

Association between HPV, CMV, EBV and HS viruses and breast cancer in Saudi Arabia

Abstract

Viruses including Human papillomavirus (HPV), Herpes Simples (HSV), Epstein Barr Virus (EBV), and Human Cytomegalovirus (CMV) infections are believed to be associated with many cancers. It is well established that infection by high-risk HPVs (HR-HPVs) is considered as a major cause of several human carcinomas including cervical carcinoma, head and neck, colorectal and breast cancers. HSV, EBV, and CMV were also reported to have some role in the pathogenesis of human cancers. The association between these viruses and human malignancies would necessitate the introduction of vaccines which may reduce the burden of viral associated cancers. The assessment of the contribution of HR-HPVs, HSV, EBV, and HCMV in the pathogenesis of breast cancer in the Kingdom of Saudi Arabia (KSA) is essential in order to evaluate the burden of these viruses, which has not been entirely studied yet. This review, presented an overview of the present epidemiological evidences regarding the presence of these viruses in human cancers with especial stress in breast cancer and the potential impact of these viruses in KSA. PubMed was searched using search terms included: Human papillomavirus (HPV), Herpes simplex virus, Herpes simplex virus 1, (HSV-1,2), Epstein Barr Virus (EBV), Human Cytomegalovirus (CMV), Breast cancer, and Saudi Arabia.

Keywords: HPVs, EBV, HS, CMV, Saudi Arabia

Volume 7 Issue 3 - 2017

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Received: December 19, 2016 | **Published:** February 15, 2017

Introduction

In recent years, there is a greater number of cancers are directly linked to infections with several viruses. It is well established that approximately 20% of the global human cancer can be attributed to virus infections.¹ Improvement in this field of research has transpired through analysis of cell signaling and growth control pathways that may be changed by the oncogenic viruses.² HPV is the commonest sexually transmitted infections that associated with cancers worldwide. About 96% of cases of cervical cancer were found positive for high-risk HPVs, especially types 16 and 18.³ HR-HPVs may have a contributory part in some breast cancers.^{4,5} HR-HPVs have been identified in benign breast tissues of the same type as in breast tumors, which later developed into cancer in the same patients.⁶

Nevertheless, only small proportion of HPV-positive cases progress in to malignancy, showing that HPV is indispensable but not enough in carcinogenesis. A number of biological and environmental cofactors have been involved in the progress of HPV-related carcinoma that includes co-infection with other sexually transmissible viruses. Such cofactors are expected to contribute to HPV persistent infection through miscellaneous mechanisms associated with immune control, effectiveness of HPV infection, and influences on tumor initiation and evolution.⁷ Therefore, HPV co-infection with other factors may also possess anti-tumor properties. Thus, this review beside HPV assessed the role of (HSV-1,2), HCMV, and EBV in breast cancer.

Herpes simplex virus type 2 (HSV-2) is the commonest cause of genital ulcers in several regions around the world. HSV-2 annually infect about 19.2million adults and adolescents aged 15–49years worldwide, which is more frequent among females.⁸ The higher infection rate among females is probably due to their more biological vulnerability to HSV-2 infection.⁹ HSV type 1 (HSV-1) usually causes non-sexually-transmitted oral herpes infection. EBV is an oncogenic virus that is associated with a number of cancers, such as Hodgkin's

lymphoma (HL), Burkett's lymphoma (BL), nasopharyngeal carcinoma (NPC), and gastric carcinoma.^{10,11} EBV contributes to the initiation, development and promotion of malignancies via the introduction of growth factors and oncogenic cytokine production.^{12–14}

HCMV is a ubiquitous herpes virus that infects 60%-100% of humans,^{15–17} with primary CMV infection arising most frequently through the first 2 decades of life. HCMV has been involved in the etiology of breast cancer and other serious diseases.^{18,19} Due to the lack of literature from KSA in this context it is important to shed some light on in-adequate research in the field in KSA. Therefore, the aim of this review was to present an overview of the present epidemiological evidence regarding the presence of these viruses in human cancers with especial stress in cancer and the potential impact of these viruses in KSA.

Human papillomavirus and breast cancer

HPVs are known to be among the major viruses associated with several cancers particularly cervical cancer.²⁰ Two groups of HPVs are categorized in to, high risk group, which is associated with the risk of cancers and low risk group, which is associated with generally self-limiting infections and do not lead to malignancy.^{21,22} High-risk HPVs (type 16, 18, 31, 33, 35, 39, 45, 51, 52, 55, 56, 58, 59, 68, 73, 82, and 83) are associated with the development of several cancers particularly cervical cancers,^{23,20} oral cancer²⁴ and esophageal cancer.²⁵ Furthermore, it was suggested that persistent infection with those viruses is essential for cervical precursors to progress into invasive cancers.^{26,27}

Moreover, it is necessary to state that the prevalence of HR-HPV infections is associated with specific global geographical distribution, which was established in several reports.^{20,28} However, there a lack of literature about HPVs and its associated cancers in the majority of the greater Middle East countries.^{29,3} The HPV genome encodes early

(E), late (L) proteins and contains a non-coding region (LCR). Early proteins consist of E1, E2, E4, E5, E6, and E7, while L1 and L2 are late proteins.³⁰ The E5, E6, and E7 onco-proteins, rise cellular change and perhaps lead to HR-HPV induced carcinogenesis.^{31,32} The E6 protein supplements the role of E7, and is supposed to prevent the initiation of apoptosis in response to unscheduled S-phase entry mediated by E7.³³ Breast cancer in Saudi females accounts for about 21% of all cancers.³⁴ Up to date there are limited reports regarding the etiology of breast cancer in Saudi Arabia.^{35,34} However, several previous studies revealed that HR-HPVs are existing in approximately 50% of breast cancers.^{36–39} Studies reporting breast carcinoma with positive HPVs shown that specific types of HR-HPV infections are associated with specific geographic locations.^{40,3}

It was found that the existence of HR-HPVs particularly types 16 and 18, in breast cancer, is associated with invasive breast carcinomas.^{39,41,42} It was also proved that E6/E7 onco-proteins of HR-HPV type 16 change non-invasive and non-metastatic breast carcinoma cells to invasive and metastatic pattern.⁴³ These studies confirm that HR-HPVs are existent and have significant roles in breast carcinogenesis and subsequent metastasis. Studies coherent to HPV from Saudi Arabia are linked to cervical cancers. Cervical cancer incidence is low in KSA, suggesting low prevalence to HPV infection because of environmental, cultural and genetic variances. HPV prevalence (82%) in cervical cancer is at the lower range of the global approximation (85 - 99%).⁴⁴ In a study assessed the prevalence and type distribution of HPV among Saudi and non-Saudi women attending routine examination, the overall prevalence of HPV was 9.8% in Saudi women, but was higher among women over 55years old, as well as among non-Saudi nationals.⁴⁵ Nevertheless, the inadequate accessible data from KSA show that HPV prevalence and genotypes' distribution in invasive cervical cancer display similar form as in the other neighboring countries.⁴⁶ Moreover, it was recently reported that more than 40% of cervical cancer cases are diagnosed at advanced stages because of the lack of a routine screening program in KSA.⁴⁷

However, deep search of literature has been performed in this review to find any relationship between HR-HPV and breast cancer, but unfortunately no study was found in this context. Nevertheless, studies from some Middle or Arabian countries have confirmed the association between HR-HPV and breast cancer.^{41,48, 49} In contrast to the global view, the incidence of cervical cancer is very low in Saudi Arabia, ranking number 12 between all cancers in females. This might be due to lack of routine screening which can be a cause of un-reported cases and hence presenting false low prevalence. Notably, presence of relatively not higher prevalence of some viruses, particular HPV among non-Saudi may predict the influence of some environmental factors. Therefore, such data indicates the association between HR-HPVs and human breast cancer in Saudi Arabia which, necessitate the need for future research in this regard.

Human herpes viruses

Human herpesviruses (HHVs) are largely disseminated pathogens that responsible of benign and malignant disease. Serological confirmation of infection with these viruses is found in the majority of the world's populations.^{50–54} Herpesviruses are large double-stranded DNA viruses. About 130 different types have been recognized, in mammals and other animals. There are eight HHVs include: herpes simplex virus (HSV-) 1, HSV-2, varicella zoster virus (VZV or HHV-3), Epstein–Barr virus (EBV or HHV-4), cytomegalovirus (CMV or HHV-5), HHV-6, HHV-7, and HHV-8. A typical characteristic of all these viruses is their capability of becoming latent, primarily in

ganglia of the nervous system and lymphoid tissue. Primary infection by any of these viruses, generally happening in childhood, is either asymptomatic or causes fever and rash of skin or mucous membranes; other organs might be infected on infrequent occasions. After primary infection, the virus becomes latent in ganglia or lymphoid tissue. Infection with each herpesvirus yields characteristic clinical features and imaging disorders.⁵⁵ HSV-1, EBV, and CMV are members of the *Herpesviridae* family that have common associations with orofacial diseases in humans. They are shelter in saliva asymptotically and consecutively at different rates and levels.⁵⁶

Herpes simplex virus and breast cancer

Although, HSV-1 mainly causes mouth, throat, face, eye, and central nervous system infections, whereas HSV-2 mostly causes anogenital infections, but both may cause infections in all areas.⁵⁷ In most instances HSV is never removed from the body by the immune system. After the initial infection, the virus enters the nerves at the site of primary infection, migrates to the cell body of the neuron, and becomes latent in the ganglion.⁵⁸ Several studies have indicated that viruses found in women with breast cancer may suggest that these viruses can be potential risk factors for breast cancer.^{59–61} In a study the existence of HSV-1 was found in 31.8% of breast carcinoma cases.⁶² Furthermore, HSV-1 contains of more than 80 genes that are expressed consecutively in a powerfully controlled cascade.^{63,64} Apoptosis of host cells denotes a vital defense mechanism against viral invasion by stopping viral replication and spreading. The extrinsic pathway of apoptosis initiation is generated by ligation of death receptors⁶⁵ or by injection of granzymes.⁶⁶ Intrinsic activates of apoptosis such as DNA damage, oxidative stress, deprivation of growth factors, and viral infection disturbs the integrity of the mitochondrial membrane, causing a release of cytochrome c into the cytoplasm.⁶⁷ It was proposed that, apoptosis related to HSV-1 latency and severity of the disease. There is a complicated balance between pro- and anti-apoptotic processes through HSV-1 infection. After anti-apoptotic pathways are suppressed, this balance is distressed and the cells die by apoptosis, and this is stated as HSV-1-dependent apoptosis.⁶⁸

However, recent studies have shown that oncolytic replication-competent HSV can infect tumor cells, replicating and killing the cells through cytopathic action and then diffusing within the tumor. Replication of oncolytic HSV results in the damage of the infected tumor cell and production of new virions, which are capable of infecting neighboring cells till actually all tumor cells are damaged. In a study examined the cytotoxicity of a third-generation oncolytic HSV vector, designated G47delta, in human breast cancer cell lines, in addition to in immortalized and normal breast cells. Anti-tumor effect of oncolytic herpes simplex virus G47delta was highly cytotoxic to breast cancer and immortalized breast cells in vitro at low multiplicities of infection (MOI), while normal breast cells remained viable 5days after infection. G47delta efficiently killed human breast cancer cells and immortalized breast cells but not normal breast cells.⁶⁹ Nevertheless, I didn't come across any study while searching about the burden of HSV in KSA. This fact should stimulate further studies in context.

Epstein barr virus and cancer

EBV is a herpesvirus and its genome encodes about 100 genes.⁷⁰ EBV is transmitted via saliva,⁷¹ and the prime infection is supposed to happen in the oral mucosa,⁷² classically early in life as a subclinical infection. When infection is delayed till late childhood or puberty, it reveals in 20–75% of individuals as infectious mononucleosis.^{73–75}

Through adulthood, over 90% of the people might be infected.⁷⁶ Primary EBV infection has a replicative (lytic) constituent noticeable by making of new virions. After the virus is controlled by immune reactions, latent infection keep on within a subset of B cells, such that healthy persons carry from 1 to 50 EBV genomes per million B cells.⁷⁷ This life-long latent infection is enabled by the virus' capacity to evade the immune surveillance,^{78,79} by expressing a few nuclear antigens (EBNA-1, -2, -3a, -3b, -3c, and -LP); latent membrane proteins (LMP-1, 2a, and -2b); and abundant, untranslated RNAs (EBER-1 and -2).⁸⁰

EBV was associated with the etiology of a number of cancers, such as, Burkitt lymphoma,⁸¹ Hodgkin, AIDS, and nasal NK/T-cell lymphomas, nasopharyngeal carcinoma, gastric adenocarcinoma, and leiomyosarcoma.⁷⁰ EBV is believed to play an active role in their development for several reasons. Viral LMP1 acts as a transforming oncogene in rodent fibroblasts.⁸²⁻⁸⁴ The majority of EBV linked cancers comprise a monoclonal form of the EBV genome in every single tumor cell.^{85,86} This denotes that infection either headed malignant transformation or considered a benefit to a previously malignant cell and its progeny. Therefore, EBV infection denotes a vital but not an enough phase in carcinogenesis, and epidemiological risk factors were also found to represent a supplementary risky role in this process.

EBV was found in breast tissues, where it was found in breast milk.⁸⁷ The transfection of EBV DNA stimulates evolution of breast milk cells.⁸⁸ EBV-related lymphomas occurred in the breast.⁸⁹⁻⁹² Breast cancer has epidemiological resemblances to young-adult Hodgkin lymphoma,⁹³⁻⁹⁵ though indication for breast cancer involves timing of initial EBV infection rather than viral oncogenesis.⁹³ EBV was found in benign breast tumors in immunosuppressed patients,⁹⁶ and in vitro, breast epithelial cells were infected by direct contact with EBV-bearing lymphoblastoid cell lines.⁹⁷ Moreover, the identification of EBV genes or gene products within breast tumors' tissues represents strong evidence for an EBV-breast cancer association.⁹⁸

However, a study reported that an EBV miRNA, EBV-miR-BART6-3p, could inhibit invasion and migration of EBV-related cancer cells and alter pressure fiber integrity, via inhibition of its target *LOC553103* expression. This results in the regulation of several mesenchymal transitions -related molecules, such as upregulated expression of E-cadherin, as well as downregulated β -catenin, Snail, and N-cadherin. This, in addition to metastatic markers, and invasion-associated genes, such as matrix metalloproteinase (*MMP2*) and *MMP9*. These findings evidenced for the first time that a new mechanism of EBV infection that EBV-miR-BART6-3p significantly disturbs cancer cell molecular phenotype.⁹⁹ There is a lack of literature from KSA regarding these issues. Non-published data on the association of EBV with breast cancer have stated conflicting results. One study has reported that EBV does not play any role in the pathogenesis of breast cancer.¹⁰⁰

Human cytomegalovirus

Human cytomegalovirus (HCMV) is a ubiquitous virus that is existing in a wide range of body fluids such as breast milk, saliva, urine, cervical secretions, and semen. It is characterized by its initial infection of epithelial cells at various body parts.¹⁰¹ CMV has been found to be a risk factor for several malignant diseases including glioma, neuroblastoma, and breast cancer.¹⁰² It is well established that not all individuals infected with CMV are similarly likely to develop malignancy, inferring the existence of host genetic factors that might temper the cancer-encouraging assets of the virus. CMV

has developed sophisticated approaches for escaping host immune-surveillance. One approach comprises encoding decoy Fc γ receptors (Fc γ R) that prevent the Fc γ -mediated effector functions, including antibody-dependent cellular Cytotoxicity.¹⁰³ CMV may be associated with breast cancer via processes that vary from those described for other virus-related cancers, such as the capability of the virus to escape immuno-surveillance through expressing only a few factors⁸⁰ and the likelihood of a 'hit and run' process where viral episome might be misplaced from malignant cells.^{104,105} Likewise, some probable approaches for CMV tumorigenesis have been recognized, such as the activities of virus-encoded interleukins, activation of telomerase, immunosuppression, and persistent infection leading to inflammation and the promotion of malignancy.¹⁰⁶

Viruses co-infections

HPV and EBV, are associated with 38% of all virus-associated cancers.¹⁰⁷ EBV and CMV are two ubiquitous and persistent herpesviruses commonly contracted during infancy.¹⁰⁸ After the resolution of primary infection, EBV and CMV become latent, express a highly restricted set of genes, and reside in B and myeloid cells, respectively. EBV and CMV can reactivate from latency to produce viral progeny.^{109,110} Despite the well-accepted causal relationship between persistent HPV infection and cervical cancer, and a continuously rising association between HPV and oropharyngeal cancers a link between HSV and HPV still remains. For example, persistent HPV infections are associated with the development of >99% of cervical cancers and \square 25% of head and neck squamous cell carcinomas (HNSCCs), whilst HSV-2 infections have been identified as cofactors in cervical cancer.¹¹¹

However, through our extensive review of literature from Saudi Arabia in this context, no study has reported any association between CMV and breast cancer. Such facts might not include or exclude incrimination of such viruses in the etiology of breast cancer in KSA. Therefore, this review may be a motivation for future search in this issue. Applicable level of knowledge, attitude, and policies are key essential for implementing a healthy lifestyle, influencing human behaviors, and accepting recently presented preventive measures. Regarding cancer-related viruses, the gap of knowledge of clinical presentation, risk factors, primary and secondary prevention has been recognized in numerous studies both in developed and developing countries.

Conclusion

HPV, CMV, EBV, and HSV are significantly associated with breast cancer, in terms of the oncogenetic mechanism and relapse-free survivals. Most HPV studies in KSA are mainly focused on the association between HPV and cervical cancer. The lack of literature in this context from Saudi Arabia necessitates the important of research in this field.

Acknowledgments

None.

Conflicts of interest

Author declares there are no conflicts of interest.

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