American Journal of BioMedicine
AJBM 2016; 4(2):54-60
Research Article doi:10.18081/2333-5106/016-3/54-60

Potential role of cytomegalovirus in risk factor of breast cancer

Maitham Ghaly Yousif, Ph.D.

Abstract

It has been hypothesized that human cytomegalovirus (CMV) may be associated with many cancers in human. However, the role of CMV infection in breast cancer remains unclear. We aimed to assess whether CMV infection have a role in development of breast cancer. A 120 women presented to breast cancer clinic with breast mass. Full history from each woman was taken, full examination including breast examination and lymph-node. Blood was aspirated from each woman for detection of CMV IgG, IgM, tp53 and CA15-3 by ELISA. A 50 patients were documented to have breast cancer by histopathological examination. The study reveal that was heights level of CMV IgG and IgM among patients with malignant breast mass (12/50) and (8/50) respectively in other side the lowest level in benign tumor (6/50) and (2/50) respectively and high prevalence of CMV in breast cancer. In conclusion There is strong evidence suggest that CMV has an important role in the development of breast cancer.

Keywords: Cytomegalovirus; Breast cancer; Cancer

*Corresponding Author: Maitham G. Yousif. Electronic address: matham.yousif@qu.edu.iq
Department of Biology, College of Science, University of Al-Qadisiyah
Received September 13, 2015; accepted February 10, 2016; published March 21, 2016

Introduction

Worldwide, breast cancer is the most frequently diagnosed life-threatening cancer in women and the leading cause of cancer death among women. In the United States, breast cancer accounts for 29% of all cancers in women and is second only to lung cancer as a cause of cancer deaths [1, 2]. The understand of breast cancer etiology is that invasive cancers arise through a series of molecular alterations at the cell level. These alterations result in breast epithelial cells with immortal features and uncontrolled growth [3].

The development of breast cancer occurs as a result of numerous internal and external factors. Carcinogenesis of breast cancer has been associated with genetic predisposition, a family history of breast cancer, ethnicity (more common in the Caucasian population), dense breast tissue, lifestyle, hormonal contraception and treatment after menopause, and obesity [2]. External factors also play major roles during

Research Article doi:10.18081/2333-5106/016-3/54-60

initiation, development, and progression of cancer. The International Agency for Research on Cancer (IARC) reports that biological carcinogens cause 18-20% of cancers [3] Recently, the roles of infections during carcinogenesis in several types of oncological diseases were comprehensively summarized [4-6]. Cancer arises from one single cell. The transformation from a normal cell into a tumor cell is a multistage process, typically a progression from a pre-cancerous lesion to malignant tumors. These changes are the result of the interaction between a person's genetic factors and 3 categories of external agents, including:

- physical carcinogens, such as ultraviolet and ionizing radiation;
- chemical carcinogens, such as asbestos, components of tobacco smoke, aflatoxin (a food contaminant) and arsenic (a drinking water contaminant); and
- biological carcinogens, such as infections from certain viruses, bacteria or parasites.

Ageing is another fundamental factor for the development of cancer. The incidence of cancer rises dramatically with age, most likely due to a buildup of risks for specific cancers that increase with age. The overall risk accumulation is combined with the tendency for cellular repair mechanisms to be less effective as a person grows older. Development of treatment and prevention strategies to manage this disease critically depends on our understanding of cancer cells and the mechanism(s) through which they arise. In general terms, carcinogenesis represents a complex, multi-step process.

During the past 30 years it has become exceedingly apparent that several viruses play significant roles in the multistage development of human neoplasms; in fact, approximately 15% to 20% of cancers are associated with viral infections [7, 8]. Oncogenic viruses can contribute to different steps of the carcinogenic process, and the association of a virus with a given cancer can be anywhere from 15% to 100% [8]. Inflammatory breast cancer (IBC) is the most lethal form of breast cancer. previous results showed that IBC carcinoma tissues possess mixed human cytomegalovirus genotypes than non-IBC carcinoma tissues [9].

Materials and Methods

Blood Sampling

From each woman, about 5 mL of blood is collected without using heparin. The blood samples were centrifuged at 3000 rpm for 15 min and then the separated serum was submitted for Enzyme-Linked Immunosorbent Assay (ELISA) to detect of CMV IgG, IgM, tp53 and CA15-3 assay (ELISA) kits from R&D Systems (Minneapolis, MN, USA), using commercially available ELISA kits (signosis) according to the manufacturer's instructions [10].

Histopathological Analysis and examination

Breast tumor excisions or biopsies are performed in the operating room after which the material is sent for analysis to the pathology laboratory. The first step

Research Article doi:10.18081/2333-5106/016-3/54-60

of the tissue preparation process is formalin fixation and embedding in paraffin. From the paraffin blocks, sections with a thickness of 3–5µm are cut using a microtome (a high precision cutting instrument) and mounted on glass slides [11].

Statistical Analysis

Statistical analyses were performed using SPSS program. In all tests, $P < 0.05$ was considered to be statistically significant.

Results

A 120 women including in our study complain of breast mass, 50 of them were documented to have breast cancer by histopathological examination **Table 1** shows that among 70 women with benign breast mass, 62 women had p53 level less than 0.08 ng/ml while no patient with malignant tumor proved by histopathology had p53 level less than 0.08 ng/ml. CA15-3 level is high among patients with malignant breast tumor and level of CA15-3 more than 30 U/ml is noted in all cases while most patients (58/70) with benign breast mass have CA15-3 less than 30 U/ml, as in **Table 2**. Our study reveal that was highest level of CMV IgG and IgM among patients with malignant breast mass (12/50) and (8/50) respectively in other side lowest level in benign tumor (6/50) and (2/50) respectively, as in showed tin **Table 3**. Our results also indicate that most patients with positive to CMV IgG and CMV IgM were high level in P53 and CA15-3 as in shown in **Table 4.** The current results revealed that the most common patient with breast cancer among age group 46-55 years who infected with CMV IgG and CMV IgM and also rural residency as in **Table 5.**

P53	Benign tumor		Malignant tumor		Total	
	No	%	No	%	No	%
Less than 0.08 (ng/ml)	62	88.57			62	51.66
0.1-1.0(ng/ml)	3	4.28	7	14	10	8.33
1.1-10(ng/ml)	2	2.85	6	12	8	6.66
10.1-20(ng/ml)	2	2.85	5	10	7	5.83
20.1-30(ng/ml)			5	10	5	4.16
30.1-40(ng/ml)			3	6	3	2.5
40.1-50(ng/ml)			8	16	8	6.66
50.1-60(ng/ml)			3	6	3	2.5
60.1-70(ng/ml)			4	8	4	3.33
70.1-80(ng/ml)			3	6	3	2.5
Total	70	58.33	50	41.66	120	100

Table 1.
Comparison of p53 serum level among patients with benign and malignant breast mass.

Research Article doi:10.18081/2333-5106/016-3/54-60

CA15-3	Benign tumor		Malignant tumor		Total	
	No	%	No	%	No	%
less than 30 U/ml	58	82.85			58	48.33
31.5-35.1 U/ml	5	7.14	8	16	13	10.83
36.2-40.5 U/ml	3	3.28	7	14	10	8.33
40.7-45.4 U/ml	2	2.85	6	12	8	6.66
50.8-55.1 U/ml	1	1.42	4	8	5	4.16
60.7-65.2 U/ml	1	1.42	4	8	5	4.16
70.0-75.2 U/ml			9	18	9	7.5
80.2-85.9 U/ml			5	10	5	4.16
100.5-110.3 U/ml			6	12	6	5.0
120.3-130.0 U/ml			1	2	1	0.83
total	70		50	41.66	120	100

Table 2.
Comparison of CA15-3 serum level among patients with benign and malignant breast mass.

Test	Benign tumor		Malignant tumor		Total
	No	%	No	%	No
CMV IgG	6	8.57	12	24	12
CMV IgM	2	5.71	8	4	10

Table 3.
Relation of serum positive CMV IgG and IgM among patients with benign and malignant breast mass

Test	CMV IgG (+)		CMV IgM (+)	
	No	%	No	%
P53 (more than 0.08 ng/ml)	11	22.0	8	16.0
P53 (less than 0.08 ng/ml)	1	2.0	0	0.0
CA15-3 (more than 30 U/ml)	10	20.0	7	14.0
CA15-3 (less than 30 U/ml)	2	4.0	1	2.0

Table 4.
Relation serum positive of CMV with breast cancer with and without P53 and CA15-3 (50 patients)

Characteristics		CMV IgG (+)		CMV IgM (+)	
		No	%	No	%
Age group (Year)	Less than 25	2	16.66	0	0.0
	26-35	0	0.0	1	8.33
	36-45	0	0.0	1	8.33
	46-55	7	58.33	4	33.33
	More than 56	3	25.0	2	16.66
Residency	Rural	8	66.6	5	41.66
	Urban	4	33.33	3	25.0

Table 5.
Some demographic characteristics of patients with breast cancer in relation to CMV infection (12 patients)

Research Article doi:10.18081/2333-5106/016-3/54-60

Discussion

Our study shows that all patients with malignant breast mass had p53 more than 0.1 ng/ml and this is similar to result of Milena Gasco *et al*., 2002 [12] that showed molecular pathological analysis of specific components of the p53 pathway is likely to have diagnostic and prognostic utility in breast cancer but Philomena George 2011 [13] found that only about 50% of human cancers can be associated with a p53 mutation including cancers of the bladder, breast, cervix, colon, lung, liver, prostrate, and skin. And this difference may be related to method of detecting p53 and gene mutation.

All malignant breast mass in our study hade CA15-3 concentration ≥ 31.5 U/ml this is consistent with finding of Keyhani M.*et al*., 2005 [14] who found that a level of CA 15-3 more than 30 U/ml in a greater number of patients in the malignant group (6 out of 43), as compared to the normal controls (3out of 39).

Healthy women are expected to have CA 15-3 assay values below 30U/ml [15]. The upper limit of the range varies depending on the laboratory and kit used for the test. The elevation of CA 15-3 (values over 120kU/L) is found in over 30% of breast cancer patients with advanced disease [16]. Initial studies indicate that CA 15-3 is abnormal in the majority of patients with metastatic breast cancer and the antigen levels are correlated with changes in the clinical status of breast cancer patients [17].

Our results not agree with Arslan *et al*., 2000 [18] who found that sens-itivities and predictive values for base line CA15-3 were not satisfactory for primary of diagnostic breast cancer.

Recently infectious agents may have implicated in pathogenesis of malignant tumor including breast cancer. In present study we investigate infection with CMV and immunological markers in documented breast cancer proved by histopathology and results showed that 24% of patients with malignant tumor had CMV IgG positive while 4% had CMV IgM positive.

Our results go with Richardson *et al*., 2004 [19]. In a case-control study of CMV and EBV and breast cancer, mean CMV IgG levels were higher in cases than controls. Also Harkins *et al*., 2010 [20] found that 31/32 (97%) of cases of breast carcinoma in their study also had evidence of CMV infection and expression based upon immunohist-ochemistry.

Our results are consistent with a previous PCR-based report that indirectly suggested CMV infection is present in breast cancer [21]. In this study, the investigators analyzed 12 specimens of normal breast from a non-cancer group, and 62 samples of invas--ive ductal carcinoma from breast cancer patients for several DNA viruses using DNA PCR followed by Southern hybridization [21].

We conclude that CA 15-3 and P53 can be used for initial diagnosis of breast cancer. infection with CMV may play a role in pathogenesis of breast cancer and

there is strong correlation between CMV infection and both P53 and CA15-3 positive cases.

Competing interests

Author declare that I have no competing interest.

References

1. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. C*A Cancer J Clin* 2015;**65**(2):87-108.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin* 2015; **65**(1):5-29.
3. The Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. *Nature* 2012; **490**(7418):61-70.
4. Aituov B, Duisembekova A, Bulenova A, Alibek K. Pathogen-driven gastrointestinal cancers: Time for a change in treatment paradigm? *Infectious agents and cancer* 2012;**7**(1):18.
5. Alibek K, Kakpenova A, Baiken Y. Role of infectious agents in the carcinogenesis of brain and head and neck cancers. *Infectious agents and cancer* 2013;**8**(1):7.
6. Alibek K, Karatayeva N, Bekniyazov I. The role of infectious agents in urogenital cancers. *Infectious agents and cancer* 2012;**7**(1):35.
7. Hausen HZ. Viruses in human cancers. *Curr. Sci* 2001;**81**:523-527.
8. Parkin DM. The global health burden of infection associated cancers in the year 2002. *Int. J. Cancer* 2006;**118**:3030-3044.
9. Mohamed HT, Abdel Fattah HH, El-Shinawi M, et al. Inflammatory breast cancer: Mixed viral infections within carcinoma tissues and the expression of Ki-67 proliferation marker. *J Clin Oncol* 2015;**33**(suppl; abstr e22238).
10. Rakha EA, Reis-Filho JS, Baehner F, Dabbs DJ, Decker T. Breast cancer prognostic classification in the molecular era: The role of histological grade. *Breast Cancer Res* 2010;**12**:207.
11. Paya C, Humar A, Dominguez E et al. Efficacy and safety of valganciclovir vs. oral ganciclovir for prevention of cytomegalovirus disease in solid organ transplant recipients. *Am J Transplant* 2004; **4**:611-620.
12. Gasco M, Shami S, Crook T. The p53 pathway in breast cancer. *Breast Cancer Res* 2002,**4**:70-76.
13. George P. P53 how crucial is its role in cancer? *Int J Curr Pharm Res* 2011;**3**: 19-25.
14. Keyhani M, Nasizadeh S, Dehghannejad A. Serum Ca15-3 measurement in breast cancer patients before and after mastectomy. *Arch Iranian Med* 2005; **8**(4):263-266.
15. Goonetilleke KS, Siriwardena AK. Systematic review of carbohydrate antigen (CA 19-9) as a biochemical marker in the diagnosis of pancreatic cancer. *Eur J Surg Oncol* 2007;**33**(3):266-70.
16. Bast RC, Ravdin P, Hayes DF. Update of recommendations for the use of tumor markers in breast and colorectal cancer: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Onc* 2001;**19**(6):1865-78.
17. Gautam A, Verma S, Pantola C, Verma S. Utility of CA 15-3 as Diagnostic and Prognostic Marker in Breast Cancer. *IOSR Journal of Dental and Medical Sciences* 2015;**14**:17-20.
18. Arslan N, Serdar M, Deveci S, et al. Use CA15-3, CEA and prolactin for the primary diagnosis of breast cancer and correlation with the prognostic factors at the time of initial diagnosis. *Annals of nuclear medicine* 2000;**14**:395-399.
19. Richardson AK, Cox B, McCredie MR, et al. Cytomegalovirus, Epstein-Barr virus and risk of breast cancer before

Research Article doi:10.18081/2333-5106/016-3/54-60

age 40 years: a case-control study. *Br J Cancer* 2004;**90**(11):2149-52.

20. Harkins LE, Matlaf LA, Soroceanu L, et al. Detection of human cytomegalovirus in normaland neoplastic breast epithel - ium. *Herpesviridae* 2010;**1**(1):8.
21. Tsai JH1, Tsai CH, et al. Association of viral factors with non-familial breast cancer in Taiwan by comparison with non-cancerous, fibroadenoma, and thyr- oid tumor tissues. *J Med Virol* 2005;**75** (2):276-81.