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The Role of Oncogenic Infectious Agents in Causing Liver, Stomach, Urinary Bladder, Head and Neck and Cervical Cancers

Abstract

Background: Understanding the pathogenesis and predisposing factors for cancer is a major concern. Several studies have elucidated the role of infection in developing certain malignancies.

Aim: The aim of this work was to assess the role of infectious agents in causing liver, stomach, urinary bladder, head and neck and cervical cancers.

Methods: This case-control study included 181, diagnosis of several infectious agents included genetic and serological tests in both groups. The relative risk of each infectious agent was then calculated.

Results: Oncogenic infectious agents cause 81.2% of studied cancers. HCV was detected in 92.2% of HCC with a relative risk of 4.6, HBV was detected in 5% of cases and relative risk of 4.8, H. pylori DNA was found in 77% of gastric cancer and a relative risk of 1.2 and S. heamatobium was found in 37.5% of urinary bladder cases with a relative risk of 31. Finally, HPV16 DNA was detected in 56.2% of head and neck cancer and 66.6% of cervical cancer with a relative risk of 3.12 and 3.7 respectively.

Conclusion: Infections play an important role in the pathogenesis of cancer. Better attention to Infection prevention and control programs must be adapted to decrease the burden of malignant diseases.

Keywords: Cancer; Infectious diseases; Relative risk; HCV

Research Article

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Abbreviations: HBV: Hepatitis B Virus; HPV: Human Papilloma Virus; HCV: Hepatitis C Virus; EBV: Epstein-Barr Virus; HIV 1: Human Immunodeficiency Virus Type 1; HTLV 1: Human T-Cell Lymphotropic Virus Type I; HBsAg: Hepatitis B Surface Antigen; HCC: Hepatocellular Carcinoma; WHO: World Health Organization

Introduction

Cancer is currently a growing problem worldwide. In Egypt, the crude incidence rate on the national level for all sites, excluding non-melanoma skin cancer was 113.1/100,000 for both sexes. As the population of Egypt is expected to increase steadily, consequently, the number of cancer cases will increase due to both population growth and demographic change due to ageing of the population [1].

Epidemiological , clinical and biological studies have provided sufficient evidences that several infectious agents are known causes of cancer. These human carcinogens include: hepatitis B virus (HBV), hepatitis C virus (HCV), certain strains of the human papilloma virus (HPV), Helicobacter pylori, Epstein-Barr virus (EBV), human immunodeficiency virus type 1 (HIV 1), human T-cell lymphotropic virus type I (HTLV 1), Kaposi's sarcoma herpesvirus (HHV8) and the parasite *Schistosoma* [2-4]**.** The aim of this study is to assess the burden of infection in causing solid cancers in cases presented to medical oncology department, Zagazig University Hospitals, Egypt.

Methodology

This is a case-control study, done in Medical Oncology and Medical Microbiology Immunology and pathology departments, Faculty of medicine, Zagazig University, Egypt. Zagazig university hospitals are regional tertiary hospital that serves more than six governors providing service to a population of more than nine million people living in the east of Egypt.

Control group: number and characters of control group were selected to adapt with age and sex for each cancer group.

Cases: Patients included in this study attended Medical Oncology department for the period of June 2013 to June 2015 and were confirmed to have cancer, clinically, laboratory and radiologically.

Inclusion criteria: Patients suffering from solid tumors where association with oncogenic infectious agent were suspected HCC, Urinary bladder cancer, Gastric carcinoma, Head and neck and cancer cervix

Exclusion criteria: Patient suffering from hematological malignancies or other solid tumors.

Further investigations were done to identify the causing infectious agent, if present. These investigations include:

Diagnosis of *H. pylori*

In control group: *H. pylori* Ag was detected in stool of 50 apparently healthy individuals using ELISA kit (International Immuno-Diagnostics MICROWELL) according to manufactures guidelines.

Patient group: *H. pylori* was detected in cancer tissue obtained during upper GIT endoscope using PCR. DNA was extracted using (Qiagen, Germany) DNA extraction kit from tissue. The following primers were used F' AAG CTT TTA GGG GTG TTA GGG GTT T , R' AAG CTT ACT TTC TAA CAC TAA CGC giving a product of 294 bp. Reactions were performed in a 50-ml volume using thermofisher master mix, 2ul of each primer, 5 ul of extracted DNA, elongation step was done at 72^0C were used. 2% agarose gel was used to detect the PCR product [5].

Diagnosis of HCV

Control group: Diagnosis depends on detecting viral Ab in serum of 100 apparently healthy individuals using Anti HCV ELISA kit (Prechek Bio, Inc, USA)

Cases were diagnosed using HCV real time PCR: Viral RNA was extracted using (Thermoscientific, USA) lysis solution. Amplification was done using TaqMan probe. The Specific Master mix contains reagents and enzymes for the specific amplification of HCV and for the direct detection of the specific amplicon in fluorescence channel Cycling A. FAM of amp icon, and HEX for the internal control using Strategen Mx Pro- Mx3005P. Simply, 15 µl of the Master Mix was pipetted into each labelled PCR tube. Then 10 µl of extracted RNA was added to each sample tube and mixed well by pipetting up and down. Quality Control: One negative control (10 µl of Water, PCR grade) was included per PCR run. In addition to one external positive control standards (10 µl of the Standards).Amplification was performed first at 45^0C for 10min and for 45 cycles at 95^0C for 5 s and 60^0C

Diagnosis of HBV:

Control group: Hepatitis B Surface Antigen (HBsAg) was detected using ELISA Kit in the serum of 100 apparently healthy individuals.

Patient group: Diagnosis was based on real time PCR. Viral RNA was extracted using (Thermoscientific, USA) lysis solution. Real-time PCR was performed in a 50 µl reaction mixture containing 25 µl TaqMan Universal PCR master mix (Applied Biosystems) with 0.2 µl primers, 0.1 µl probes, and 10 µl extracted DNA. 50 cycles of 95°C for 15 s and 60°C for 1min were performed with an (Stratgen real-time PCR detectionsystem). Internal and external control were used.

Diagnosis of HPV:

In control group: Diagnosis depends on detection of HPV16 antibody in the serum of 50 individuals in the control groups using ELISA kit (Abcam, UK).

Diagnosis of HPV by PCR form the tumor mass: DNA was extracted from frozen tumor tissue, and amplified according to venceslau et al. [6] using the following pairs of primers F' 5'CGTCCMARRGGAWACTGATC3', R' 5'GCMCAGGGWCATAAYAATGG3' that amplify 450pb [6]. 2% agarose gel stained with ehidium bromide and 50 bp DNA ladder (Qiagen, Germany) were used to detect the PCR product.

Diagnosis of *Schistosoma*

Control group: Diagnosis depends on detection of *Schistosoma* heamatopium egg in urine in 50 healthy individuals.

Cases: Schistosmal DNA was detected from tumor tissue obtained during cystoscope Extraction o the parasite DNA was done using (Qiagen). The PCR was carried out using the following primers (forward: 5′-GATCTCACCTATCAGACGAAAC-3′ and reverse: 5′-TCACAACGATACGACCAAC-3′), in 20 µl reaction volume containing 10 µL master mix (Fermantas, UK), 1 µM of each of the amplification primers and 5 µL of template DNA. Using the following protocol: denaturing step of 15 min at 95°C, followed by 33 cycles of 95°C for 30 sec, annealing temperature of 53°C for 1.5 min, and expansion at 72°C for 1 min, followed by a final extension step at 60°C for 5 min. The products were examined on a 2% agarose gel stained with ethidium bromide (10 mg/µL) and visualized with UV light. The size marker 50 bp ladder was used to estimate band size of 121bp [7].

Statistical analysis: Statistical analysis was performed using the Statistical Package for the Social Sciences for Windows (version 17.0; SPSS, Chicago, IL, USA). Data were expressed using descriptive statistic (mean± standard deviation) and were analyzed using One-way analysis of variance (ANOVA) test to compare different parameters between more than two groups. Relative risk was calculated to determine the risk of each infectious disease.

Results

During the period of the study from June 2013 to June 2015, 926 patients suffering from cancer attended Medical Oncology Department, Faculty of Medicine, Zagazig University, of those, 181 cases suffering from liver cancer, urinary bladder cancer, gastric cancer, head and neck cancer and cervical carcinoma figure 1-2 and figure 3.

According to our results, 147cases were associated with oncogenic infectious agents, this represent (15.8%) of all cancer cases (926) and (81.2%) of cases included in the study (181). The most common cases were presented with HCC (95 patients), followed by gastric cancer then urinary bladder cancer. Age range, mean and standard deviation were calculated; analysis of variance showed that there is no significant difference regarding age in different types of cancer $P > 0.05$ (Table 1).

The total number of males presented with cancers associated with oncogenic infectious was 114(77.5%). HCC was the first cause of cancer in males 81 cases followed by Gastric cancer 14 cases. While, The total number of Females presented with cancers associated with oncogenic infectious was 33 (22.4%), HCC was the first cause of cancer in females 14 cases followed by cervical cancer 8 cases, Number and percentage of distribution of different tumours in male and female are shown in Table 1 and Table 2.

When we evaluated infection as a risk factor for causing cancer, we found that studied infectious agents significantly increase the risk of cancer Relative risk (RR) is > 1 with P-value >0.05 except H. pylori and HBV which although having RR of 1.2 and 4.8 respectively, the calculated P-values were >0.05 as described in Table 3 and figure 2. Both HBV and HCV exert risk. Of the 95 cases associated with hepatitis viruses, 95 were infected with HCV, of these cases 5 were co-infected with both types of viruses.

Citation: Shabrawy RME, Abdelateef RS, Reheem AA, Salem AA (2016) The Role of Oncogenic Infectious Agents in Causing Liver, Stomach, Urinary Bladder, Head and Neck and Cervical Cancers. J Hum Virol Retrovirol 3(2): 00087. DOI: 10.15406/jhvrv.2016.03.00087

Table 1: Patients included in the study ad frequency of different types of cancers.

Site of Cancer	Different Types of Cancer Cancers			Age		
	Number	Male (No/Percentage)	Female (No/Percentage)	Range/ Mean± SD	F*	P
HCC	103	85 (82.5%)	18 (17.4%)	(40-75) 58.7±6.7	1.632	0.154
Urinary Bladder	24	19 (79.1%)	5 (20.8%)	(42-71) 60.6±9.6		
Gastric Cancer	26	17 (65.3%)	9 (34.6%)	(44-71) 57.1±9.2		
Head and Neck	16	12 (75%)	2 (25%)	(39-67) 55.7±9.9		
Cervical Cancer	12	------	12	(47-62) 54.6±7.5		
Total	181					

*F: F ratio of ANOVA

Table 2: Frequency of different cancers associated with infectious agents in males and females.

Site of Cancer	Total Number of Cases	Cancers Associated with Infectious Agents No/ Percentage	Male	Female
HCC	103	95 (92.2%)	81 (85.2%)	14 (14.7%)
Urinary bladder	24	15 (62.5%)	12 (80%)	3 (20%)
Gastric cancer	26	20 (77%)	14 (70%)	6 (30%)
Head and neck	16	9 (56.6%)	7 (77.7%)	2 (22.2%)
Cervical cancer	12	8 (66.6%)	------	8
Total	181	147 (81.2%)	114 (77.5%)	33 (22.4%)

Table 3: Risk factor for different infectious agents.

Infectious Agents	Site of Cancer/No	Case (No %)	Control (No %)	Relative Risk/ CI[1]	P-Value
HCV	HCC	95 (92.2%)	20 (20%)	4.6 (3.1-6.8)	<0.0001
HBV	HCC	5 (5%)	2 (2%)	4.8 (0.57 to 40.4)	0.148
H. pylori	Gastric Cancer	20 (77%)	31 (62%)	1.2 (0.91-1.6)	0. 621
S. heamatobium	Urinary Bladder	9 (37.5%)	1 (2%)	31 (4.38-222.4)	0.0006
HPV	Head and Neck	9 (56.2%)	9 (18%)	3.1 (1.5-6.5)	0.0023
HPV	Cervix	8 (66.6%)	9 (18%)	3.7 (1.8-7.56)	0.0003

[1]CI: Confidence Interval

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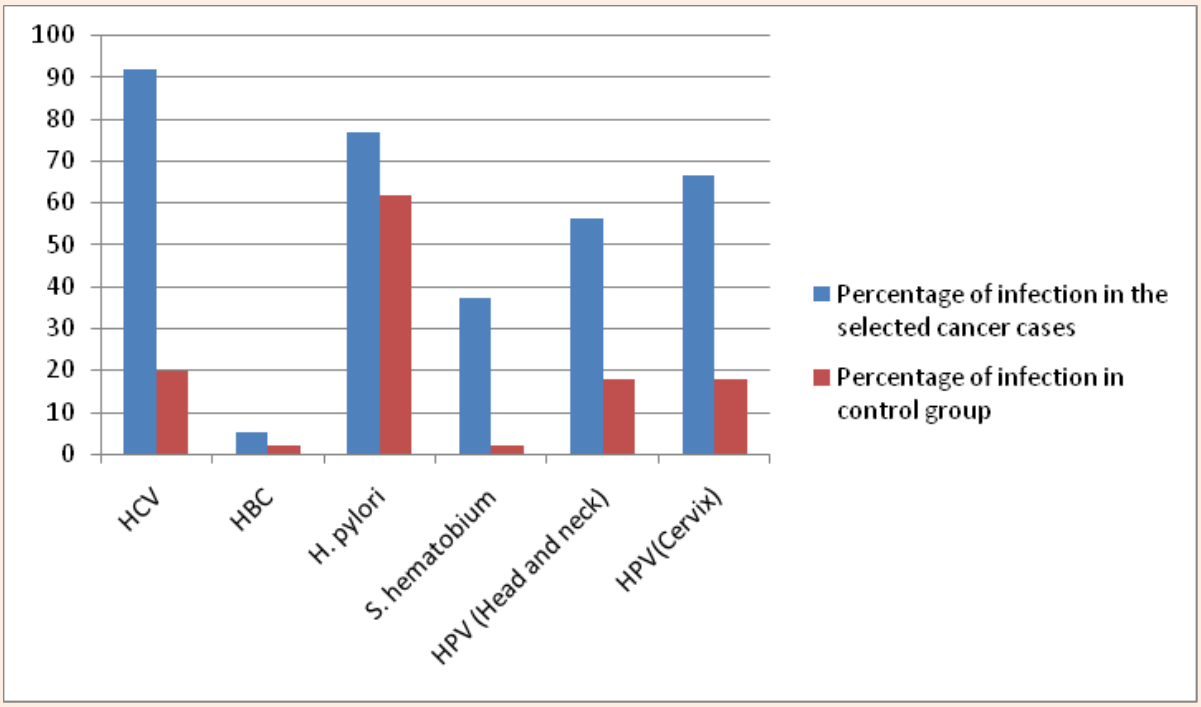

Figure 1: Relative Risk for different infectious agents.

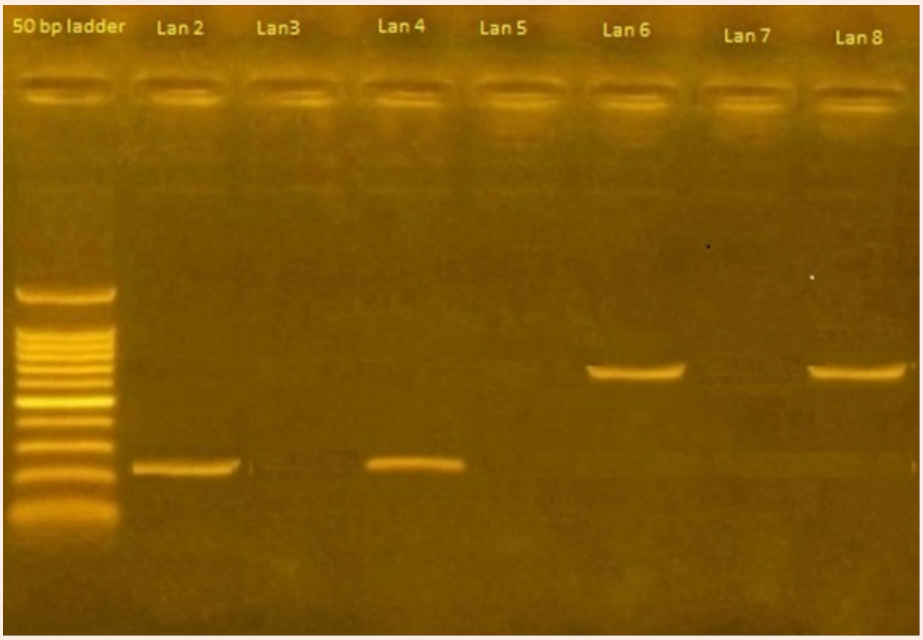

Figure 2: Agarose gel electrophoresis of HPV and *S. heamatopium* detection bands.

Lan 1: Shows 50 bp ladder.

Lan2 and 4: Shows 120bp of *S. heamatobium.*

Lan 6 and 8: Shows 450 bp of HPV.

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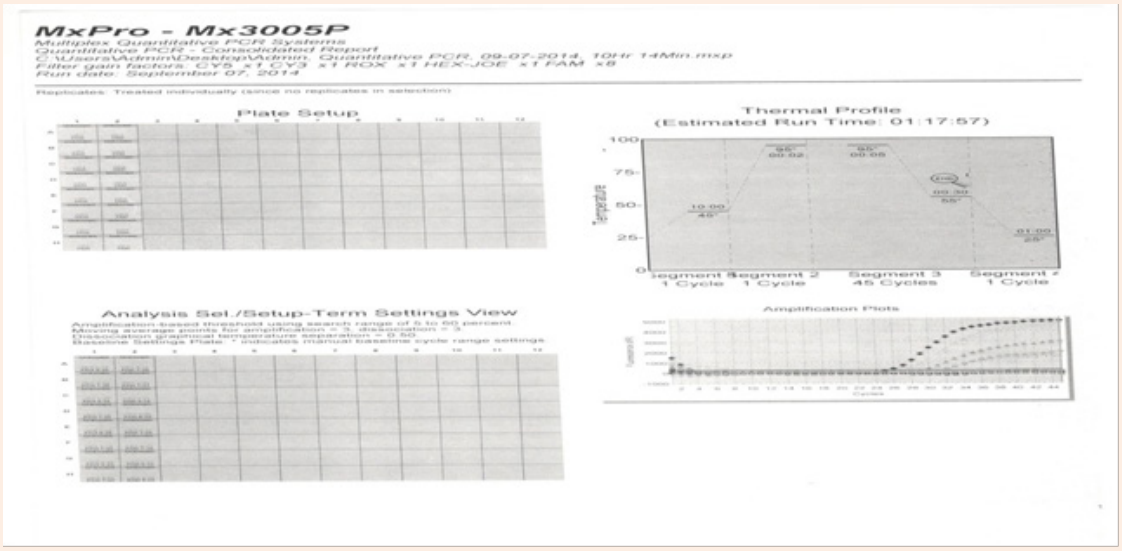

Figure 3: HCV real time report.

Discussion

According to our results, Cancers associated with (HCV, HBV, HPV and H. pylori and S. heamatopium) infections represent 15.8% of all cancer cases presented to Medical oncology department, Faculty of Medicine, Zagazig University. Where HCV, HBV and HPV viruses and S. heamatobium, H. pylori cause 181 cases. This incidence is accepted in view of the fact that Infection with human oncogenic viruses is the cause of ~10.8% of human cancers worldwide [8].

Hepatocellular carcinoma (HCC) is the fifth most common cancer and third most common cause of cancer related mortality worldwide [8]. According to this study, both HCV and HBV increase the risk of HCC more than four times. Both viruses, however, are known cause of chronic liver infections, which lead to liver cirrhosis and liver cancer [9-11].

The World Health Organization (WHO) estimated that worldwide, 240 million people are chronically infected with hepatitis B (WHO 2015), while 130-150 million people globally have chronic hepatitis C infection [11,12]. According to our results, Hepatoma is the most common solid tumor. This finding is consistent with other findings in many Egyptian regional registries liver cancer is reported to be the first cancer in men and the second in women. In Gharbiah population-based cancer registry, liver cancer represents 12.7% of male cancers and 3.4% of female cancers [1,12]. The relative high incidence of liver cell cancer in Egypt in our study and other studies reflects the high prevalence of viral hepatitis in Egypt[13]. These results are also supported by reports from other places of the world. In Ghana, for example, HCC is considered to be the first cause of cancer mortality [14]. Worldwide HBV is more accused to cause HCC than HCV, however this is not the case in this study and other studies in Egypt, as HCV incidence is highly variable among different geographic locations [15]. The Egyptian Ministry of Health estimated that the incidence of HCV infection among Egyptians is 10-15% of Egyptian population and about 2% are chronically infected with HBV [16]. In this study the RR of HCV to cause HCC was 4.6 with highly significant p value <0.05, regarding HBV, the RR was 4.8, however, the p value was not significant, this can be explained by small sample size.

World health organization considered *Schistosoma* as being carcinogenic to human [17]. In Egypt, bladder cancer accounts for 17% of all cancers in males and 5% in females. Carcinogenic mechanism may include either direct election of excessive inflammatory molecule caused by the parasite itself or the parasite may permit co-infection by other viruses or bacteria. Other factors like tobacco smoking and nitrosamines intake may also play a role [18].

In the current study, Urinary bladder cancer is the second most commonly occurring cancers in Males after HCC. Schistosoma heamatobium were detected in 9 cases with a RR of 31. It should be noted that prevalence of the parasite has markedly decreased from 70-80% in 1920 to 1.2% due to the successful mass treatment which was also accompanied by aggressive public awareness campaigns [19,20].

HPV is associated with several forms of cancers, oropharyngeal tumors and cervical tumors are of special interest due to increased incidence of these cancers worldwide [21-23]. According to our results 12 cases were diagnosed as cervical carcinoma. HPV16 infects 18% of the females in the control group and was detected in 66.6% of cervical cancer cases representing About four times higher risk for developing cancer in females In Egypt, current estimates indicate that every year, 514 women are diagnosed with cervical cancer and 299 die from the disease. Most cases of cervical carcinoma are due to HPV16 [24].

Worldwide, Cervical cancer is the second most common malignancy in women, over 466,000 new cases of cervical cancer are diagnosed and 231,000 women die from this type of cancer each year. High risk HPV is the major cause of 80% of this cancer [25]. Rueusser and colleague found that 99% of cancer cervix is attributed to HPV infection where HPV16 is the most prevalent genotype [26].

The role of High risk HPV subtypes in causing cancer cervix was the main activator for applying screening programs and vaccination to adolescent girls. Which have significantly reduced the rates of cancer cervix over the past 50 years [27]. Unfortunately, these strategies are not applied in Egypt till now. According to our results 26 cases were diagnosed as Head and neck carcinoma. Nine (56.2%) of them were associated with HPV16 infection. HPV doubled the risk of occurrence of head and neck cancer. The incidence of oropharyngeal SCC is increasing worldwide depending on the data obtained from reports from United States and Europe [28].

In Egypt, Gastric carcinoma is the 12th-14th most common cancer. *H. pylori* is considered carcinogenic bacteria that has been involved in the process of gastric abnormal growth and metaplasia [29-34]. According to the results of this study, *H. pylori* was detected in 62 % of control patients and in 77% of cases, calculated RR was 1.2, However, P value = 0.621 was no significant. These results can be explained by the high prevalence of the bacteria in the Egyptian population and so further studies with larger number of patients may be needed to accurately determine the role of the bacterium in causing gastric cancer in Egyptian population.

Conclusion

Infections play an important role in the occurrence of cancer, more effort and more resources must be allocated to screen, prevent and treat carcinogenic infections.

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