


# High Seroprevalence of Hepatitis C Virus Antibody in Breast Cancer Patients in Egypt

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## ABSTRACT

**BACKGROUND:** Hepatitis C virus (HCV) is a known risk factor for hepatocellular carcinoma. Several epidemiological studies have pointed out to an association of HCV infection with other extrahepatic malignancies. The role of chronic HCV in breast cancer causation is less clear. Egypt is an endemic area of HCV infection with resulting significant morbidity. The association between HCV status and breast cancer risk in Egyptian women is hitherto unknown.

**METHODS:** A retrospective study was performed. The prevalence of anti-HCV seropositivity was estimated in a sample of women with a breast cancer diagnosis, retrieved from the hospital records, and was compared to the raw data of a population study in Egypt. Anti-HCV negative and positive patients were compared regarding the disease course and outcome.

**RESULTS:** Retrospective analysis revealed a markedly high prevalence of anti-HCV seropositivity in young breast cancer patients. In patients younger than 45 years, 13.4% were anti-HCV positive. Seropositivity was 6-fold higher in these patients than in adult females of the same age without cancer diagnosis ( $P = .003$ ). The biological type, tumor size, nodal status, and disease-free survival were not affected by the patients' HCV status.

**CONCLUSION:** Young Egyptian breast cancer patients have a dramatically high prevalence of HCV seropositivity. Further population studies are strongly required to investigate the epidemiological association of these two significant health problems.

**KEYWORDS:** Breast cancer, hepatitis C virus, Egypt, oncovirus

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## Background

Since the classic description of the “milk virus” in rodents,<sup>1</sup> several authors have speculated a viral origin to breast cancer. Several groups have detected a similar sequence to the mouse mammary tumor virus (MMTV) in human breast cancer samples. Lawson and Glenn reviewed 17 publications that reported the examination of breast cancer tissues and normal breast samples for the presence of a conserved MMTV-specific sequence using polymerase chain reaction (PCR) technique.<sup>2</sup> A significant correlation of the viral-specific sequence with tumor tissue was consistent across the studies. Based on their meta-analysis of these studies, Lawson and Glenn concluded that the MMTV-specific sequence had a 15-fold higher prevalence in breast cancer tissues relative to normal breast tissue control.

Other viruses have been isolated from the human breast tissue and a link to cancer causation was suggested. A recent meta-analysis of 30 case-control studies reported a pooled association of Epstein-Barr virus (EBV) with the risk of breast cancer. In that meta-analysis, The odds ratio was 4.74 (95% CI: 2.92–7.69;  $P < .0001$ ).<sup>3</sup> This and other meta-analyses confirmed an epidemiologic association of breast cancer with EBV.<sup>3,4</sup> The human papillomavirus (HPV) is another DNA virus that has been evaluated for a possible breast cancer risk. Human papillomavirus is a well-known oncovirus with an established causal role in cancer of multiple mucosal sites.<sup>5</sup> However, evidence of an association with breast cancer is limited to anecdotal reports.<sup>6,7</sup> In recent years, the DNA of the bovine leukemia virus (BLV) was identified with increased frequency in breast cancer samples.<sup>8–10</sup>



In contrast to EBV and HPV, the BLV is a retrovirus that is oncogenic to cattle and has a great similarity to the human T-cell leukemia virus.<sup>11</sup> In a retrospective study from MD Anderson Cancer Center, DNA of BLV was more likely to be found in breast cancer specimens compared to normal or benign breast tissue. More importantly, viral DNA was also more common in premalignant breast lesions.<sup>12</sup> Although inconclusive, indications that breast cancer may be induced or at least facilitated by viral oncogenesis are still accumulating.

Hepatitis C virus is strongly associated with hepatocellular carcinoma (HCC), non-Hodgkin's lymphoma (NHL), and to less extent, other cancers.<sup>13-15</sup> The association of the virus with cancer incidence was particularly notable in geographical areas of endemic HCV infection.<sup>14,15</sup> An association with breast cancer is elusive. A population-based, case-control study from Taiwan reported a prevalence rate of HCV infection affecting 2.9% and 2.4% of breast cancer patients and healthy controls, respectively. The authors found a significant 2-fold increase in breast cancer risk in HCV positive women younger than 50 years.<sup>16</sup> In a longitudinal study from France, the authors reported a trend toward a higher prevalence of breast cancer in HCV-infected women that did not reach statistical significance.<sup>17</sup> Several cohort studies failed to detect an association between breast cancer risk and HCV status.<sup>18-21</sup> A US multi-center cohort of chronic liver patients was compared to Surveillance, Epidemiology, and End Results (SEER) data regarding cancer incidence, progression, and mortality. Hepatitis C virus-infected people had a 0.7 (95% CI=0.6-0.8) standardized rate ratio of breast cancer compared to SEER's (2006-2010) population. Age at diagnosis, stage, and cancer-related mortality did not statistically differ from the control group.<sup>18</sup> Similarly, in a large Danish population cohort, the standardized incidence ratio of breast cancer in HCV patients was 0.25 (95% CI=0.03-0.90).<sup>20</sup>

Given the uncertain relation of HCV infection with breast cancer risk, we undertook this study to determine the anti-HCV prevalence in breast cancer patients presented to a referral cancer hospital at Dakahlia, Egypt.

## Methods

This is a retrospective study. The study protocol was prospectively registered on the US National Library of Medicine Clinical Trials registration system (ClinicalTrials.gov ID: NCT04090164) and was approved by the Faculty of Medicine Institutional Research Board (protocol #R.18.02.34.R1.R2). The hospital medical record system was searched to identify patients with the "malignant neoplasm of the breast" diagnosis. All consecutive patients with this diagnosis treated at the surgery department from January 2013 through December 2018 were identified. The list of identified patients was alphabetically arranged and the data of an unselected sample of those patients were retrieved from the system.

The sample size was calculated based on finite population size (the total number of breast cancer patients in the records),

a hypothesized frequency of HCV 50% at 95% confidence level, and a design effect of 1, a sample of 343 breast cancer records needed for the study. To compensate for losses due to incomplete data, we included initially 650 records.

The following information was collected for all patients: name, age, hospital number, tumor stage information (T, N, M), tumor grade, tumor biological type, anti-HCV serological status at diagnosis, Hepatitis B surface antigen status at diagnosis, and the date and status at the last hospital visit.

Anti-HCV antibody was determined in patients' sera using the third-generation enzyme-linked immunosorbent assay (ELISA; Biotech, UK). Mann-Whitney, chi-square, and log-rank tests were used for comparison of anti-HCV positive with anti-HCV negative patients regarding age, tumor characteristics, and disease-free survival (DFS), respectively.

The raw data from a published population-based study<sup>22</sup> were used as a measurement of anti-HCV status in the non-cancer adult female population of Dakahlia (El-Ghitany; unpublished communication). Fisher's exact test was used to compare the proportions of seropositive cases in the breast cancer cohort to that of the Dakahlia population.

A significant difference was considered when less than 5% of the difference might occur by chance ( $P < .05$ ). Statistical calculations used Epi Info V.7 (www.cdc.gov), GraphPad Quick Calculator, and GraphPad Prism V.4 (GraphPad Software, Inc.) software.

## Results

In total, 3125 breast cancer patients were identified in the hospital's medical record. The information of an unselected sample of 650 patients was retrieved from the system; 245 patients with incomplete data were excluded, and the remaining 405 patients were subjected to further analysis.

In total, 88 patients (21.7%) were seropositive for HCV antibodies, 23 patients (5.7%) were hepatitis-B virus (HBV) positive, and none had concomitant HCV and HBV diagnosis. In patients younger than 45 years, anti-HCV seropositivity was detected in 17 out of 127 patients (13.4%). A significantly higher prevalence of anti-HCV (25.5%) was detected in patients 45 years or older ( $P < .01$ ) (Table 1).

The pathological disease characteristics were similar in both groups (Table 2). At the time of analysis, median survival has not been reached. The DFS was similar in both anti-HCV positive and negative patients: hazard ratio=1.650 (95% CI=0.7388-3.207;  $P = .2494$ ) (Figure 1).

Overall, 145 adult females from Dakahlia governorate were sampled in a published population-based cross-sectional study from 2015 to 2017.<sup>22</sup> Anti-HCV positive women constituted 10.3% of cases. In women younger than 45 years, only 2.2% were seropositive for HCV.

The percentage of seropositive subjects was statistically higher in breast cancer patients than in adult female Dakahlia residents without a cancer diagnosis. The difference was observed in the total cohort of the adult female population and

**Table 1.** Prevalence of anti-HCV serology in breast cancer patients.

	HCV SERONEGATIVE	HCV SEROPOSITIVE	P-VALUE
Median age (range)	49.0 (25-82)	55.5 (30-84)	MW $P < .0001$
Patients < 45 years	110 (86.6%)	17 (13.4%)	FE $P = .0062$
Patients $\geq$ 45 years	207 (74.5%)	71 (25.5%)	

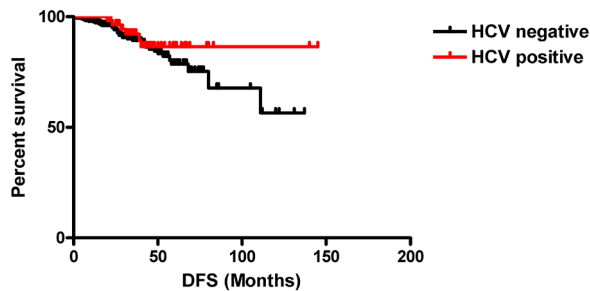
Abbreviations: FE, Fisher's exact test; HCV, hepatitis C virus; MW, Mann-Whitney test.

Hospital records were reviewed for the anti-HCV serology status of breast cancer patients at diagnosis. Positive anti-HCV serology correlated with older age at diagnosis.

**Table 2.** Clinicopathological criteria of breast cancers relative to anti-HCV serology status.

	HCV SERONEGATIVE	HCV SEROPOSITIVE	P-VALUE
<b>Biological type</b>			
HER2+	39 (12.3%)	14 (15.9%)	$\chi^2 P = .4814$
Luminal A	144 (45.4%)	33 (37.5%)	
Luminal B	98 (30.9%)	31 (35.2%)	
TripleNegt	28 (8.8%)	10 (11.4%)	
Unknown	8 (2.5%)	0	
<b>Clinical tumor size</b>			
Tis	2 (0.6%)	1 (1.1%)	$\chi^2 P = .8818$
T1	74 (23.3%)	25 (28.4%)	
T2	206 (65.0%)	54 (61.4%)	
T3	26 (8.2%)	7 (8.0%)	
T4	5 (1.6%)	1 (1.1%)	
Unknown	4 (1.3%)	0	
<b>Clinical node status</b>			
N0	128 (40.4%)	27 (30.7%)	$\chi^2 P = .0446$
N1	174 (54.9%)	53 (60.2%)	
N2	6 (1.9%)	6 (6.8%)	
N3	4 (1.3%)	2 (2.3%)	
Unknown	5 (1.6%)	0	
<b>Clinical node status</b>			
N0	128 (40.4%)	27 (30.7%)	FE $P = .0840$
N+	184 (59.0%)	61 (69.3%)	
<b>Grade</b>			
G I	4 (1.3%)	4 (4.5%)	$\chi^2 P = .0945$
G II	228 (71.9%)	64 (72.7%)	
G III	71 (22.4%)	15 (17.0%)	
Unknown	14 (4.4%)	5 (5.7%)	

Abbreviations: FE, Fisher's exact test; HCV, hepatitis C virus; HER2, human epidermal growth factor receptor 2; TripleNegt, triple negative;  $\chi^2$ , chi-square test. Anti-HCV serology status did not affect the clinicopathological criteria of breast cancers.



**Figure 1.** The disease-free survival of anti-HCV positive and negative breast cancer patients. Hazard Ratio = 1.650. (95% CI = 0.7388 to 3.207). P-value = 0.2494 (Log Rank test). DFS, disease-free survival; HCV, hepatitis C virus.

was even more notable in younger patients ( $P = .0027$  and  $P = .003$ , respectively) (Table 3).

## Discussion

In this study, we observed a high prevalence of anti-HCV in breast cancer patients treated at a referral cancer hospital in the Egyptian governorate of Dakahlia. Seropositivity for anti-HCV was particularly high in younger patients, in striking difference from the healthy adult population in this locality. In breast cancer patients younger than 45 years, the percent of seropositive individuals was 6-fold higher than the reported percentage in adult female Dakahlia residents without a cancer diagnosis.

Egypt has recorded the highest global rate of (HCV) infection.<sup>22</sup> Although the disease prevalence has been recently decreasing,<sup>23</sup> persistent infection rates are still high and it is believed that morbidity related to the virus will continue through the next decades.<sup>22</sup> Hepatitis C virus is an oncovirus and an established risk factor for HCC. The mechanism of HCV-induced liver carcinogenesis is less characterized than that of HBV. However, the high prevalence of HCV in the community linked most liver cancers in Egypt to HCV. Anti-HCV seropositivity affects 14.75% of Egyptian people.<sup>22</sup>

Males are much more affected than females.<sup>22,23</sup> Chronic HCV is tightly linked to the age of the population and increases dramatically after the age of 44.<sup>22,23</sup> In the 2015 Egyptian Health Issues Survey (EHIS), anti-HCV positive adult females constituted 9% and 14.8% of 40–44-year and 45–49-year female population, respectively.<sup>23</sup> At the Dakahlia governorate, 2.2% of healthy adult females younger than 45 years tested positive for anti-HCV (El-Ghitany, unpublished communications), in sharp contrast with our data of women affected with breast cancer.

While data from countries with low infection rates failed to show an association of breast cancer with HCV, the association of the virus with cancer incidence was particularly notable in geographical areas of endemic HCV infection.<sup>14</sup> A study from Taiwan linked HCV infection to breast cancer in younger patients. This population-based study found a non-significant increase in breast cancer risk in patients with viral hepatitis. However, HCV patients aged less than 50 years had a significant 2-fold higher risk of breast cancer in these authors' experience.<sup>16</sup> More recently, the same group conducted a population study to investigate the relation of HCV infection to colorectal cancer (CRC) risk. They detected a significantly higher prevalence of chronic HCV infection in CRC patients relative to matched controls. Similar to their earlier findings related to breast cancer, they reported a stronger association of CRC with HCV in patients younger than 45 years.<sup>15</sup>

Currently, there is a well-defined association of HCV with HCC<sup>24,25</sup> and NHL of B-cell origin,<sup>13,26–29</sup> (Table 4). Viral RNA is uncommonly detected in HCV-infected hepatocytes.<sup>24</sup> While desirable, detection of viral RNA is not mandatory to indicate an oncogenic viral role. Hepatitis C virus can induce carcinogenesis through various mechanisms, including induction of reactive oxygen species,<sup>30</sup> modulation of gene expression through viral micro RNA (miRNA),<sup>31</sup> and manipulation of host immune response. Viruses maintain persistent infection

**Table 3.** Prevalence of positive anti-HCV serology in breast cancer patients relative to healthy adult population of Dakahlia governorate.

ALL SUBJECTS			
FE $P = .0027$	HCV SERONEGATIVE	HCV SEROPOSITIVE	TOTAL
Healthy population	130 (89.7%)	15 (10.3%)	145
Breast cancer patients	317 (78.3%)	88 (21.7%)	405
SUBJECTS < 45 YEARS			
FE $P = .0030$	HCV SERONEGATIVE	HCV SEROPOSITIVE	TOTAL
Healthy population	91 (97.8%)	2 (2.2%)	93
Breast cancer patients	110 (86.6%)	17 (13.4%)	127

Abbreviations: FE, Fisher's exact test; HCV, hepatitis C virus.

Anti-HCV seropositivity was statistically higher in breast cancer patients relative to the healthy adult population of the locality. The difference was particularly evident in subjects younger than 45 years.

**Table 4.** Oncogenic role of HCV.

CANCER TYPE	REFERENCES
Hepatocellular carcinoma	Mitchell et al, <sup>24</sup> Goossens and Hoshida <sup>25</sup>
B-cell non-Hodgkin's lymphoma	Fiorino et al, <sup>13</sup> Su et al, <sup>26</sup> Zhu et al, <sup>27</sup> Schöllkopf et al, <sup>28</sup> and Carloni et al <sup>29</sup>

Abbreviation: HCV, hepatitis C virus.

Chronic HCV infection has an established role in hepatocellular carcinoma and B-cell non-Hodgkin's lymphoma (NHL). Less evidence exist for a possible role of HCV in breast, colorectal, and pancreatic carcinomas.<sup>13-21</sup>

through immune evasion strategies. The same strategies could prevent adequate tumor surveillance and induce proliferation.<sup>32</sup> Induction of cytokine production is a major mechanism of HCV-induced lymphoproliferation and B-cell lymphoma formation.<sup>29</sup>

Our findings indicate a significantly higher prevalence of anti-HCV positivity in breast cancer patients than in a healthy population and suggest the need for further investigations. It remains to be determined whether viral genomic material can be recovered from breast tissues and whether it is particularly abundant in cancer cells relative to normal breast cells.

Although HCV infection was previously correlated with poor prognostic markers in Egyptian breast cancer patients,<sup>33</sup> the present study directly provides survival data for the first time in breast cancer patients with HCV seropositivity.

In this study, we did not confirm persistent HCV infection with PCR testing. However, the third-generation ELISA test is highly specific for the presence of HCV antibodies.<sup>34</sup> In a cross-sectional study in a hospital setting, we cannot establish an epidemiologic causation between HCV and breast cancer. Further studies are needed to evaluate the impact of HCV infection on breast cancer risk in Egyptian women.

## Conclusion

In this study, we confirmed a high prevalence of anti-HCV seropositivity in Egyptian breast cancer patients, which was 6-fold higher than the prevalence in the healthy young adult female population. Our findings indicate the need for a case-control, population study to determine the role of HCV as a risk for breast cancer.

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## Author Contributions

OH (first author) conceived the study, analyzed and interpreted the data, and wrote the manuscript. EME analyzed and interpreted the data and wrote the manuscript, and other authors collected the data. All authors discussed the data and approved the manuscript. MO, GM, EAE, RH, AG, MMZ, and AN contributed equally to this work.

## Availability of Data and Material

The data at Ibn Sina Hospital Management System are not in the public domain. Data may be available from the corresponding author according to the Mansoura University policies.

## Consent for Publication

Patients are not identified in the manuscript and their confidentiality has been all respected. Consent for publication is not applicable.

## Ethical Approval and Consent to Participate

This is a retrospective study. The study was approved by the Mansoura Faculty of Medicine's Institutional Research Board (protocol #R.18.02.34.R1.R2).

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