

Leading Article

Association of Human Cytomegalovirus and Epstein-Barr Virus with Breast Cancer

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Breast cancer forms the most common cancer in women worldwide [1,2] and in Arab countries [3]. Breast cancer accounts for about 1/3 of the registered female cancer in Iraq [4] and with incidence rate of 31.1/ 100 000 in Iraqi women , while it was 18.4 for Iran, 22.4 for Saudi Arabia, 23.0 for Syria, 28.3 for Turkey, 47.0 for Jordan, and 47.7 for Kuwait [5,6]. Recent study in Iraq reported a trend for breast cancer to affect younger age group [7]. This study shows that the highest frequency of breast cancer (32.4%) was in women with age of 21-30 years. Unfortunately, 79.7% of breast cancer cases were in women with age of ≤ 40 years. In addition, 14.9% of breast cancer cases were in women with age of 16-18 years and 52.7% were in those with age of ≤ 30 years. This age shift pattern of breast cancer in Iraqi women was not consistent with previous studies in Iraq [6-12], Arab countries and globally [13,14]. The peak frequency of our study was 21-30 years, while previous studies in Iraq [15-21] indicated that breast cancer frequency peak was in fifth decade of life, in Asian countries in 40-50 years and it was 60-70 years in Western countries [22].

The mean age of women with breast cancer in our recent study was 30.6 ± 11.5 years and was not agreed to previous studies in Iraq [6,15-25], Arab countries [13,26] and globally [27]. Thus breast cancer diagnosis age was a decade earlier than previous Iraqi and Arab countries studies and two decade earlier than Western countries [7].

The high incidence of breast cancer in younger age group may be attributed to the environmental pollution in Iraq during the period from 1991 to date, which may act as a risk factor for breast cancer development [28-34]. In addition, possibility of that cancer may be of infectious origin may contribute to the increase in the cancer incidence in younger age group. Viruses was implicated to play a role in cancer induction [35-37]. *Herpesviridae* family has been implicated as a cause of breast cancer [1]. Both Human cytomegalovirus [HCMV] and Epstein –Barr virus [EBV] infections in Arab countries including Iraq was with high rate of infection [38-41]. Previous studies suggest that HCMV and EBV infections are linked with the development of breast cancer [42-45]. CMV transform cells *in vitro* [46-48] and thus may induce cancer *in vivo* through many

mechanisms [7], including their ability for induction of immunosuppression [49-50].

The association between HCMV and EBV infections and development of breast cancer depend on the detection of viral particle in breast cancer tissue and / or serological studies [36,37,44,51-58]. Previous studies found that HCMV was detected in 7.4% to 100% in breast cancer tissue [45,51,54,57,59-62], however, other studies did not detected CMV in breast cancer tissue [42,53,59]. In a recent study we detected HCMV DNA in 20% of breast cancer tissue by using PCR [63], which was lower to that reported by others [64,65] in Iraqi population. While EBV was detected in 26.7% in our recent study [63], however, other studies detected EBV in 6.5% to 35.25% in breast cancer tissue [43,55,60,66-80]. In addition, EBV detection rate in breast cancer tissue was the lowest in USA (18.27%) and the highest in Asia (35.25%) [81], while Zerki et al [82], reported that EBV was detected in 28% of Iraqi women and in 40% of Egyptian women. Furthermore, Hanna et al [82] detected EBV in 40% of breast cancer tissue in Iraqi women.

In our recent study [63], we found that mean serum and frequency of positivity for CMV IgG, EBV VCA IgG, EBV EBNA -1 IgG and heterophile antibodies were significantly higher in women with breast cancer as compared to controls. In addition, area under Receiver Operating Characteristic curve [ROC] and Odd Ratio [OR] confirmed an association between CMV and EBV infections and breast cancer. Previous studies from other geographical areas show high prevalence of IgG positivity as compared to controls [44,36,37,52,53]. In addition, EBV seropositivity and mean serum antibody were significantly associated with breast cancer [53,83-86]. However, other studies not confirmed such association [44,52].

In conclusion, HCMV and EBV may play a role in the development of breast cancer. These two viruses may be an etiology of breast cancer or it may induce immunosuppression [87] that enhance the development of breast cancer. Multiple viral infections may increase the risk of breast cancer development in women and viral co-infection may be an important mechanism that play a role in the induction of breast cancer as demonstrated by viral co-infection high prevalence in breast cancer tissue.

References

1. Alibek K, Kakpenova A, Mussabekova A, Sypabekova M, Karatayeva N. Role of viruses in the development of breast cancer. *Infect Agent Cancer* (2013) 8:32. doi:10.1186/1750-9378-8-32
2. WHO. Breast Cancer: prevention and control. <http://www.who.int/cancer/detection/breastcancer/en/index1.html>.
3. El Saghir NS, Khalil MK, Eid T, et al. Trends in epidemiology and management of breast cancer in developing Arab countries: a literature and registry analysis. *Int J Surg* 2007; 5:225-33.
4. Iraqi national cancer research center, Brief historical introduction, establishing the breast & cervical cancer research unit and the Iraqi National Cancer Research Center/Program, 2013.
5. Globocan. Breast cancer incidence and mortality worldwide, 2008. International Agency for Research on Cancer; 2010.

6. Al-Hashimi MM, Wang XJ. Breast cancer in Iraq, incidence trends from 2000-2009. *Asian Pacific J Cancer Prev* 2014;15:281-286.
7. Alsamarai AGM, Abdula SS. Breast cancer frequency rate shift toward younger age in IRAQ. *International J Scientific Research Science Engineering Technology* 2015;1 (5):407-414.
8. Alwan NA . Breast cancer: demographic characteristics and clinico-pathological presentation of patients in Iraq. *East Mediterr Health J* 2010;16: 1159-64.
9. Alwan N. Iraqi initiative of a regional comparative breast cancer research project in the Middle East. *J Cancer Biol Res* 2014;2:1016.
10. Mahmoud MM. Breast cancer in Kirkuk city, hormone receptors status (estrogen and progesterone) and Her2/Neu and their correlation with other pathologic prognostic variables. *Diyala J Med* 2014;6:1-14.
11. Alobaidi AHA, Jalaly A, Alsamarai AGM, Sarhan HH. Biomarkers in women with breast cancer: I. CEA, CA 15.3, CA 27-29, BRCA-1, BRCA-2 predictive value. *International J Scientific Research Science Engineering Technology* 2015; 1(4):442-449.
12. Alobaidi AHA, Jalaly A, Alsamarai AGM. Biomarkers in women with breast cancer:II. Hormones, calcium, vit D, glucose, and IGF predictive value. *World J Pharmacy Pharmaceutical Sciences* 2015;4 (8):74-100.
13. Najjar H, Easson A. Age at diagnosis of breast cancer in Arab nations. *Int J Surg* 2010;8:448-452.
14. Al Diab A, Qureshi S, Al Saleh KA, AlQahtani FH, Aleem A, et al . Review on breast cancer in the Kingdom of Saudi Arabia. *Midd East Sci Res* 2013;14:532-543.
15. Results of the Iraqi Cancer Registry. Iraqi Cancer Registry Center. Iraqi Cancer Board, Ministry of Health, 2004.
16. Al-Alwan N. A. S.: Clinicopathological evaluation of nuclear DNA ploidy and hormone receptor contents in breast tumors. Ph.D. thesis submitted to the college of medicine and the committee of post graduate studies of the University of Baghdad, 1998.
17. Al-Alwan N. A.: Iraqi breast cancer: A review on Patient Demographic Characteristics and Clinico-Pathological Presentation. Proceeding from the 27th San Antonio Breast Cancer Symposium. Dec.8-11, 2004. San Antonio, USA.
18. Al-Anbari S. S.: Correlation of the clinicopathological presentations in Iraqi breast cancer patients with the findings of biofield breast cancer diagnostic system (BDS), HER-2 and Ki-67 immunohistochemical expression, a thesis submitted to the college of medicine and the committee of post graduate studies of the University of Baghdad in partial fulfillment of the requirement for the degree of Ph. D. in Pathology.2009.
19. Hasoon S.: Correlation of the findings of biofield breast cancer diagnostic system (BDS) with clinicopathological parameters of mammary carcinoma in Iraq, a thesis submitted to Iraqi Board of Medical specialties in partial fulfillment of the requirement for the degree of fellowship of the Iraqi Board of Medical Specialization in Pathology, 2007.

20. Ameen A.: Breast cancer in Iraqi female patients a clinicopathological and immunohistochemical study, a thesis submitted to Iraqi Board of Medical specialties in partial fulfillment of the requirement for the degree of fellowship of the Iraqi Board of Medical Specialization in Pathology, 2009.
21. Ahmad N. Y.: Current status of breast cancer in Kurdish women in Erbil (Kurdistan of Iraq). Zanco J for medical sciences, 2004; 8: 13-23.
22. Leong SPL, Shen ZZ, Liu TJ, Agarwal G, Tajima T, et al. Is breast cancer the same disease in Asian and Western countries? World J Surg 2010;34:2308-2324.
23. Al-Alwany SHM, Ali SM. Molecular detection of human cytomegalovirus in Iraqi patients with breast cancer. Intern Nation J Advan Biol Res 2013;3:454-459.
24. Majid RA, Mohamed HA, Hassan HA, Abdulmahdi W, Rashed R, Hughson M. A population based study of Kurdish breast cancer in Northern Iraq: hormone receptor and HER2 status. A comparison with Arabic women and United States SEER data. BMC Women's Health 2012;12:16.
25. Chasib TJ, Hawaz M, Jasim NH. Evaluation of the estrogen and progesterone receptors in female breast cancer in respect to age, grade and stage. Basrah J Surg 2013;19:9-14.
26. Tarawneh M, Nimri O, Arkoob K, et al. Cancer Incidence in Jordan 2009. Non-Communicable Diseases Directorate, Jordan Cancer Registry. Ministry of Health, 2009.
27. Coleman MP, Forman D, Bryant H, et al. Cancer survival in Australia, Canada, Denmark, Norway, Sweden, and the UK, 1995–2007 (the International Cancer Benchmarking Partnership): an analysis of population-based cancer registry data. The Lancet 2011; 377:127-38.
28. Alwan A. Health in Iraq: The Current Situation, Our Vision for the Future and Areas of Work. Ministry of Health 2nd, December 2004.
http://www.who.int/hac/crises/irq/background/Iraq_Health_in_Iraq_second_edition.pdf?ua=1.
29. Al-Azzawi SN. Depleted Uranium radioactive contamination in Iraq: an overview. brusseltribunal.org/pdf/DU-Azzawi.pdf.
30. Al-rudainy LA, Ajeel NA, Al- saad HT. Depleted Uranium and incidence of cancer in Basrah: a preliminary ecological study. Med J Basrah Univ 2009;27:1-6.
31. Yacoub AAH, Ajeel NAH, Al-Waswasy MK. Incidence and pattern of malignant disease (excluding leukemia) during 1990–1997. The Medical Journal of Basrah University 1999; 17: 35-41.
32. Habib OS, Al- Ali Jk, Al-Wiswasy MK, Ajeel NAH. Theburden of cancer in Basrah: the state of the art – first report [Online]. 2005.
<http://www.basmedcol.com>
33. Al-Azzawi SN. Depleted Uranium Radioactive Contamination In Iraq: An Overview. Presented at The 3rd ICBUW International Conference Hiroshima, 2006. http://www.brusseltribunal.org/pdf/DUJ2_Souad.htm.

34. Al-Azzawi SN, Maarouf, B., and Hussein, S. Environmental consequences resulted from the use of DU weapons on soil and air at selected areas in al-Basrah governorate. *Journal of Engineering* 2002; 7 (1): 234 – 239. - See more at: <http://ijsrset.com/IJSRSET151553.php#sthash.62VWAI6w.dpuf>
35. Zur Hausen H. The search for infectious causes of human cancers: where and why. *Virology* (2009) 392:1–10.
36. Hsu CR, Lu TM, Chin LW, Yang CC. Possible DNA viral factors of human breast cancer. *Cancers* 2010;2:498-512.
37. Lawson JS, Heng B. Viruses and Breast cancer. *Cancers* 2010;2:752-772.
38. Hala MM, Alsamarai AGM, Aljumaili ZKM, Alobaidi AH. Association Between Cytomegalovirus Infection and Bad Obstetric Outcomes in Women from Kirkuk . *International Journal of Public Health Science (IJPHS)*2014;3:29-42.
39. Aljumaili ZK, Alsamarai AGM, Najem WS. Seroepidemiological Study of Toxoplasma, Rubella, Cytomegalovirus and Herpes Simplex in Women with Bad Obstetric History. *Midl East J Intern Med* 2013;6:21-33.
40. Aljumaili ZK, Alsamarai AM, Najem WS. Cytomegalovirus seroprevalence in women with bad obstetric history in Kirkuk, Iraq. *J Infect Public Health*. 2014 Jul-Aug;7(4):277-88.
41. Omer AR, Salih JI, Al- Nakshabandi AA. Frequency of blood born viral infections among leukemic patients in central Iraq. *Saudi Med J* 2011;32:56-61.
42. Antonsson A, Bialasiewicz S, Rockett RJ, Jacob K, Bennett IC, Sloots TP. Exploring the prevalence of ten polyomaviruses and two herpes viruses in breast cancer. *PLoS One* (2012) 7:e39842. doi:10.1371/journal.pone.0039842
43. Mazouni C, Fina F, Romain S, Ouafik L, Bonnier P, Brandone JM, et al. Epstein-Barr virus as a marker of biological aggressiveness in breast cancer. *Br J Cancer* (2011) 104:332–7.
44. Cox B, Richardson A, Graham P, Gislefoss RE, Jellum E, Rollag H. Breast cancer, cytomegalovirus and Epstein-Barr virus: a nested case-control study. *Br J Cancer* (2010) 102:1665–9.
45. Harkins LE, Matlaf LA, Soroceanu L, Klemm K, Britt WJ, Wang W, et al. Detection of human cytomegalovirus in normal and neoplastic breast epithelium. *Herpesviridae* (2010) 1:8. doi:10.1186/2042-4280-1-8.
46. Geder KM, Lausch R, O'Neill F, Rapp F. Oncogenic transformation of human embryo lung cells by human cytomegalovirus. *Science* (1976) 192:1134–7. doi:10.1126/science.179143.
47. Clanton DJ, Jariwalla RJ, Kress C, Rosenthal LJ. Neoplastic transformation by a cloned human cytomegalovirus DNA fragment uniquely homologous to one of the transforming regions of herpes simplex virus type 2. *Proc Natl Acad Sci U S A* 1983; 80:3826–30. .
48. Lepiller Q, Abbas W, Kumar A, Tripathy MK, Herbein G. HCMV activates the IL-6-JAK-STAT3 axis in HepG2 cells and primary human hepatocytes. *PLoS One* 2013; 8:e59591. doi:10.1371/journal.pone.0059591
49. Dziurzynski K, Chang SM, Heimberger AB, Kalejta RF, McGregor SR, et al . Consensus on the role of human cytomegalovirus in glioblastoma. *Neuro-oncology* 2012;14:246-255.

50. Loenen WA, Bruggeman CA, Wiertz EJ. Immune evasion by human cytomegalovirus : lessons in immunology and cell biology. *Seminars in Immunology* 2001;13:41-49.
51. Herbein G, Kumar A. The oncogenic potential of human cytomegalovirus and breast cancer. *Front Oncol* 2014;4:230. doi: 10.3389/fonc.2014.00230
52. Richardson A. Is breast cancer caused by late exposure to a common virus? *Med Hypotheses* (1997) 48:491–7.
53. Richardson AK, Currie MJ, Robinson BA, Morrin H, Phung Y, et al . Cytomegalovirus and Epstein-Barr virus in breast cancer. *PLOS ONE* 2015; 10(2):e0118989.doi:10.1371/journal.pone.0118989.
54. Taher C, de Boniface J, Mohammad AA, Religa P, Hartman J, Yaiw KC, et al. High prevalence of human cytomegalovirus proteins and nucleic acids in primary breast cancer and metastatic sentinel lymph nodes. *PLoS One* (2013) 8:e56795. doi:10.1371/journal.pone.0056795
55. Bonnet M, Guinebretiere JM, Kremmer E, Grunewald V, Benhamou E, et al. Detection of Epstein-Barr virus in invasive breast cancers. *J Natl Cancer Inst* 1999;1: 1376–1381.
56. Glaser SL, Hsu JL, Gulley M. Epstein-Barr virus and breast cancer: state of the evidence for viral carcinogenesis. *Cancer Epidemiology Biomarkers Prevention*, 2004; 13: 688-697.
57. Eghbali M, Ghane M, Mirinargesi M. Frequency of cytomegalovirus (CMV) in benign and malignant tumors. *Int J Mol Clin Microbiol*, 2012; 2: 175-179.
58. Mazouni C, Fina F, Romain S, Ouafik L, Bonnier P, Martin P. Outcome of Epstein-Barr virus associated primary breast cancer. *Mol Clin Oncol*, 2015; 3: 295-298.
59. Utrera-Barillas D, Valdez-Salazar HA, Gómez-Rangel D, Alvarado-Cabrero I, Aguilera P, Gómez-Delgado A, et al. Is human cytomegalovirus associated with breast cancer progression? *Infect Agent Cancer*, 2013; 8: 12. doi:10.1186/1750-9378-8-12.
60. Tsai J-H, Tsai C-H, Cheng M-H, Lin S-J, Xu F-L, et al. Association of viral factors with non-familial breast cancer in Taiwan by comparison with non-cancerous, fibroadenoma, and thyroid tumor tissues. *J Med Virol*, 2005; 75: 276–281.
61. El-Shinawi M, Mohamed HT, El-Ghonaimy EA, Tantawy M, Younis A, Schneider RJ, et al. Human cytomegalovirus infection enhances NF-kappaB/p65 signaling in antinflammatory breast cancer patients. *PloS one*, 2013; 8(2): e55755
62. Mohammed AH, Kadhim HS, Ghani AH. Investigation the role of human cytomegalovirus in the invasive ductal breast carcinoma. *Clin Cancer Invest J*, 2015; 4: 199-205.
63. Alsamarai AGM, Abdula SS, Alkhiat ZA. Role of Cytomrgalovirus and Epestein – Barr virus in breast cancer. *World J Pharmacy Pharmaceutical Sciences* 2015; (11):115-142.
64. Mohammed AH, Kadhim HS, Hussein AA. Investigation the role of human cytomegalovirus in the invasive ductal breast carcinoma using real time PCR. *Int J Current Microbiol Applied Sci*, 2015; 4: 537-542.
65. Al-Alwany SH, Ali SM. Molecular detection of human cytomegalovirus in Iraqi patients with breast cancer. *Int J Advan Bio Res*, 2013; 3: 454-459.
66. Labrecque LG, Barnes DM, Fentiman IS, Griffin BE. Epstein-Barr virus in epithelial cell tumors: a breast cancer study. *Cancer Res*, 1995; 55: 39–45.

67. Fawzy S, Sallam M, Awad NM. Detection of Epstein-Barr virus in breast carcinoma in Egyptian women. *Clin Biochem*, 2008; 41: 486–492.
68. Preciado MV, Chabay PA, De Matteo EN, Gonzalez P, Grinstein S, et al. Epstein-Barr virus in breast carcinoma in Argentina. *Arch Pathol Lab Med*, 2005; 129: 377–381.
69. Kalkan A, Ozdarendeli A, Bulut Y, Yekeler H, Cobanoglu B, et al. Investigation of Epstein-Barr virus DNA in formalin-fixed and paraffin embedded breast cancer tissues. *Medical principles and practice: international journal of the Kuwait University, Health Science Centre*, 2005; 14: 268–271.
70. Perrigoue JG, den Boon JA, Friedl A, Newton MA, Ahlquist P, et al. Lack of association between EBV and breast carcinoma. *Cancer Epidemiol Biomarkers Prev*, 2005; 14: 809–814.
71. Preciado MV. Lack of evidence for an association of Epstein-Barr virus infection with breast carcinoma—another point of view. *Breast Cancer Res*, 2003; 5: 6-7.
72. Grinstein S, Preciado MV, Gattuso P, Chabay PA, Warren WH, et al., Demonstration of Epstein-Barr virus in carcinomas of various sites. *Cancer Res*, 2002; 62: 4876–4878.
73. Fina F, Romain S, Ouafik L, Palmari J, Ben Ayed F, et al., Frequency and genome load of Epstein-Barr virus in 509 breast cancers from different geographical areas. *Br J Cancer*, 2001; 84: 783–790.
74. Subramanian C, Robertson ES. The metastatic suppressor Nm23-H1 interacts with EBNA3C at sequences located between the glutamine- and proline-rich domains and can cooperate in activation of transcription. *J Virol*, 2001; 76: 8702–8709.
75. Subramanian C, Knight JS, Robertson ES. The Epstein Barr nuclear antigen EBNA3C regulates transcription, cell transformation and cell migration. *Front Biosci*, 2002; 7: d704–716.
76. Kraus RJ, Mirocha SJ, Stephany HM, Puchalski JR, Mertz JE. Identification of a novel element involved in regulation of the lytic switch BZLF1 gene promoter of Epstein-Barr virus. *J Virol*, 2001; 75: 867–877.
77. Fan H, Gulley ML. Epstein-Barr viral load measurement as a marker of EBV-related disease. *Mol Diagn*, 2001; 6: 279–289.
78. Yasui Y, Potter JD, Stanford JL, Rossing MA, Winget MD, et al. Breast cancer risk and “delayed” primary Epstein-Barr virus infection. *Cancer Epidemiol Biomarkers Prev* 2001; 10: 9–16.
79. Trabelsi A, Rammeh S, Stita W, Mokni M, Mourou A, et al. Detection of Epstein-Barr virus in breast cancers with lymphoid stroma. *Ann Biol Clin*, 2008; 66: 59–62.
80. Aguayo F, Khan N, Koriyama C, Gonzalez C, Ampuero S, et al. Human papillomavirus and Epstein-Barr virus infections in breast cancer from Chile. *Infectious Agents Cancer*, 2011; 6: 7.
81. Huo Q, Zhang N, Yang Q. Epstein-Barr virus infection and sporadic breast cancer risk: a meta-analysis. *PLOS ONE*, 2012; 7(2): e31656. Doi:10.1371/journal.pone.0031656.
82. Zerki AN, Bahnassy AA, Mohamed WS, El-Kassem AR, El-Khalidi SJ, et al. Epstein-Barr virus and breast cancer: epidemiological and molecular study on Egyptian and Iraqi women. *J Egyptian Nat Cancer Institute* 2012;24:123-131.
83. Hanna BJ, Habib MA, Al-Mousawi HA. The expression of Epstein-Barr virus in breast cancer in relation to age. *Al-Kindy Col Med J.*, 2011; 7: 78-83.

84. Murray PG, Lissauer D, Junying J, Davies G, Moore S, Bell A, et al. Reactivity with A monoclonal antibody to Epstein-Barr virus (EBV) nuclear antigen 1 defines a subset of aggressive breast cancers in the absence of the EBV genome. *Cancer research*, 2003 May 1; 63(9): 2338–43.
85. Richardson AK, Cox B, McCredie MR, Dite GS, Chang JH, Gretig DM, et al. Cytomegalovirus, Epstein-Barr virus and risk of breast cancer before the age 40 years: a case control study. *Br J Cancer* 2004;90 (11):2149-52.
86. Joshi D, Buehring GC. Are viruses associated with human breast cancer? Scrutinizing the molecular evidence. *Breast Cancer Research Treatment* 23012;135:1-15.
87. Alsamarai AGM, Hassan HM, Alsalihi FG, Alobaidi AH, Aljumaili ZK. Toxoplasma gondii, rubella and cytomegalovirus co-infection as a risk factors for abnormal pregnancy outcome. *Middle East J Family Medicine*.2014;12:15-23.