

## Review Article

# Role of Various Types of Viruses in Development of Early Aged Breast Cancer: A Brief Review

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## Abstract

World widely, Breast cancer is the most common type of cancer amongst women. External and internal factors both are responsible for beginning, advancement and development of breast cancer and from many studies it is well known that environmental elements have a significant effect in etiology of breast cancer. When it comes to environmental factors, effects of viruses are of great concern. Virus-associated cancer brings up a cancer in which the malicious conversion of the host's diseased cells results due to any viral infection. Until now it has learned that human papillomaviruses (HPV), Epstein-Barr (EBV) and mouse mammary tumor virus (MMTV) are the prime candidate viruses that act as agents of causing breast cancer. The initiator is only one in a sequence of steps essential for malignant cells development. Breast cancer could be a hereditary disease but it is expected to account for a very small percentage of breast cancer cases. From this idea it is obvious that there should be more efforts required in evaluating the role of viruses in carcinogenesis that could be characterized by further confounding and synergistic special effects of carcinogenic aspects still exact role of viruses in tumorigenesis is unclear, but it seem like that these are responsible for causing the disease.

## Keywords

Tumerogenesis, Breast Cancer, Human Papillomaviruses, Epstein-Barr, Mouse Mammary Tumor Virus

## Abbreviations

**HPV:** Human papillomavirus, **EBV:** Epstein-Barr virus, **HCV:** Hepatitis C virus, **HBV:** Hepatitis B virus, **HCMV:** Human cytomegalovirus, **MMTV:** Mouse mammary tumour virus, **SV40:** Simian virus 40, **Env protein:** Envelope protein, **BKV:** BK virus.

## Introduction

Globally, breast cancer is the most repeated cancer in women (Tarver, T., 2012). Due to its high prevalence, it constitutes the highest mortality that involves 458,000 deaths per year, with continuous increasing cases. The progression of breast cancer take place as result of frequent inner and external elements. Breast carcinogenesis has been

linked with inherent susceptibility (i.e. transmutations in BRCA1 or BRCA2 and some additional genes), ethnicity (mostly common in the Caucasian populace), family history of breast cancer, dense breast tissues, standard of living, use of contraceptives, obesity and any hormonal cure after menopause (Stewart, B., & Wild, C. P., 2016).

External factors are also responsible in and during beginning, progression and development of cancer. According to report of International Agency for Research on Cancer (IARC), the genetic carcinogens causes 20% of cancers (Parkin, D. M. 2006). Lately many different studies explain the roles of infections in breast related carcinogenesis in numerous kinds of oncological illnesses with broad summarization (Aituov, 2012; Alibek, 2013; Alibek, 2012). Therefore, we appraised several studies with endeavor in order to conclude that certain viruses might be associated in causation of breast tumorigenesis, reviewing relationship of breast malignances with retrovirus, papillomavirus, and herpesvirus. Many other mechanisms of tumorigenic exploit of transmittable mediators has been suggested including HIF1 $\alpha$ , NF- $\kappa$ B pathways, cofactors effects and STAT3 (Mantovani, et. al. 2018; de Martel, 2009; Porta, et. al. 2011; Aggarwal, et. al. 2006; Lu, et al 2006). Yet, facts and figures on virus-related existence and its oncogenical mechanisms described in the current literature are quiet varying while comprehensive tools of relations between these transmittable agents and the host cells till now have to be effusively revealed.

#### ***Herpesvirus Commonly Epstein-Barr Virus (EBV) And Human Cytomegalovirus (HCMV)***

HCMV is the most important agent in causation of breast cancer due its high oncogenical potential. EBV and HCMV of the Herpesviridae family has been ensnared as the reason for abnormal breast growths. EBV is been named class I cancer-causing agent according to report of IARC (Alibek, et. al. 2013). Examination of EBV's relationship with breast abnormal growth hazards indicates conflicting outcomes

(Amarante, M. K., & Watanabe, M. A. E. 2009). Mainly it is trusted that its inconsistencies emerge from utilized distinctive systems (Khan, et. al. 2011). In polymerase chain response based studies, progressive relationship was demonstrated (Amarante, M. K., & Watanabe, M. A. E. 2009), but the immediacy of EBV DNA was linked with further extreme types of breast malignancy (Mazouni, et. al. 2011). Interestingly, thinks about utilizing EBV encoded RNA as a part of situ hybridisation have demonstrated no or negative relationships notwithstanding with PCR results, were assured. In further studies, contiguity of EBV as result of EBER-ISH demonstrated 47.5% of cases. Be that as it may, the infection was confined to invading leucocytes in tumor microenvironment instead of present within tumor cells (Khan, et. al. 2011). This may recommend that causal relationship of the breast growth and EVB could be because of alterations in viral expression, bringing about changes in the tumor microenvironment. Reliable with this plausibility, expansion in IgA antibodies contrary to EBV virus-related capsid substance and atomic EBNA-1 was decidedly connected with breast malignancy hazard. In addition, EBNA-1 activity system could be connected with hereditary interferon- $\gamma$  polymorphisms (He, J. R., et. al 2011; He, J. R., et al 2012). Finally, factual relationship of infection in relation to expanded breast carcinoma danger has appeared after late examination of approximately 1535 cases (Huo, Q., Zhang, N., & Yang, Q. (2012).

HCMV has appeared to require in numerous tumors including threatening glioma, colorectal diseases, prostate and skin. Mother's milk includes the fundamental sequence of transmission of the infection, and bosom epithelium might thusly be a

noteworthy spot of idle as well as dynamic HCMV contamination. At the point when utilizing immunohistochemistry to think about biopsy instances from mammary tumor patients versus controls, demonstrated that the HCMV contamination might happen equally in epithelium of ordinary and infected patients. In any case, disease progression has a considerable higher rate upto 97% in breast malignancy cases (Harkins, L.E., et al 2010). There's likewise a relationship amongst rise of CMV IgG serum levels and breast related diseases (Cox, B., et al 2010). Investigation of GM IgG allotypes connected with certain tumor antigens, demonstrated that the utmost significant antigen in breast growth patients is HCMV, hypothesizing that the immediacy of specific seropositivity and allotype for HCMV can have aggregated impacts prompting breast malignancy progression (Pandey, J.P. et al 2012). Notwithstanding, CMV has not identified via late RT-PCR examination while researching pervasiveness of infections lying in mammary tumorigenesis (Antonsson, A. et al, 2012; Utrera-Barillas, D. et al 2013).

There are few methods which gives information about how does CMV bring about breast tumor initiation and movement. Firstly, it's been demonstrated that HCMV quality items influence cell cycle control, hindering apoptosis, initiate metastatic phenotype and angiogenesis, and cause expanded change frequency, in this manner covering with every single built up sign of growth cells. Also, HCMV displays immunosuppressive properties, prompting departure of tumor cells from insusceptible reconnaissance components (Dziurzynski, K. et.al. 2012; Loenen, W. A. et al 2001). Furthermore, particular activities of infection encoded IL could be embroiled. Late surveys might talked about function of

IL-10 in breast tumor. Curiously, breast tumor hindering and advancing impacts of the cytokine were appeared equally. IL-10 has been appeared differentially communicated in bosom tumor cells including invading leucocytes raising IL-10 serum level within bosom disease effectors. The way HCMV communicates with viral sample of IL-10 might prompt the conclusion that it can act as one of the instruments on bosom tumor advancement as a result of infection.

#### ***Polyomavirus: John Cunningham Virus (JCV) And Sv40***

Individuals from the polyoma-virus family, for example BK, SV40, Merkel cell polyomavirus and JCV have been connected with oncogenical ailments. As of late, 54 new solidified breast tumor tests were breaking down for nearness of 10 polyomaviruses (Antonsson, A. et al, 2012). The outcomes demonstrated no location of BK and JCV in obtrusive ductal sort carcinomas, rather than past reports. This distinction in results could be because of varying lab strategies and/or little specimen size. Strikingly, an interrelated BK infection (BKV), in similar contextual investigation, gave negative outcomes by uninterrupted sequencing (Hachana, et al 2012). Bosom malignancy tests were found to likewise negative MCPyV (Khan, G. 2012). In spite of a fact that, the nearness of polyomaviruses inside a tumor test can demonstrate a connection to tumor development, it's imperative to distinguish virus-related instruments leading to carcinogenesis. Beneath, we examined results demonstrating polyoma-viruses can specifically bring about cell immortalization, hyper methylation of tumor silencers, and unconstrained hereditary shifts. Consequently, they assume a vital part in mammary growth.

SV40 infection was first brought into people in the 1950s, when tainted polio-virus immunization were infused in a huge number of individuals. From that point forward, the inclusion of SV40 in different diseases (e.g., lung, mind, colon, prostate, and bosom) has been questionable (Carbone, M., et al 2003). That growths contains SV40 DNA, the most part of which was distinguished by PCR (Bergsagel, D. J., et al 1992; Galateau-Salle, F., et al 1998; Martini, F., et al. 1996). SV40 nearness were examined by PCR focusing on Tag in 109 bosom carcinomas, demonstrating SV40 DNA grouping accounts for 22% of growths. Immunohistochemical investigations affirmed the nearness of infection in tumor cells.

Improvement of bosom disease inside typical epithelial cells has been concentrated on in mice, and has been identified with consecutive changes in a tolerant microenvironment (Wu, M., et al. 2009). Mice and rodent models demonstrated SV40 T/t-antigen expressions in mammary epithelium results in pre-neoplastic sores that spread to prominent as well as metastatic tumors (Hoenerhoff, M. J., et al. 2011, Marcotte, R., & Muller, W. J. 2008). In addition, the immortalization of typical human mammary epithelial cells can be accomplished by SV40-affected change. SV40 substantial T-antigen contains a Rb-restricting area which causes adjusted quality expression and damage of p16(INK4a) manifestation (Huschtscha, L. I., et al.2001). In conclusion, SHP1, RASSF1A, TIMP3, and BRCA1 methylation were higher in SV40-positive cases, with more elevated amounts of P53 protein (Hachana, M., et al. 2009).

Further examinations of JCV in soft tissue of bosom malignancy patients demonstrated

JCV T-antigen DNA was identified in 23% of breast carcinoma tissues (Changkija, B., & Konwar, R. 2012). JCV T-antigen ties and influences wild sort p53, balances out b-catenin, and causes chromosomal precariousness. It enacts ATM-and ATR-intervened G2 checkpoint pathways and causes G2 cell cycle capture (Orba, Y., et al. 2010). Articulation of that protein additionally cause a metastatic phenotype in colo-rectal malignancies (Link, A., et al. 2009).

#### ***Papillomavirus: HPV***

HPV is a little DNA infection that is all the more regularly connected with cervical tumor in ladies. High-hazard HPV sorts 16 and 18 have been involved in 70% of all instances of cervical growth (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2007). HPV was additionally found in oral and urogenital carcinomas. In light of this proof, HPV was named an onco-virus by IARC. HPV for the most part contaminates keratinocytes and mucous layers. The infection can incorporate itself within host cell genome and utilize its interpretation apparatus to express popular proteins. Two of these early proteins, protein 6 and 7 (i.e., E6 and E7) deactivate tumor silencer proteins pRb and p53, separately, while early protein 5 (E5) could influence receptor tyrosine kinases thru connecting with cell layer (Wang, T., et al. 2012).

There is significant debate in regards to the HPV function in breast disease. A late control study outlined the aftereffects of atomic studies on the identification of high HPV hazards in breast tumor tests and reasoned that positive affiliations extended to 86% (Simões, P.W., et al. 2012). The larger part of sub-atomic studies utilized standard or settled PCR are used as

techniques for discovery utilizing industrially accessible preliminaries for L1 quality (codes used for capsid protein). Be that as it may, in the wake of getting positive results, groundworks for E6 and E7 qualities, or for sequencing, reported conceivable wellsprings of false positive or false negative results and impediment components connected with location strategies utilized as a part of those concentrates, for example, affirmation of DNA/RNA quality, and alteration for puzzling variables (Joshi, D., & Buehring, G. C. 2012). Hernandez et al. conducted a study and reported absence of L1 expressions in obtrusive butt-centric and also in cervical carcinomas utilizing immunohistochemical assessment (Hernandez, J., et al. 2011). This may likewise be the situation with cutting edge bosom malignancy tests. It is likewise conceivable that the degree of HPV embroiled in breast malignancy is higher than studies have reported. Besides, it has been accounted for as of late that HPV is available in human breast milk (Glenn, W. K., et al. 2012), which demonstrates that the infection to be sure can taint bosom tissue and amass in it. Conceivable components of HPV in breast disease carcinogenesis could be the same as in anogenital, head and neck tumors, by means of E6 and E7, or through an alternate path. High-chance HPV disease was connected with upregulated articulation of the Id-1 interpretation calculate (a group of helix-loop-helix translation elements) in forceful breast growth tissues, and recommended that the infection can instigate cell intrusion and metastasis by means of Id-1 (Yasmeen, A., et al. 2007; Akil, N., et al. 2008). Predictable with this probability, Frega et al. did not watch articulation of E6 and E7 in HPV-positive breast growth tissues (Frega, A., et al. 2011). Be that as it may, Dimri et al. could deify human

mammary epithelial cells in society utilizing E6 and E7 oncogenes (Dimri, G., Band, H., & Band, V. 2005).

Overexpression of c-MYC quality is a mark of the larger part of breast growths (Imyanitov, E. N., & Hanson, K. P. 2004), and there is a critical relationship between hoisted levels of c-Myc and HPV 16 disease. It was additionally demonstrated that HPV 18 incorporates in the vicinity of c-myc in cervical carcinoma (Ferber, M.J., et al. 2003), and that there is HPV-intervened actuation of c-Myc. E6 was not just found to raise levels of c-Myc, additionally could connect with the Myc complex and drive articulation of its objective qualities. Also, c-Myc prompts TERT (telomerase reverse transcriptase) translation within the sight of E6 (McMurray, H. R., & McCance, D. J. 2003), which prompts expanded telomerase action, and consequently deifies HPV-tainted cells. E7 was likewise found to hoist levels of c-Myc. This was seen in murine C127 cells contaminated with cow-like papillomavirus sort 1 (Fan, X., Liu, Y., & Chen, J. J. 2003) and in cells communicating HPV E7 (Gewin, L., & Galloway, D. A. 2001; DeFilippis, R. A., et al 2003). Wang et al. could discover that E7 improves c-Myc authoritative to the hTERT promoter, and recommended that E6 and E7 may work synergistically with a specific end goal to affect interpretation from the TERT promoter (Wang et al. 2007).

There is likewise a probability that inactive infections can be actuated by sex hormones. Aceto et al. identified HPV 16 in two instances of adolescent breast malignancy after menarche, and one instance of breast tumor after pregnancy and lactation. One instance of adolescent breast tumor was certain for both HPV 16 and HPV 18. They were likewise ready to recognize E6 in

fringe blood tests from patients with stage IV adolescent breast malignancy (Aceto, G.M., et al 2010). The likelihood of this DNA part originating from dormant urogenital disease was prohibited in light of the fact that this was just the case in cutting edge cervical carcinoma. This is predictable with the finding that steroid hormones can tie to a few locales in the control area of the HPV genome (LCR), upgrading articulation of E6 and E7 of high-hazard HPVs (de Villiers, E. M. 2003).

### ***Beta Retrovirus: Human Mammary Tumour Virus (HMTV)***

Examiners have attempted to decide the inclusion of HMTV in human breast diseases since 1943, when mouse mammary tumor infection (MMTV) was appeared to bring about mammary malignancies in mice (Bittner, J. J., & Imagawa, D. T. 1953). A few gatherings set up that MMTV-like groupings were available in human breast tumor tests, however truant in typical tissues (Pogo, B. G. T., & Holland, J. F. 1997). Besides, HMTV secluded from essential societies of breast disease cells have 95% homology thru MMTV. In mice, the HMTV homolog advances tumor development through the insertion mutagenesis of Wnt oncogenes, consequently advancing its initiation. In a late study, Wnt-1 expression was higher in examples which were certain for env, an envelope protein of MMTV, contrasted and env-negative examples (Lawson, J.S., et al. 2010). Env is ordinarily truant in typical tissues and present in breast growth tissues in both mice and human. Notwithstanding the Wnt district, the normal mix locales for MMTV were observed to be in loci 35 that contain areas of the Fgf and Rspo quality families. The destinations were as often as possible enacted in tumors instigated by MMTV, which principally brought about mammary premalignant

hyperplastic outgrowth. Different qualities were additionally deregulated, including Phf19 and Fox1. For instance, Phf19 expanded cell intrusion capacity and Fox1 advanced mooring autonomous province arrangement of MMTV contaminated cells. Around 20 of the HMTV regular insertion site-related qualities are deregulated and/or changed in human breast tumors (Callahan, R., et al. 2012). HMTV groupings for env, choke, and sagfrom patients with ductal carcinoma and mammary hyperplasia have been cloned and sequenced, uncovering the viral quality presence. The study estimated that the declaration of HMTV groupings could be a danger component for genome precariousness and for illness improvement (Zenit-Zhuravleva, E. G., et al. 2012). Additionally, the localisation of the MMTV envsequences to the cores of human breast disease cells showed that the provirus coordinated into growth cells (Lawson, J.S., et al. 2010). These MMTV viral groupings were more normal in conditions, for example, gestational (Wang, Y., et al. 2003) and familial breast malignancies, demonstrating that a provirus could be transmitted or acquired. What's more, geographic localisation may likewise assume a part in infection conveyance. For instance, the most noteworthy predominance of viral succession positive breast disease was in Tunisia, a Country known not the most elevated commonness of quickly advancing incendiary breast tumor on the planet (Labidi, S.I., et al. 2008). Provocative breast growth is a type of bosom malignancy in which the nearness of viral arrangements is observed to be connected with tumor forcefulness in patients (Pogo, B. G. T., et al 2010). At the point when the specialists inspected tests from patients with both sicknesses, they discovered viral successions in breast tissues and in addition in lymphoma tissues.

Cells contaminated with MMTV, in the same way as other disease cells, have exceedingly dynamic Src kinase. MMTV communicating cells escape apoptosis by initiation of safe receptor tyrosine kinase-based actuation theme intervened Src tyrosine kinase flagging pathways (Kim, H. H., et al. 2012) [67]. EBV (68%), HPV (half) and MMTV (78%) quality successions are available and exist together in numerous human breast diseases. Ordinary controls demonstrated these infections were likewise present in epithelial cells in human milk with less event contrasted with breast tumor cells. The nearness of these infections in breast disease is connected with more youthful period of conclusion and perhaps an expanded evaluation of breast malignancy (Floor S. L., et al. 2012). These discoveries give additional proof to a potential part of HMTV in bosom tumor, yet should be further explored.

### Conclusion

Carcinogenesis can include a few variables, including hereditary inclination, environment, and changes in the invulnerable framework. The part of infections in most basic tumors is absolutely critical, and as we would see it, exceptionally belittled. Infections can go about as immediate changing operators and as activating cofactors.

The most plausible instrument of carcinogenesis may include a blend of hereditary modifications, resistant framework dysfunctions, and viral diseases (Floor S. L., et al. 2012).

The information audited in this article accentuates the significance of further studies, which could illustrate viral instruments that can prompt bosom disease. It is likewise vital to get more clinical and epidemiological information on the blend of

components which may, together with disease, lead to growth advancement. The likelihood of incorporating antiviral operators in breast malignancy treatment ought to be considered, as they are in other disease related growth sorts, for example, hepatocellular carcinoma, cerebrum tumors, Kaposi sarcoma, nasopharyngeal carcinoma, and some hematopoietic diseases (Alibek, K., et al. 2012). Further examination of the part of infections in breast growth may bring about new revelations that could prompt better finding, aversion, and treatment of these diseases.

### Conflict of Interest

N/A

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N/A

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