in the US SEER registry for this period.

METHODS

Characteristics of the study region

GHARBIAH PROVINCE IS located in the middle of the Nile Delta, approximately 100 km north of Cairo. The province population (4.2 million people, 5.7% of Egypt) has a density of ~1752/km², making it the tenth most densely populated province in Egypt (Egypt has a total of 27 provinces). The male : female ratio in the Gharbiah Province is 1.02:1, and the age structure resembles that of the rest of the country, with 47% of the population <20 years and 3.6% >65 years.²⁰ Gharbiah Province is considered an urban–rural province by the Central Agency for Public Mobilization and Statistics with 31% of the population in urban areas and 69% in rural areas.²⁰ Each of its eight districts has its own main city. The capital of Gharbiah Province is the city of Tanta, which serves as the headquarters for the population-based cancer registry. Gharbiah has a total

of 316 villages and is mainly agricultural, but one district (El Mehalla) is a major textile producer in Egypt. The annual incidence rates of HCC were based on population data estimated using linear interpolation between pairs of published government census population information. This preliminary study used an annual linear interpolation from the 1996 census data and the 2001 and 2005 population projections.²⁰

GPCR data

The GPCR was established in 1998 as part of the Middle East Cancer Consortium (MECC) Joint Cancer Registration Project,²¹ and it is affiliated with the Egyptian Ministry of Health and Population. The registry actively seeks all cases in Gharbiah Province, regardless of inpatient/outpatient status or whether patients were seen in public or private hospitals. Information is gathered from medical records of government and private hospitals and clinics, death certificates, and histopathology laboratories and radiology clinics. A team of registrars trained by the International Agency for Research on Cancer (IARC) and Emory University School of Public Health in Atlanta, USA, conduct regular visits with each collaborating center to obtain the data and review its quality using the standard review process of the IARC. Data quality was assessed in 2002 for completeness of coverage and reliability of registration. In addition to computer checks through CanReg software; external auditing was done by Emory University staff in 2002. Coverage was found to exceed 90% of the Gharbiah population.²²

The registry conducts routine data cleaning by standardizing field entries and removing duplicate entries. Inconsistencies were addressed by reviewing medical records. We obtained the data of all liver cancer cases diagnosed and included in the registry from January 1 1999 to December 31 2003 ($n = 1309$). Our case definition was restricted to those with an International Classification of Diseases (ICD)-10 topology code of 22.0 and HCC morphology. Cases were excluded if they did not satisfy both elements of the case definition or if they had missing values, and if inconsistencies were not resolved after examining medical records. This process reduced the total number of cases to 1186 (removing 123 cases). The following variables were obtained for each case: registry patient number, sequence number, age at diagnosis, date of birth, sex, usual residential address, date of diagnosis, basis of diagnosis, primary site code (ICD-0–3), morphology codes, histology type, behavior, grade/differentiation/cell indicator, and summary stage at diagnosis. Additional variables

included family history, marital status, smoking history, religion, occupation, and treatment data. Unfortunately, hepatitis data are not currently included in the management protocol for HCC cases at the GPCR. Thus, patient HBV and HCV status were unavailable for this study. Additionally, because this study was retrospective and the cases in our sample were all deceased, there was no way to independently acquire HBV/HCV data.

Statistical analyses

The annual and average age- and sex-specific incidence rates for the period 1999–2003 were calculated using the number of HCC cases as the numerator and age–sex-specific population data from Egypt as the denominator. Univariate analyses were used to develop a descriptive profile for the cases using demographic indicators and information regarding the geographic location of residence at the time of diagnosis for each case. Interannual variation in the number of cases during the 5-year period in Gharbiah and in individual districts was examined using χ^2 -test analyses. Rate ratios (RR) were calculated to examine the differences among the eight districts of Gharbiah. We also calculated and compared the incidence rates for HCC among the cases residing in urban and rural regions of Gharbiah.

We also compared the HCC incidence rates for the years 1999–2003 in Gharbiah to those for 1999–2002 from the US SEER.²³ The age-specific incidence rates for Gharbiah and the USA were adjusted to the world million,²⁴ and the age-adjusted rates of the two regions were compared. The RR estimates and 95% confidence intervals (CI) were used to estimate an age-specific incidence variation between Gharbiah and the USA. All statistical operations were conducted using SAS software, version 9.1 (SAS Institute, Cary, NC, USA).

Ethical oversight

Our study protocol was approved by the Internal Review Board at the University of Michigan and the registry ethical committee in Egypt.

RESULTS

Incidence and descriptive features of HCC

THE NUMBER OF HCC cases registered in the GPCR from 1999 through 2003 was fairly stable over the 5-year study period, with 200–250 cases per year (Table 1). Cytohistopathological confirmation of the primary tumor was the basis of diagnosis in 33.5% of cases. Non-microscopic (laboratory marker/

Table 1 Characteristics of people diagnosed with hepatocellular carcinoma in Gharbiah, Egypt, 1999–2003

	Descriptive feature	No. cases	Cases (%)
Sex	Male	949	80.0
	Female	237	20.0
Age	0–39	41	3.5
	40–49	178	15.0
	50–59	411	34.7
	60–69	358	30.2
	70–79	180	15.2
	80+	18	1.5
Religion	Muslim	1162	98.0
	Christian	24	2.0
Governorate of birth†	Gharbiah	1062	89.5
	Other	123	10.5
Region of residence	Tanta	362	30.5
	El Mehalla	307	25.9
	Kafr El Zayat	113	9.5
	Kotour	105	8.9
	El Santa	93	7.8
	Zefta	81	6.8
	Basyoon	75	6.3
	Samanoud	50	4.2
Urban/rural distribution	Urban	585	49.3
	Rural	601	50.7
Year of diagnosis	1999	212	17.9
	2000	242	20.4
	2001	236	19.9
	2002	249	21.0
	2003	247	20.8
Basis of diagnosis	Microscopic	397	33.5
	Non-microscopic	512	43.2
	Death certificate only	277	23.4

†n = 1185; missing birth place information for one patient.

radiological) diagnosis was the basis of diagnosis in 43.2% of cases. Approximately 23% of cases were diagnosed by death certificate only. The majority of cases (96.5%) were aged 40 years and older. Of the 1186 HCC cases, 949 (80%) were males and 237 (20%) were females. Males had consistently higher incidence rates than females for all age groups above 40 years (Table 2).

Geographic patterns in incidence among districts

Geographically, 1062 cases (89.5%) were reported being born in Gharbiah, supporting the notion that

the population in this region is fairly stable and suggesting that relevant exposures largely occurred in Gharbiah. The eight districts varied considerably in population, representing the following percentages of the total provincial population: Tanta 23.9%, El Mehalla 22.6%, Kafr El Zayat 8.7%, Zefta 9.7%, El Santa 9.2%, Samanoud 7.4%, Kotour 7.2%, Basyoon 6.3%.²⁰ In addition to being the most densely populated districts, Tanta and El Mehalla jointly account for approximately 56.4% of the cases in the registry. The remaining six districts, however, did not all contribute cases in relative proportion to their population densities. The interannual variation in the number of cases during the 5-year period in Gharbiah and in individual districts was examined using χ^2 -test analyses. No significant differences were found, except in Zefta ($P = 0.01$; data not shown), which had more cases diagnosed in 2000 than in any other year.

A similar proportion of cases came from rural and urban regions of the governorate, accounting for 50.7% and 49.3%, respectively. However, the mean age-adjusted incidence rates were greater for the cases residing in urban (15.8/100 000 person/year [PY]) than in rural (8.6/100 000 PY) areas. Urban residents had an incidence rate 1.84 times greater than that among rural residents (95% CI 1.42, 3.13).

The mean age-adjusted incidence rates for HCC in Gharbiah and its eight districts for males, females, and the total population (1999–2003) also varied (Table 3; Fig. 2). The χ^2 -test analysis of the HCC incidence rates of the eight districts showed statistically significant variations ($P < 0.0001$), largely the result of variations among males ($P < 0.0001$). Overall, Kotour had the highest incidence rates among males and the total population (24.1/100 000 PY and 12.9/100 000 PY, respectively), with Samanoud having the lowest rates (10.3/100 000 PY and 6.1/100 000 PY, respectively). The incidence rates among females showed a different distribution, with the highest occurring in Tanta and El Mehalla (5.8/100 000 PY) and the lowest in Zefta (1.5/100 000 PY). Statistically significant differences were not observed among females, most likely as a result of the small sample size and insufficient power.

The RR for the HCC incidence rates among the eight districts varied considerably (Table 4). Among the largest RR were those of Kotour compared with Samanoud (2.34 times greater) and Kotour compared with Zefta (1.94 times greater). People in Tanta had 1.94 times the rate of HCC as those in Samanoud. Other significant RR varied between 1.29 and 1.85.

Table 2 Comparison of mean age-specific incidence rates of hepatocellular carcinoma for males and females in Gharbiah, Egypt, 1999–2003

Age group (years)	No. male cases	Male IR per 100 000 PY	No. female cases	Female IR per 100 000 PY	RR males versus females (95% CI)
0–24	0.6	0.4	0.4	0.3	1.42 (0.03, 56.1)
25–29	0.6	0.5	0.2	0.1	3.30 (0.02, 161.0)
30–34	1.0	0.8	1.4	1.1	0.73 (0.1, 13.8)
35–39	2.2	1.8	1.6	1.3	1.42 (0.2, 9.1)
40–44	10.0	9.4	2.2	2.1	4.40 (1.0, 8.7)
45–49	19.4	21.0	4.0	4.8	4.37 (1.5, 7.3)
50–54	30.4	48.1	7.2	11.3	4.24 (1.9, 6.5)
55–59	35.8	73.8	8.8	19.2	3.85 (1.8, 5.9)
60–64	36.0	86.0	6.4	13.9	6.19 (2.7, 8.5)
65–69	23.2	75.6	6.0	19.7	3.84 (1.6, 6.3)
70–74	19.4	101.5	6.8	31.5	3.22 (1.3, 5.6)
75+	14.8	105.2	2.2	13.6	7.76 (1.9, 11.9)

CI, confidence intervals; IR, incidence rate; PY, person/year; RR, rate ratios.

Comparisons between incidence rates in Gharbiah versus the USA

Our results showed that the overall age-adjusted HCC incidence rate in Gharbiah (10.6/100 000) is significantly higher than the rate observed in the USA (3.0/100 000), with a rate ratio of 3.53 (95% CI 3.11, 4.67). The incidence rates among males were significantly higher than those among females in both Egypt and the USA. Males in Egypt had incidence rates 4.3 times higher than females (95% CI 3.11, 5.66), and males in the USA had rates 3.3 times higher than females (95% CI 3.16, 4.34). In addition, age-specific incidence rates were significantly higher in Egypt compared to the USA for all age

groups older than 40 years (Table 5). Significant differences in the rates among the younger age groups were not apparent. These age patterns remained consistent when examining males and females separately.

DISCUSSION

ANALYSES FROM THIS population-based cancer registry were based on HCC cases that appear to be largely complete and highly representative. Case data

Table 3 Mean age-adjusted incidence rates per million for hepatocellular carcinoma in Gharbiah, Egypt and its districts per 100 000 PY, 1999–2003. Rates standardized to world million

Region	Male incidence rate	Female incidence rate	Total incidence rate
Gharbiah (all)	16.7	4.0	10.6
Kotour	24.1	3.3	12.9
Tanta	19.9	5.8	12.3
El Mehalla	18.4	5.8	12.1
Kafr El Zayat	19.0	3.7	11.1
Basyoon	17.9	3.2	10.4
El Santa	15.4	2.6	8.8
Zefta	12.5	1.5	6.9
Samanoud	10.3	2.2	6.1

PY, person/year.

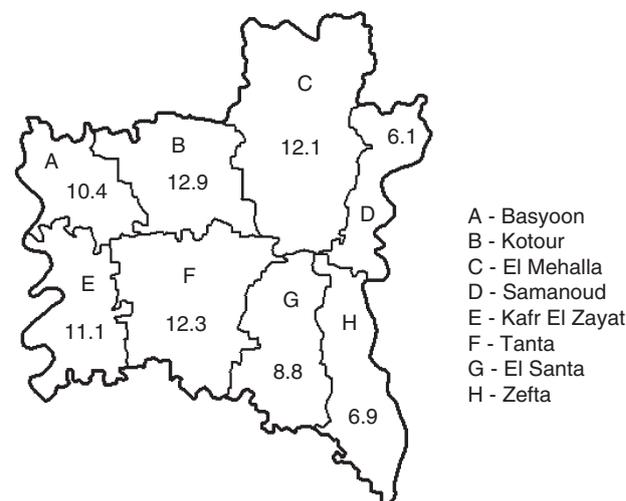
**Figure 2** Mean age-adjusted incidence rates for hepatocellular carcinoma in the eight districts of Gharbiah (1999–2003), standardized to the world million (Parkin *et al.* 1997). (Map: <http://www.meccegypt.org>).

Table 4 Mean incidence rate ratios (RR) for hepatocellular carcinoma among Gharbiah districts per 100 000 PY, 1999–2003

RR = R↓/C→	Kotour	Tanta	El Mehalla	Kafr El Zayat	Basyoon	El Santa	Zefta	Samanoud
Kotour	–	NS	1.31 (1.03, 1.67)	NS	NS	1.57 (1.16, 2.12)	1.94 (1.42, 2.64)	2.34 (1.61, 3.40)
Tanta		–	NS	NS	NS	1.29 (1.01, 1.66)	1.60 (1.23, 2.07)	1.94 (1.39, 2.70)
El Mehalla			–	NS	NS	NS	1.48 (1.13, 1.92)	1.79 (1.28, 2.50)
Kafr El Zayat				–	NS	NS	1.53 (1.12, 2.08)	1.85 (1.28, 2.68)
Basyoon					–	NS	1.43 (1.02, 2.01)	1.74 (1.17, 2.58)
El Santa						–	NS	1.50 (1.02, 2.19)
Zefta							–	NS
Samanoud								–

RR: row district : column district. 95% confidence limits are given in parentheses. NS, not significant; PY, person/year.

from the GPCR were obtained from virtually all sources in the province, and there is no reason why agencies from various sectors would not have participated in the registry. GPCR is financially and scientifically supported by the US National Cancer Institute, and has quality assurance from SEER and the International Association of Cancer Registries. Standard procedures for training registrars and for data collection, processing, and transmission enhanced the accuracy of data. In addition, the population-based structure improves our ability to draw conclusions about the entire province from the study results. For these reasons, our study is unlike other hospital- or clinic-based reports that have previously appeared for HCC in Egypt, as it includes essentially all cases in the study area. Thus, the results represent a high degree of internal and external validity. Furthermore, data on the vast majority of cases included complete demographic and geographic information. It is reassuring that the number of HCC cases reported per year did not vary during the 5 years of this study. Therefore, the case data that we analyzed should be considered valid for the populations at risk and the results generalizable, at least to the people of Gharbiah Province.

At first glance, the approximately 23% of cases diagnosed using only the death certificate might seem overly high. This percentage, however, is not unusually high for liver cancer.¹ Due to the difficulty in diagnosing HCC, even in developed countries, many cases are not diagnosed until death.^{1,25} This is more a limitation of current technology than specific registry methods. In fact, the overall proportion of cancers diagnosed by death certificate only in the Gharbiah registry is only

6–7%. It is also unlikely that missed cases would significantly alter our findings. The GPCR has a reported coverage rate of greater than 90% for Gharbiah Province.²² The number of cases could be underestimated due to HCC being misclassified as cirrhosis, but there is no reason to believe that this underestimation is biased in any way. Access to health care is similar across the province, and there is nothing to suggest

Table 5 Age-specific Egyptian hepatocellular carcinoma incidence rates for 1999–2003 compared to US Surveillance Epidemiology and End Results (SEER) data (1999–2002). Rates standardized to world million

Age category	Gharbiah IR per 100 000 PY	SEER IR per 100 000 PY	RR vs SEER	95% CI
0–24†	–	–	–	–
25–29	0.3	0.3	1.10	0.12, 10.21
30–34	1.0	0.5	2.09	0.57, 7.66
35–39	1.6	0.6	2.47	0.89, 6.87
40–44	6.1	1.8	3.37	1.90, 5.96
45–49	13.9	5.2	2.70	1.79, 4.06
50–54	31.2	7.3	4.28	3.10, 5.93
55–59	49.7	8.9	5.58	4.14, 7.53
60–64	51.1	11.9	4.28	3.10, 5.93
65–69	50.1	16.5	3.05	2.11, 4.39
70–74	67.8	19.6	3.46	2.35, 5.08
75+	39.1	18.3	2.14	1.19, 3.85
Total	10.6	3.0	3.53	3.11, 4.02

†Complete SEER data unavailable. CI, confidence intervals; IR, incidence rate; PY, person/year; RR, rate ratios.

that physicians diagnose differently in any systematic way.

This study presents various findings that are similar to, but also different from, those that have previously addressed HCC in the Middle Eastern region. As has been shown consistently in other studies, male incidence was considerably greater than that for females. Worldwide, estimates show males to be 1.3–3.6 times as likely to develop HCC as females.¹ In high-risk countries, sex ratios tend to be higher, and this is demonstrated here by the lower rate ratio seen in the USA versus Egypt. A satisfactory biologic interpretation has yet to be demonstrated. Several hypotheses have been investigated, including the interaction of sex hormones with HBV, leading to a different natural history depending on the sex of the individual or the impact of sex-specific exposure.^{26,27}

Interestingly, the incidence rate of HCC in Gharbiah was 3.5 times higher than that reported in the USA. Such results were seen in the overall age-adjusted incidence rates, as well as the age-specific rates in age groups older than 40 years, among both males and females. This finding expands upon reports in the US NCI and MECC publications for a shorter period, 1999–2001.¹⁹ Our similar findings for a longer period suggest that variation in rates truly reflect different risk factor profiles of these two populations, warranting further prospective studies.

The most notable finding of this study, however, was the statistically significant geographic variation in incidence of HCC among districts within Gharbiah Province. The incidence ranged from 12.9/100 000 PY (Kotour) to less than half that rate at 6.1/100 000 PY (Samanoud). Districts were similar with respect to age distribution and sex ratios, suggesting that the at-risk populations were fairly homogeneous. Consequently, this observed heterogeneity was likely attributable to variations in local risk factors that future studies may investigate.

Another interesting finding demonstrated that HCC incidence among urban individuals was nearly twice that of rural residents. Several studies have postulated that the HCV epidemic in Egypt has disproportionately affected rural populations, which should be reflected in the distribution of HCC cases.^{28,29} The HCV epidemic in Egypt is unique. Egypt developed the world's highest rates of HCV infection over a short period of time, largely due to a massive public health campaign. The vast majority of infections among individuals aged 30 years and older can be explained by parenteral anti-Schistosomiasis therapy (PAT) and other iatrogenic exposures.^{29–32} The anti-Schistosomiasis campaign extended from the 1950's to the 1980's, with peak

transmission probably occurring during the 1960s and 1970s. In 1982, praziquantal, an oral treatment for Schistosomiasis, was introduced, and the use of PAT declined. Since Schistosomiasis was a greater problem in rural regions, these populations were more affected by the PAT campaign, and consequently, HCV transmission.^{30,32} With iatrogenic infections nearly eliminated, person-to-person transmission is presently the dominant route, which should preserve the urban/rural disparity. Higher rates of HCV infection should manifest as higher rates of HCC.

The higher HCC incidence among urban residents could represent better access to medical facilities, resulting in an underestimate of HCC in rural populations. It is also possible that the peak of the cohort with PAT-related HCV transmission has not yet matured, suggesting the incidence of HCC due to HCV is still increasing and competing with HBV-related HCC incidence. This could mean a shift in the burden from urban to rural regions is currently underway and will be discernible in the near future. It should also be noted that disease progression from HCV to HCC may take up to 20 years and the incidence of HCC can increase in both urban and rural area in Egypt over the next few years. The risk factors of most importance in this region include HBV, HCV, and dietary aflatoxins. Unfortunately, we were unable to acquire data on the HBV and HCV status of our cases, as testing is not standard protocol for patient intake and management at the GPCR. Due to the retrospective nature of our study, we were unable to independently test cases, as they were all deceased at the time of study initiation. Nevertheless, several studies in Egypt have documented the general prevalence of HCV and HBV throughout the country, and we can use these results to help guide our inference.

Several small-scale hospital-based studies have been conducted to examine the etiologic significance of the primary HCC risk factors in Egypt, although it should be noted that they have not assessed geographic variation. These studies have shown the increasing importance of HCV in liver cancer, estimated to account for 40–50% of liver cancer cases, and the declining influence of HBV and HBV/HCV infection, 25% and 15%, respectively.^{10–12} These studies also have documented an overall increase in the relative frequency of liver cancer in Egypt from approximately 4.0% in 1993 to 7.3% in 2003.¹⁰ Such increases in liver cancer are generally attributed to HCV.

Since chronic HCV does not typically lead to carcinogenesis for 10–30 years following infection, the rates of liver cancer can be expected to continue increasing until the cohort of PAT-related infected individuals has

worked its way through.^{10,29} This suggests that the true burden of liver cancer in Egypt has yet to be realized.

Data on schistosomiasis infection in these cases were unavailable. While the role of hepatic schistosomiasis has long been controversial, the prevailing view today is that it has limited influence in the etiology of HCC in Egypt. Epidemiological studies of HCC clearly identified HBV, HCV, or HBV/HCV coinfection as important, but schistosomiasis could not be identified as a statistically significant independent risk factor.^{19,33} For these reasons, we do not feel that the lack of schistosomiasis infection data influences our conclusions.

As in many developing countries, Egypt is undergoing an epidemiologic transition. With increasing urbanization, smoking rates, environmental exposures, and aging, in addition to the maturing HCV epidemic, it is likely that HCC will continue to rise in the next few decades. Therefore, further studies to assess the magnitude and risk factors of HCC in Egypt and other developing countries seem warranted. Our study produced important preliminary insights that can be used to develop more refined, prospective analyses of HCC risk in Egypt. Ongoing collaborations are building upon these preliminary findings to develop studies that will examine cases from the point of intake and acquire HBV/HCV test results to expand our inference regarding the relative importance of certain risk factors on HCC in Egypt. Such analyses should help define the complex etiology of HCC, enabling policy makers to create targeted and more efficient prevention programs.

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REFERENCES

- 1 Bosch FX, Ribes J, Cleries R, Diaz M. Epidemiology of hepatocellular carcinoma. *Clin Liver Dis* 2005; 9: 191–211.

- 2 Yu MC, Yuan JM, Govindarajan S, Ross RK. Epidemiology of hepatocellular carcinoma. *Can J Gastroenterol* 2000; 14: 703–9.
- 3 Beasley RP. Hepatitis B virus: the major etiology of hepatocellular carcinoma. *Cancer* 1988; 61: 1942–56.
- 4 Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. *Lancet Infect Dis* 2005; 5: 558–67.
- 5 Wasley A, Alter MJ. Epidemiology of hepatitis C: geographic differences and temporal trends. *Semin Liver Dis* 2000; 20: 1–16.
- 6 Arafa N, El Hoseiny M, Rekacewicz C *et al.* Changing pattern of hepatitis C virus spread in rural areas of Egypt. *J Hepatol* 2005; 43: 418–24.
- 7 El-Gafaary MM, Rekacewicz C, Abdel-Rahman AG *et al.* Surveillance of acute hepatitis C in Cairo, Egypt. *J Med Virol* 2005; 76: 520–5.
- 8 Khella AK, Faris L, Helmy S, Yosif A, Esmail S. Hepatocellular carcinoma: characteristics and possible etiologies in a group of Egyptian patients. *J Egypt Public Health Assoc* 1992; 67: 741–52.
- 9 Yates SC, Hafez M, Beld M *et al.* Hepatocellular carcinoma in Egyptians with and without a history of hepatitis B virus infection: association with hepatitis C virus (HCV) infection but not with HCV RNA level. *Am J Trop Med Hyg* 1999; 60: 714–20.
- 10 El-Zayadi AR, Badran HM, Barakat EM *et al.* Hepatocellular carcinoma in Egypt: a single center study over a decade. *World J Gastroenterol* 2005; 11: 5193–8.
- 11 Hassan MM, Zaghloul AS, El-Serag HB *et al.* The role of hepatitis C in hepatocellular carcinoma: a case control study among Egyptian patients. *J Clin Gastroenterol* 2001; 33: 123–6.
- 12 Strickland GT, Elhefni H, Salman T *et al.* Role of hepatitis C infection in chronic liver disease in Egypt. *Am J Trop Med Hyg* 2002; 67: 436–42.
- 13 El-Zayadi AR, Abaza H, Shawky S *et al.* Prevalence and epidemiological features of hepatocellular carcinoma in Egypt – a single center experience. *Hep Res* 2001; 19: 170–9.
- 14 Sayed HA, El Ayyat A, El Dusoki H *et al.* A cross-sectional study of hepatitis B, C, some trace elements, heavy metals, aflatoxin B1 and schistosomiasis in a rural population, Egypt. *J Egypt Public Health Assoc* 2005; 80: 355–88.
- 15 Ezzat S, Abdel-Hamid M, Eissa SA *et al.* Associations of pesticides, HCV, HBV, and hepatocellular carcinoma in Egypt. *Int J Hyg Environ Health* 2005; 208: 329–39.
- 16 Badawi AF, Michael MS. Risk factors for hepatocellular carcinoma in Egypt: the role of hepatitis-B viral infection and schistosomiasis. *Anticancer Res* 1999; 19: 4565–9.
- 17 Settin A, El-Bendary M, Abo-Al-Kassam R, El Baz R. Molecular analysis of A1AT (S and Z) and HFE (C282Y and H63D) gene mutations in Egyptian cases with HCV liver cirrhosis. *J Gastrointest Liver Dis* 2006; 15: 131–2.
- 18 Rivers CA, Barton JC, Acton RT. A rapid PCR-SSP assay for the hemochromatosis-associated Tyr250Stop mutation in the TFR2 gene. *Genet Test* 2001; 5: 131–4.

- 19 Freedman LS, Edwards BK, Ries LAG, Young JL, eds. *Cancer Incidence in Four Member Countries (Cyprus, Egypt, Israel, and Jordan) of the Middle East Cancer Consortium (MECC) Compared with US SEER*. Bethesda, MD: National Cancer Institute, 2006.
- 20 Central Agency for Public Mobilization and Statistics. *Statistical Year Book*. Cairo, Egypt: Central Agency of Public Mobilization and Statistics, 2005.
- 21 Freedman LS, Al-Kayed S, Qasem MB *et al*. Cancer registration in the Middle East. *Epidemiology* 2001; **12**: 131–3.
- 22 Ibrahim AS, Seif-Eldin IA, Ismail K *et al.*, eds. *Cancer in Egypt, Gharbiah: Triennial Report of 2000–2002, Gharbiah Population-based Cancer Registry*, Cairo, Egypt: Middle East Cancer Consortium, 2003.
- 23 Cancer Registry Public Information Data: 1999–2002 WONDER on-Line Database. United States Department of Health and Human Services, National Program of Cancer Registries, Centers for Disease Control and Prevention. Data: 1999–2002 WONDER On-Line Database 2005.
- 24 Parkin DM, Whelan SL, Ferlay J, Raymond L, Young J, eds. *Cancer Incidence in Five Continents*, vol VII. Lyon: IARC, 1997.
- 25 Hoel DG, Ron E, Carter R, Mabuchi K. Influence of death certificate errors on cancer mortality trends. *J Natl Cancer Inst* 1993; **85**: 1063–8.
- 26 Donato F, Tagger A, Gelatti U *et al*. Alcohol and hepatocellular carcinoma: the effect of lifetime intake and hepatitis virus infections in men and women. *Am J Epidemiol* 2002; **155**: 323–31.
- 27 Yu MW, Yang YC, Yang SY *et al*. Hormonal markers and hepatitis B virus-related hepatocellular carcinoma risk: a nested case-control study among men. *J Natl Cancer Inst* 2001; **93**: 1644–51.
- 28 Deuffic-Burban S, Mohamed MK, Larouze B, Carrat F, Valeron AJ. Expected increase in hepatitis C-related mortality in Egypt due to pre-2000 infections. *J Hepatol* 2006; **44**: 455–61.
- 29 Halim A-B, Garry RF, Dash S, Gerber MA. Effect of schistosomiasis and hepatitis on liver disease. *Am J Trop Med Hyg* 1999; **60**: 915–20.
- 30 Frank C, Mohamed MK, Strickland GT *et al*. The role of parenteral antischistosomal therapy in the spread of hepatitis C virus in Egypt. *Lancet* 2000; **355**: 887–91.
- 31 El-Zayadi AR. Curse of schistosomiasis on Egyptian liver. *World J Gastroenterol* 2004; **10**: 1079–81.
- 32 Strickland GT. Liver disease in Egypt: hepatitis C superseded schistosomiasis as a result of iatrogenic and biological factors. *Hepatology* 2006; **43**: 915–22.
- 33 Angelico M, Renganathan E, Gandin C *et al*. Chronic liver disease in the Alexandria governorate, Egypt: contribution of schistosomiasis and hepatitis virus infections. *J Hepatol* 1997; **26**: 236–43.