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ORIGINAL ARTICLE

Epidemiologic risk factors of hepatocellular carcinoma in a rural region of Egypt

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Abstract
Background Hepatocellular carcinoma (HCC) is a major health problem worldwide, including Egypt. In the recent past, HCC has become the second most prevalent cancer among men in Egypt. Since HCC has not been well studied in the rural population of Egypt, this case–control study was conducted to investigate the epidemiologic risk factors of HCC in the predominantly rural region of Gharbiah, Egypt.
Methods A total of 150 cases and 150 controls matched to cases on age (±5 years) and sex were recruited from the Gharbiah Cancer Society and Tanta Cancer Center. Exposure data were collected by an interviewer-administered standardized questionnaire about epidemiologic, occupational, medical and family history of HCC. Conditional logistic regression was utilized to calculate unadjusted and adjusted odds ratios (ORs) and 95% confidence intervals (CI). The effect modification of HCC risk between viral infection and environmental risk factors was also assessed.
Results Being an industrial worker was an independent risk for developing HCC (OR 3.54, 95% CI 1.18, 10.63) after adjusting for viral infection, schistosomiasis and tobacco smoking. High relative risk of HCC was observed among HCV-infected individuals who were farmers (OR 9.60, 95% CI 3.72, 24.76), industrial workers (OR 12.90, 95% CI 4.33, 38.43) or active smokers (OR 5.95, 95% CI 2.20, 16.08).
Conclusion Occupational exposure may play an important role in the development of HCC. Farming, industrial exposures and cigarette smoking may increase the risk of HCC among HCV-seropositive individuals. Future research focusing on mechanisms of occupational exposures among HCV patients in this population is needed.

Keywords Hepatocellular carcinoma · Rural · Gharbiah · Egypt

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Introduction

Hepatocellular carcinoma (HCC) has become the third most common malignancy worldwide with very poor prognosis, rendering it the fourth highest cause of cancer-related deaths [1, 2]. The distribution of liver cancer varies by region and more than 80% of cases and deaths occur in developing countries [3]. In Africa, liver cancer has been ranked as the fourth common cancer, and most of liver cancers are HCC [4]. Of all the HCC cases, it is estimated that 66% are attributable to hepatitis B virus (HBV) and 42% are attributable to hepatitis C virus (HCV), assuming that the relative risk of disease in both carriers is 20 [5]. However, in North Africa, infection with HBV is less common than in other regions [2], and the higher HCV prevalence is expected to contribute to the rising incidence of HCC over the next decade in an aging cohort.

Epidemiologic research to explore the risk factors of liver cancer is important because of the high incidence of the disease and the high level of viral exposures in countries such as Egypt. The Gharbiah is a predominately rural province in Egypt and the home of the only population-based cancer registry that is funded by the National Cancer Institute, USA. It is an interesting place for investigating the epidemiology of liver cancer because of the high incidence of the disease there and also the high viral exposures in the region. According to the report of the population-based cancer registry of Gharbiah, the incidence of liver cancer is ranked as the second highest in men and the seventh in women during 2000–2002 [6]. Moreover, there has been an alarming increase in incidence of liver cancer in Egypt, which is now three times higher than that in the USA [7]. Also, the prevalence of HCV infection is one of the highest in the world [8]. Several reports showed seropositivity for HCV ranging from 12.7% in seashore governorate to 36.3% in the Nile delta region of Egypt [9, 10] with an overall estimate of approximately 22% [11–15]. Hepatitis B virus (HBV) was found at high rates, but after increase in HCV prevalence the rates of HBV declined [16]. In addition, the national program for HBV started in 1992, but it focused on newborns with little attention to vaccination of older children [17].

Risk of liver cancer among workers of textile industry, cleaning trades, farming-related industry, petroleum-producing industry, metal industry and restaurant business has been examined in the early literature [18–22]. Furthermore, agents such as chlorinated hydrocarbons, pesticides and herbicides, certain dyestuffs and cleaning solvents have been plausibly associated with liver cancer [21, 23–25]. None of these occupational factors has been studied in relation to the risk of liver cancer in Egypt.

In Egypt, several hospital- or community-based studies have tried to identify and establish associations between viral hepatitis and HCC over a decade [14, 16, 26, 27]. The potential mode of transmission of HCV through occupational exposures and parenteral anti-schistosomal therapy (PAT) has also been discussed [28, 29]. Some investigations aimed at determining aflatoxin levels in food items in Egypt produced conflicting results [16, 30, 31]. Our recent population-based study suggested that environmental factors might contribute to the incidence of HCC in Egypt [7]. A hospital-based case–control study investigated the association between pesticides and HCC adjusting for viral factors. A slightly higher risk of HCC attributed to pesticides was observed in rural men, with adjusted odds ratio greater than two [27]. However, the participants were recruited from Cairo, which was a highly urbanized province and thus might not be representative of rural areas of Egypt. Similarly, HCC cases diagnosed in Mansoura Gastroenterology Center increased annually with predominantly rural residents and farmers among HCV patients, suggesting some environmental etiology to HCC [32]. Therefore, we conducted this study to investigate the demographic, occupational and medical histories that might be related to the risk of HCC in this predominantly rural region in Egypt.

Materials and methods

Study design and study population

This hospital-based case–control study was prospectively conducted from December 2007 to January 2009 and was carried out at the Tanta Cancer Center (TCC) and the Gharbiah Cancer Society (GCS) in Tanta, Gharbiah, Egypt. According to the Central Agency for Public Mobilization and Statistics (CAPMAS) of Egypt, 31% of the population of the Gharbiah Province is urban [33]. A total of 150 liver cancer patients representing about 80% of the overall liver cancer patients seen during the period of the study in the Gharbiah population-based cancer registry were recruited in this study. Cases were diagnosed by radiological and specific tumor markers, and 27.33% of them had histological confirmation. Controls were recruited from the TCC and GCS from healthy individuals who were visiting or accompanying patients of TCC and GCS during the period of the study. Relatives of liver cancer patients were ineligible to be controls. Each control subject was individually matched to cases by sex and age (±5 years).

For all participants, interviewer-administered interviews using a standardized questionnaire were conducted. The study questionnaire elicited the information of demographic, residential, occupational, lifestyle and medical histories as well as reproductive changes for female subjects. The questionnaire had been used in our previous studies on the epidemiology of cancer in Egypt [34–36]. Following the interviews, blood samples were taken from all study subjects. A few participants refused to provide a blood sample at the end of the interview and were excluded from our final analyses of matched sets (12 cases and 1 control).

Data management

From 1999 to 2002, there were approximately 200–250 liver cancer cases registered in the Gharbiah Cancer Registry per year [7]. According to the data from 2000 to 2002, age-standardized incidence rate was 21.7/100,000 for males, 4.2/100,000 for females and 13/100,000 for the total Gharbiah population [6]. Since about 36.44% of the population in Gharbiah is engaged in agricultural occupation, we recruited 150 cases and 150 age- and sex-matched controls to detect the 15% difference in the proportion of farming exposure among cases and controls with an 80% power.

The study outcome clinically or pathologically confirmed HCC. Environmental exposures were recorded based on residential and occupational histories. The subjects were asked to recall every previous job that they had engaged in along with their job activities and time frames. Residential histories were collected by asking subjects to report their moving history retrospectively from their current residence to the place of birth. Rural and urban information was then identified according to their living histories. For those who had ever moved between rural and urban areas, the longest place of living was applied to decide whether they were rural or urban residents. Occupation was defined as the longest job that the subject ever had and was categorized into agricultural, industrial, administrative and housewife. To capture any possible farming exposure in the past even in a relatively short period, farming exposure variable (farmer/non-farmer) was generated by pooling those who had ever worked at a farm as well as housewives who lived in the rural area. A major confounder was viral profile, including HBV and HCV infection (HBsAg positive or/and HCV antibody positive). Other potential confounding variables were as follows. (1) Demographic variables: sex, age, education and marital status. (2) Smoking and tobacco use: type of tobacco, duration, frequency, current status, lifetime active and passive exposure. (3) Diet: preference for peanut consumption and frequency and amount of alcohol consumption. (4) Medical history: family history, schistosomiasis, cirrhosis, injection treatment and blood transfusion.

Statistical analysis

Statistical analysis was performed using SAS statistical package version 9.1.3 (SAS Inc. Cary, NC, USA) to complete two-sided analyses of descriptive statistics, and adjusted and unadjusted odds ratios. In the univariate analysis, Mantel–Haenszel Chi-square test was used to evaluate the crude association between HCC and exposures: demographic, diet and smoking characteristics, and medical history by stratifying sex and age to take matching into account. Conditional logistic regression was employed to calculate the crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs), and to assess the effect measure modification. The joint effects of exposure to both environmental exposure variables and HCV status were compared with the sum of their independent effects. This additive interaction effect is defined as departure from additivity of absolute effects and was calculated as:

$$\mathrm{OR}(a^{+}b^{+}) - \mathrm{OR}(a^{+}b^{-}) - \mathrm{OR}(a^{-}b^{+}) + 1$$

where $\mathrm{OR}(a^{+}b^{+})$ denotes the relative odds for those exposed to both environmental (a) and viral (b) exposures compared to the odds for the reference group ($a^{-}b^{-}$). An additive interaction effect value of 0 means no interaction; if the value is greater than 0, it indicates the presence of a positive additive interaction effect.

Results

The study population comprised 84% males ($n = 252$) and 16% females ($n = 48$). The mean age was 56.02 years (SD 10.59) for cases and 55.43 years (SD 10.25) for controls (Table 1). The youngest subject was 17 years old and the oldest was 81 years old. The proportion of less than primary school education was higher among cases (75.33%) than controls (49.33%). Significant different education profiles between cases and controls was found even when taking sex and age into account (Table 1). Strong associations between education and each exposure status were found as well. Marital status for cases and controls was similar, with more than 80% of the study population being married. About 77% of the cases ($n = 116$) were from Gharbiah, whereas 96% of the controls ($n = 144$) were current Gharbiah residents (data not shown). This is plausible since some patients from other governorates came to Gharbiah to seek treatment at TCC, but controls were less motivated to cross governorates for reasons of visit only.

As shown in Table 2, subjects with a schistosomiasis condition had three times higher risk of developing HCC (OR 3.08, 95% CI 1.61, 5.91). Different treatment methods for schistosomiasis were also associated with HCC risk, with the greatest risk for participants who received injection treatment only (OR 3.57, 95% CI 1.78, 7.15), suggesting the adverse effect of parenteral anti-schistosomal therapy (PAT). The effect of having history of schistosomiasis became non-significant after controlling for treatment methods (OR 8.19, 95% CI 0.82, 81.95, data not shown). In addition, having cirrhosis (OR 5.00, 95% CI 2.62, 9.55) and having ever received blood transfusion (OR 6.75, 95% CI 2.36, 19.29) were strongly associated with HCC (Table 2). As expected, viral infection was the single most important risk factor of HCC (OR 13.80, 95% CI 5.57, 34.21). Among our study population, about 89.19% of cases were seropositive for HCV antibody, whereas among controls it was only 49.33%.

Table 3 demonstrates the effect of diet and smoking on HCC. Although being an active smoker (OR 3.06, 95% CI 1.34, 6.96) and having used any water pipe (OR 1.94, 95% CI 1.06, 3.54) conferred some risk in unadjusted models. These effects were obliterated in our full models (Table 2).

The results of multivariable analysis for residential and occupational exposures are presented in Table 4. The most important observation to be noted here is the higher risk of

Table 1 Demographic characteristics of the study population in the case–control study on hepatocellular carcinoma, Gharbiah, Egypt

Variables by level	Case ($n = 150$)		Control ($n = 150$)		p
	No.	%	No.	%	
Sex					
Male	126	84.00	126	84.00	1.0000[a]
Female	24	16.00	24	16.00	
Age					
<40	6	4.00	6	4.00	0.9988[a]
40–49	34	22.67	32	21.33	
50–59	55	36.67	56	37.33	
60–69	38	25.33	38	25.33	
≥70	17	11.33	18	12.00	
Education					
Less than primary school	113	75.33	74	49.33	<0.0001[b]
Primary to secondary school	32	21.33	53	35.33	
College or more	5	3.33	23	15.33	
Marital status[c]					
Married	127	84.67	130	86.67	0.5198[b]
Not married	23	15.33	20	13.33	

[a] Chi-square test

[b] Mantel–Haenszel Chi-square test adjusting for sex and age

[c] Includes widowed, divorced and never married

Table 2 Characteristics of medical history of the study population in the case–control study on hepatocellular carcinoma, Gharbiah, Egypt

Variables by level (n)	Case		Control		OR[a] (95% CI)	p
	No.	%	No.	%		
Cancer family history (149, 150)						
Yes	12	8.05	15	10.00	0.80 (0.37, 1.71)	0.5645
No	137	91.95	135	90.00	1	
Schistosomiasis (145, 144)						
Yes	121	83.45	92	65.52	3.08 (1.61, 5.91)	0.0007
No	24	16.55	52	34.48	1	
Age of first diagnosis with schistosomiasis (121, 92)						
<15	55	45.45	36	39.13	1.09 (0.22, 5.50)	0.7231
15–40	57	47.11	53	57.61	0.84 (0.16, 4.41)	
>40	9	7.44	3	3.26	1	
Cirrhosis (142, 141)						
Yes	63	44.37	17	12.06	5.00 (2.62, 9.55)	<0.0001
No	79	55.63	124	87.94	1	
Schistosomiasis treatment (150, 150)						
Oral and injection	28	18.67	29	19.33	2.09 (0.98, 4.48)	0.0041
Injection only	55	36.67	33	22.00	3.57 (1.78, 7.15)	
Oral only	36	24.00	31	20.67	2.43 (1.19, 4.94)	
None	31	20.67	57	38.00	1	
Blood transfusion (149, 150)						
Yes	29	19.46	6	4.00	6.75 (2.36, 19.29)	0.0004
No	120	80.54	144	96.00	1	
Age of first blood transfusion (mean, SD) (28, 6)	39.4	19.30	43.1	20.27	0.63 (0.13, 3.04)	0.5694
Viral infection (148, 150)						
Yes[b]	139	93.92	76	50.67	13.80 (5.57, 34.21)	<0.0001
No	9	6.08	74	49.33	1	

[a] Conditional logistic regression

[b] HBsAg(+)/HCVab(−):HBsAg(−)/HCVab(+):HBsAg(+)/HCVab(+) for infected cases are 3:7:129; for infected controls are 2:2:72

Table 3 Characteristics of diet and smoking history of the study population in the case–control study on hepatocellular carcinoma, Gharbiah, Egypt

Variables by level	Case		Control		Unadjusted OR[a] (95% CI)	Adjusted OR[b] (95% CI)
	No	%	No.	%		
Peanut consumption frequency (times/year)						
>2	26	17.45	32	21.33	0.37 (0.13, 1.08)	0.59 (0.13, 2.61)
1–2	108	72.48	111	74.00	0.45 (0.17, 1.18)	0.64 (0.16, 2.57)
0	15	10.07	7	4.67	1	1
Smoking over 100 cigarettes						
Yes	83	55.33	79	52.67	1.18 (0.67, 2.09)	1.42 (0.71, 2.83)
No	67	44.67	71	47.33	1	1
Cigarette use[c]						
Heavy	55	37.16	54	36.73	1.23 (0.66, 2.29)	1.68 (0.77, 3.67)
Moderate	27	18.24	21	14.29	1.63 (0.77, 3.41)	1.84 (0.75, 4.50)
None	66	44.59	72	48.98	1	1
Passive smoking						
Active and passive smoker	62	41.33	65	43.33	1.88 (0.82, 4.30)	1.50 (0.58, 3.87)
Active smoker	48	32.00	30	20.00	3.06 (1.34, 6.96)	2.07 (0.77, 5.55)
Passive smoker	21	14.00	24	16.00	1.18 (0.46, 3.03)	0.92 (0.31, 2.71)
None	19	12.67	31	20.67	1	1
Water pipe use						
Any	35	23.33	20	13.33	1.94 (1.06,3.54)	1.13 (0.62, 2.78)
None	115	76.67	130	86.67	1	1

[a] Conditional logistic regression

[b] Conditional logistic regression adjusting for viral infection

[c] Categories were based on the product of total smoking amount. If cigarette number-year > 300, then cigarette use is heavy, if 0 < number-year < 300 then cigarette use is moderate

developing HCC among people working in industrial occupations compared to people with administrative jobs (OR 3.54, 95% CI 1.18, 10.63). We did not find any risk of HCC for people working in farms when compared to those not working in farms.

In Table 5, the additive effect of modification due to HCV infection is presented. Among individuals infected with HCV, farmers (OR 9.60, 95% CI 3.72, 24.76) and industrial workers (OR 12.90, 95% CI 4.33, 38.43) had a higher risk of developing HCC compared to non-farmers (OR 4.51, 95% CI 1.82, 11.15) and non-industrial workers (OR 6.54, 95% CI 3.18, 13.46) indicating an apparent additive effect. The excess risk of developing HCC due to HCV infection for farmers and industrial workers was 5.17 and 6.05, respectively. Similarly, among those infected with HCV, being an active smoker conferred a higher risk (OR 5.95, 95% CI 2.20, 16.08) than not being an active smoker (OR 2.95, 95% CI 1.19, 7.35) on an additive scale. Using a water pipe and being infected with HCV did not confer any additional risk for developing HCC on an additive scale.

Discussion

This case–control study in Egypt had several interesting observations. First, medical conditions such as viral infection, cirrhosis and blood transfusion were associated with HCC. Second, workers engaged in industrial activities had increased risk of HCC, whereas rural/urban residence and farming-related activities did not appear to be risk factors of HCC. Moreover, occupational exposures and tobacco smoking were observed to increase the risk of HCC among the HCV-infected population. Third, diet and smoking status were not direct risk factors for HCC in our study.

In Egypt, the independent effect of hepatitis virus in the etiology of HCC had been recognized earlier [16, 26], as confirmed in our study. The strong association of cirrhosis and HCC was supported by the evidences of its intermediating role in the pathogenesis of HCC due to chronic viral hepatitis [14]. In contrast to cirrhosis, the observed association between blood transfusion and HCC might be accounted for by its role in transmission of viral infection

Table 4 Residential and occupational exposures of the study population in the case–control study on hepatocellular carcinoma, Gharbiah, Egypt

Variables by level	Case ($n = 150$)		Control ($n = 150$)		Unadjusted OR[a] (95% CI)	Adjusted OR[b] (95% CI)
	No.	%	No.	%		
Longest residence						
Rural	135	90.00	133	88.67	1.17 (0.54, 2.52)	0.63 (0.22, 1.83)
Urban	15	10.00	17	11.33	1	1
Longest occupation[c]						
Agricultural	81	54.00	69	46.00	2.15 (1.14, 4.06)	2.13 (0.89, 5.09)
Industrial	29	19.34	20	13.34	2.73 (1.21, 6.13)	3.54 (1.18, 10.63)
Housewife	16	10.67	19	12.67	1.11 (0.29, 4.21)	0.87 (0.07, 11.34)
Administrative	24	16.00	42	28.00	1	1
Farmer/non-farmer[d]						
Farmer	89	59.33	72	48.00	1.68 (1.02, 2.76)	1.58 (0.79, 3.16)
Non-farmer	61	40.67	78	52.00	1	1
Farming exposure[e]						
Farming exposure	103	68.67	90	60.00	1.48 (0.91, 2.41)	1.40 (0.71, 2.74)
No farming exposure	47	31.33	60	40.00	1	1

[a] Conditional logistic regression

[b] Conditional logistic regression, adjusting for viral infection, schistosomiasis, water pipe and active/passive smoking exposure

[c] Agricultural includes farming, fishing and farming-related workers; industrial includes construction, installation, production, transportation, armed forces, service (cleaner, cook, barber), laboratory technician and health-care personnel; administrative includes management, government employee, sales, service (waiter, prayer caller, security) and no work

[d] Ever been engaged in farming-related works

[e] Farming exposure includes housewife who lives in rural area

Table 5 Modification effect of hepatitis C virus (HCV) infection on environmental/behavioral exposures in the case–control study on hepatocellular carcinoma, Gharbiah, Egypt

Joint and component effects of occupational exposures and HCV	OR[a] (95% CI)	Joint and component effects of smoking exposures and HCV	OR[a] (95% CI)
Farmer		Active smoker	
Farmer and HCV (+)	9.60 (3.72, 24.76)	Active smoker and HCV (+)	5.95 (2.20, 16.08)
Farmer and HCV (−)	0.92 (0.29, 2.93)	Active smoker and HCV (−)	0.459 (0.118, 1.785)
Non-farmers and HCV (+)	4.51 (1.82, 11.15)	Non-active smoker and HCV (+)	2.95 (1.19, 7.35)
Non-farmers and HCV (−)	1	Non-active smoker and HCV (−)	1
Excess risk due to interaction	5.17	Excess risk due to interaction	3.53
Industrial worker		Water pipe	
Industrial workers and HCV (+)	12.90 (4.33, 38.43)	Use of water pipe and HCV (+)	9.69 (3.66, 25.64)
Industrial workers and HCV (−)	1.31 (0.30, 5.68)	Use of water pipe and HCV (−)	4.18 (0.95, 18.33)
Non-industrial workers and HCV (+)	6.54 (3.18, 13.46)	No water pipe and HCV (+)	8.72 (3.87, 19.67)
Non-industrial workers and HCV (−)	1	No water pipe and HCV (−)	1
Excess risk due to interaction	6.05	Excess risk due to interaction	−2.21

[a] Conditional logistic regression given matching factors

[15, 37]. By the same token, PAT treatment was a major risk factor of HCV seropositivity [15, 28], which leads to HCC. By contrast, the relative importance of the etiologic effect of schistosomiasis on liver cancer is still inconclusive [38, 39]. Schistosomiasis per se may cause the persistence of viremia due to reduced immunity [40] or could play a minor role in the pathogenesis of HCC as a result of the copper sulfate sprayed in canals for snail control [41]. Therefore, schistosomiasis is still treated as a covariate in our multivariable analysis.

Given the unique HCV prevalence and transmission mode in Egypt, environmental risk factor such as cigarette

smoking also contributes in a distinct way compared to other countries. In animal models, various chemical components of cigarette smoking have been proven to be hepatic carcinogens [42]. This causal relationship between cigarette smoking and HCC was established in a population-based case–control study among American whites [43]. Likewise, about twice the risk of HCC was found for smokers among patients with chronic liver disease in a prospective study in Japan [44]. Nevertheless, no independent effect of cigarette smoking was observed in our study. A multistage survey conducted in Egypt did not find significant association between HCV seropositivity and water pipe "goza" smoking [45]. Although a case–control study suggested an additive role of smoking in the pathogenesis of HCC in Egypt [46], no adjusted estimate was available, implying confounding effect. Our study not only identified different types of smoking (cigarette, water pipe, goza and cigar), but also analyzed the data with consideration of smoking frequency and duration. Thus, the lack of additional etiological effect of smoking is less prone to measurement error. More consistent results should be reported to draw a firm conclusion regarding the small effects such as tobacco smoking on HCC.

In terms of residential and occupational exposures, previous studies either treated residence as a confounder [26, 27] or restricted their study in rural areas [12, 14, 15] given the fact that the prevalence of viral infection greatly varied by geographical regions [12, 14, 15]. To explore its additional effect on HCC, both residential and occupational factors were exposures of interest in our study. After adjusting for viral infection and schistosomiasis, rural residence did not show independent effect related to HCC, which suggested that residential variations were largely explained by the individual medical conditions. Furthermore, while different occupational categories were examined, workers in agricultural field with farming-related exposure such as pesticides seemed not to have an elevated risk of HCC as was originally hypothesized. This observation was different from the conclusion drawn by Ezzat et al. [27], who suggested that agricultural pesticides might have an additive risk of HCC among rural males. Yet, lacking schistosomiasis-related information as well as employing unconditional logistic regression method for matched case–control data, their conclusion was possibly undermined by the biased estimates away from the null. Although the biological plausibility of carbamates and organophosphate pesticides are reported in animal models [47], the causal inference of human HCC as the consequences of insecticide or pesticide exposure are far from conclusive due to some methodological difficulties in observational studies [27, 48]. By comparison, industrial workers have higher risk of HCC with administrative workers as reference group. Construction, installation, production, transportation, armed forces, service (cleaner, cook, barber), laboratory technician and health-care personnel were categorized as industrial workers because of their greater likelihood of being injured or exposed to occupational chemicals or hazardous toxins. To our best knowledge, only a small number of studies had examined the association between occupation other than farmer and HCC risk in Egypt. An early study reported that there was no difference in the risk for HCC between sedentary or active workers, who were categorized arbitrarily [37]. A recent study conducted in Lower Egypt revealed that HCC presented at a younger age among medical personnel, teachers and housewives versus farmers and workers [32]. However, this finding might be biased due to the earlier awareness of disease and seeking for medication among higher education groups. Internationally, farm laborers, and laundering, cleaning and road building workers were observed to have a higher risk for HCC in retrospective studies [18, 49]. If we extend the outcome from HCC to all primary liver cancer, oil refinery workers, plumbers, pipe fitters, cooks, laundry workers, lithographers, and those who work in long-term offset printing or auto repair shops, as well as restaurant and hotel businesses were discovered to be of potential high risk [20, 21, 50, 51]. Workers exposed to solvents, toluene or xylene were also associated with primary liver cancer [19, 52]. Recently, a case–control study suggested a mild association between metal machining jobs and HCC among those without viral infection [53]. Nevertheless, a multicenter international liver tumor study failed to establish the association between occupational exposures and liver cancer among women, even though the viral factor was carefully considered and occupation-exposure matrix was constructed [54]. Taken together, those international studies from North American or European countries were less capable to efficiently assess the interplay between viral profile and occupational or environmental exposures to the risk of HCC due to the low prevalence of HBV/HCV.

The interaction between various risk factors of HCC was examined only among HCV, HBV and schistosomiasis in Egypt [26], and no other similar research was documented for other environmental risk factors. In southern Europe, such epidemiologic interactions between various risk factors of HCC were systematically reviewed by Donato et al. [55]. In their meta-analysis, alcohol consumption and tobacco smoking were found to have positive interaction with HBV/HCV; however, no occupational exposure was available for interaction assessment. Since alcohol consumption is relatively rare and tobacco smoking is unbelievably high in Egypt, the epidemiologic interaction effect between smoking and HCV infection should be evaluated. In the effect modification analysis, we suggested that the concomitant exposure to occupational exposures and HCV

might have additive risks compared to exposure to HCV or occupational exposures. Also, similar additive modification effect was observed among active smokers with HCV infection. Although the use of water pipe appeared to reduce the risk of HCC among the HCV infected, the estimates could be biased due to the small stratum of exposure to water pipe only (4 cases and 7 controls). The excess risk for active smokers among the HCV infected was in concordance with the findings of a nested case–control study in Japan [56] and a prospective study conducted in Taiwan [57], although the relative strength of these minor risk factors varied in different populations.

Compared to other hospital-based case–control studies, our study had several strengths. We collaborated with GPCR; hence, the base population to which our study cases belonged was more likely to have been identified and our study cases were expected to be representative of the overall HCC cases in Gharbiah. The participant rate was close to 100%, which could be explained by the trustful relationship between participants and recruiters, who were trained oncologists at TCC. Alcohol consumption and aflatoxin, two important risk factors, were unlikely to be the uncontrolled confounders in our study since alcohol consumption was forbidden in a Muslim country and fungi do not survive in the extremely hot arid desert climate of Egypt. These facts helped us to rule out these two risk factors in the etiology of HCC in Egypt. Furthermore, this is also the first study that tries to assess the occupational and residential effects on HCC in Egypt.

Our study also had some limitations. Compared to previous studies that aimed to explore risk factors of HCC in Egypt [16, 26, 27], we had a slightly smaller sample size. However, the matched case–control study design and use of conditional logistic analyses allowed us to obtain the estimates more efficiently. During data collection, the recruiters tended to systematically recruit visitor controls who were family members of patients with other types of cancer being treated at TCC. Potential selection bias can be suspected to attenuate the effect of environmental exposures, which were greatly shared by various patients and might commonly be experienced among family members. In terms of the comparability of the base population, our study cases had profiles for sex, age and rural/urban distribution similar to the cases reported by the Gharbiah Cancer Registry [7]. While our study did not reveal a relationship between aflatoxin exposure and liver cancer risk, previous studies from Egypt had shown a high level of aflatoxin in the food and samples of liver cancer patients [58–63]. Future studies should continue to investigate the role of aflatoxin in relation to other risk factors for liver cancer in Egypt.

In terms of information bias, potential misclassification of exposure status might be a concern due to the nature of the retrospective study. However, although exposure status was self-reported for residential and occupational variables, specific time frames were drawn to assist in recalling every residence and job precisely and completely during the interview. Therefore, less information bias was introduced for these two exposure variables. Still, misclassification might have occurred for smoking behaviors and medical history. The prevalence of overall smoking among Egyptian males was estimated to be 47%, according to a national survey conducted in 2002 [64]. Over 60% of our study controls smoked (including all types), which was higher than the earlier survey. However, there is no reason to suspect non-differential misclassification for tobacco smoking between cases and controls. As for schistosomiasis prevalence, an average of 37.7% of the population in 34 Gharbiah communities was infected with *S. mansoni*, ranging from 17.9 to 79.5% [65]. As much as 65% of our study controls had a history of schistosomiasis, which fell in the range of schistosomiasis infection prevalence for the Gharbiah population. The proportions of subjects who could not recall their schistosomiasis history were similar between cases and controls, which suggested a non-differential misclassification.

In conclusion, our study confirmed that hepatic viral infection and schistosomiasis treatment were independent risk factors of HCC. Also, occupational exposure may play an important role in the development of HCC in addition to viral profile. Moreover, occupational exposure and cigarette smoking may generate an excess risk of HCC among HCV-seropositive individuals. Specific mechanisms of occupation-specific toxins and their interactions with viral activity need to be examined in future studies. Further health education and occupational safety programs should be launched, targeting HCV-seropositive industrial workers to prevent the increasing incidence of HCC in Egypt.

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