Review Article

Human papilloma virus (HPV) profiles in breast cancer: future management

Md. Saimul Islam, Balarko Chakraborty, Chinmay Kumar Panda

Department of Oncogene Regulation, Chittaranjan National Cancer Institute, Kolkata, West Bengal, India

Contributions: (I) Conception and design: MS Islam, CK Panda; (II) Administrative support: CK Panda; (III) Collection and assembly of data: MS Islam, B Chakraborty; (IV) Data analysis and interpretation: MS Islam, B Chakraborty; (V) Manuscript writing: All authors; (VI) Final approval of manuscript: All authors.

Correspondence to: Chinmay Kumar Panda. Department of Oncogene Regulation, Chittaranjan National Cancer Institute, 37, S.P. Mukherjee Road, Kolkata, West Bengal 700026, India. Email: ckpanda.cnci@gmail.com.

Abstract: Breast cancer (BC) is frequent among women in worldwide as well as in India. Several studies have reported a wide variation (1.6–86.2%) in the frequency of incidence of human papillomavirus (HPV) infection in BC with high prevalence of high risk HPV16 subtype. HPV infection in breast can occur through different routes like body fluid or by micro-lesion of breast skin from genital/agential sites, though the actual mode of HPV transmission is not yet known in details. Frequent integration and sequence variation with low copy number of HPV16 were seen in this tumour. In addition, high frequencies of methylation in p97 promoter region of HPV16 were evident in this tumour. Novel splice variants of E6/E7 along with other common variants and their protein expression were seen in the tumour. This indicates the importance of HPV in this tumor, its early diagnosis and prognosis. Thus, HPV may be targeted through vaccination to control the disease. However, detailed analysis of HPV associated molecular pathogenesis of BC is warranted for proper therapeutic intervention.

Keywords: Breast cancer (BC); human papillomavirus (HPV); HPV transmission; management

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Introduction

Globally, breast cancer (BC) is the most common cancer among the women registering a total of 2.08 million new cases (11.6% of all new cases among females) in the year 2018 alone (1). Accounting for 15% of the total cancer-related deaths, it is the first most common cause of cancer deaths among women, worldwide (1). In Indian context, BC remains the most frequent (27.7%) cancer among women with the urban and metropolitan regions reporting high rates of incidence than rural region (1,2). Going by the numbers, in 2018 about 87,090 women died due to BC in India (11.1% of total women cancer) (1).

The BC has several etiological factors like prolonged or elevated exposure to estrogen due to early age of menarche (younger than 12 years), nulliparity, late age of menopause (over 55 years), exposure to high doses of ionizing radiation, regular alcohol consumption and high fat diet (3). Among the different etiological factors, infection with several viruses has also been reported in BC (4). However, these etiological factors were involved in only 20–50% of BC cases (5). Recently, different studies suggested association of human papillomavirus (HPV) with BC (6). But, frequency of HPV infection in BC varied widely (1.6–86%) among different studies (7,8). Inconsistent HPV infection was also reported in different molecular subtypes of BC (9,10). The possible mode of HPV transmission in breast and its role in breast carcinogenesis are not well studied. In this review our aim is to discuss the role of HPV infection in breast carcinogenesis and its future management.

Association of HPV infection with BC

Prevalence of HPV infection in breast

Recently, HPV infection in BC in different population around the world was reported by several authors (*Table 1*). However, many of them have not identified any HPV DNA in breast tumour. The prevalence of HPV in BC varied widely from 1.6–86.2% among the different continents of the world (7,8). According to screening methods, comparatively high frequency of HPV was detected in polymerase chain reaction (PCR) with sequencing or in-situ hybridization than only PCR method alone (*Figure 1A*). While a comparatively lower frequency of HPV DNA was found when the tissue source was formalin fixed paraffin-embedded tissue (PET) than the cryo-preserved tissue (CPT), the reason can be attributed towards the fact that the total DNA is severely degraded during the whole process of formalin fixation and paraffin embedding (47). So, this detection based difference in results might account partly for the wide range of frequency of HPV infection in BC, as reported by several studies (*Figure 1B*). On the other hand, HPV infection did not show significant variation among the different continents of the world (*Figure 1C*). To date, nine HPV types (HPV6, 11, 16, 18, 31, 33, 35, 45 and 52) are evident in BC across different population of the world. The prevalence of these HPV types showed variation among different population. The HPV16 was prevalent in American BC patients, whereas HPV18 and HPV33 were frequent in Australian and Chinese BC patients (*Table 1*). Apart from the above mentioned three subtypes, prevalence of other subtypes in BC patients among different population are as follows: HPV6/HPV11 in 5–12.6% patients of Iran and Spain (39,40), HPV31 in 1.5–11.5% patients of Brazil and UK (37,48), HPV35 in 16–19.2% of patients of Thailand and UK (37,49), HPV45 in 23% of UK BC patients (37) and HPV52 in 1.5–11% of Brazil, UK and Thailand patients (37,48,49).

HPV infection was also evident among the different subtypes of BC (*Table 2*). Among these subtypes, comparative high HPV infection was observed in Luminal B than other BC subtypes indicating that these cells might be favourable for HPV survival or may serve as an initial target of HPV infection due to the cooperative interaction with HER2 as well as ER (*Figure 1D*) (55,56). HPV infection in Triple Negative Breast Cancer (TNBC) varied from 15–50% in different studies, in which HPV16 was the most prevalent subtype (*Table 2*). In addition, HPV infection was also reported in adjacent normal and benign breast tissue (*Table 1*) (57) as well as in BC cell lines MDA-MB-175-VII, SK-BR-3 and MCF7 (20,38). HPV infection was also reported in nipple tissue, breast ductal lavage, nipple discharge and even from breast milk (8,58-62). Interestingly, presence of HPV was also observed in the serum-derived extracellular vesicles (58). In many studies, the presence of HPV genome in Indian, Italian and Australian BC patients was confirmed by sequencing analysis apart from PCR based methods (35,38,58).

Significant association between HPV infection, clinical grade, young age of the patients and histology were reported by different investigators worldwide (38,53,56), which further establish the clinical implication of HPV infection in BC. In addition, HPV associated poor prognosis of BC patients was also reported by our group and Ohba *et al.* (38,56).

Possible route of HPV infection in breast:

HPV infection can be transmitted through both sexual and nonsexual contacts. The genital HPV is mostly transmitted by direct skin-to-skin contact during sexual intercourse with an infected person (63). Generally, HPVs enter into the body through the skin and epidermal injuries, mucous membranes, skin abrasions and infects the cells of the basal layer of the stratified epithelium (64). The internalization of virions occurs slowly by endocytosis of clathrin coated vesicles in the presence of heparin sulphate. This ultimately leads to the transport of viral DNA to the nucleus and in the process disruption of the intracapsomeric disulphide bonds of the viral capsid occurs in the reducing environment of the cell (65-70). However, there can be three possible mode of HPV infection in breast tissue (*Figure 2*). According to the first one, HPV may be transmitted to breast from the genital region of the patients having a previous history of HPV-positive uterine cervical cancer (CACX) through blood, lymphatic systems or any other body fluid (71). It may be the case where a secondary malignant transformation of breast tissue could occur by an HPV infected malignant cell, which is derived from the primary tumour of any other site (72,73). It may also be due to spill over of HPV virion to the circulation system from HPV infected primary tumour site (74). As per the second mechanism, transmission of HPV can occur to breast from any oral site due to oral sexual practices (46). Third one suggests that the transmission of HPV may occur to breast by nipple or micro-lesion of breast skin due to genital-breast sexual activity (75,76).

Table 1 Worldwide HPV prevalence in breast tumour and adjacent normal breast tissue

Country	Benign	Breast tumour					Adjacent normal breast	Tissue preservation type	Methods of detection
		Malignant							
	HPV (%)	HPV (%)	HPV16 (%)	HPV18 (%)	HPV33 (%)	Other HPV (%)	HPV (%)		
China [Yu *et al*. 1999] (11)	1/20, 5.0	18/52, 34.6	1/52, 1.9	0/52, 0.0	–	–	–	PET	PCR/Southern
China [Yu *et al*. 2000] (12)	4/72, 5.0	14/32, 43.8	–	–	14/32, 43.8	–	–	PET	PCR/Southern
USA [de Villiers *et al*. 2004] (8)		25/29, 86.2	3/29, 10.3	0/29. 0.0	0/29,0.0	12/25, 48.0	–	PET	PCR/In-situ
Brazil [Damin *et al*. 2004] (13)	0/41, 0.0	25/101, 24.7	14/101, 13.8	10/101, 9.9	–	–	–	PET	PCR/Seq
Turkey [Gumus *et al*. 2006] (14)		37/50, 74.0	–	20/50, 40.0	35/50, 70.0	–	16/50, 32.0	CPT	PCR
Greece [Kroupis *et al*. 2006] (15)		17/107, 15.9	14/17, 67.0	–	–	7/17, 41.1	–	CPT	PCR
Korea [Choi *et al*. 2007] (16)		8/123, 6.5	–	–	–	–	0/31, 0.0	PET	PCR/Chip
China [Tsai *et al*. 2005] (17)		8/62, 12.9	–	–	–	–	8\62 12.9	CPT	PCR/Southern
Japan [Khan *et al*. 2008] (18)		26/124, 20.9	24/26, 92.3	3/124, 2.4	1/124, 0.8	–	0/11. 0.0	PET	PCR
Mexico [de León DC *et al*. 2009] (19)		15/51, 29.4	10/51, 19.6	3/51, 5.8	–	–	0/43. 0.0	PET	PCR
Australia [Heng *et al*. 2009] (20)		1/26, 3.8	–	–	–	–	–	PET	PCR/In-situ
China [He *et al*. 2009] (21)		24/40, 60.0	–	–	–	–	1/20. 5.0	CPT	PCR
Mexico [Mendizabal-Ruiz *et al*. 2009] (22)		3/67, 4.4	–	–	–	–	0/40, 0.0	PET	PCR
Mexico [Herrera-Goepfert *et al*. 2011] (23)		6/60, 10.0	6/60, 10.0	–	–	–	7/60, 11.6	PET	PCR
China [Mou *et al*. 2011] (24)		4/62, 6.4	3/62, 4.8	1/62, 1.6	–	–	0/46, 0.0	CPT	PCR
Italy [Frega *et al*. 2012] (25)		9/31, 29.0	–	–	–	–	0/12	PET	INNO-Lipa HPV
Australia [Glenn *et al*. 2012] (26)		25/50, 50.0	25/50, 50.0	–	–	–	8/40, 20.0	CPT	PCR
Iran [Sigaroodi *et al*. 2012] (27)		15/58, 25.8	4/79, 5.0	4/79, 5.0	–	–	1/41, 2.4	PET	PCR/Seq
China [Liang *et al*. 2013] (28)		48/224, 21.4	–	–	–	–	6/37, 16.2	Lump	HC2
China [Wang *et al*. 2014] (29)	2/2, 100.0	7/7,100.0	–	–	–	–	–	CPT	HC/seq
Iraq [Ali *et al*. 2014] (30)		60/129, 46.5	33/129, 25.5	35/129, 27.1	16/129, 12.4	–	3/44, 6.8	PET	In-situ
Iran [Ahangar-Oskouee *et al*. 2014] (31)		22/65, 33.8	1/65, 1.5	–	–	–	0/65, 0.0	PET	PCR/Seq
Iran [Manzouri *et al*. 2014] (32)		10/55, 18.1	2/55, 3.6	1/55, 1.8	1/55, 1.8	–	7/51, 13.7	PET	PCR
China [Peng *et al*. 2014] (33)		2/100, 2.0	2/100, 2.0	–	–	–	0/50, 0.0	CPT	MS-PCR
China [Fu *et al*. 2015] (34)		25/169, 14.7	–	–	–	–	1/83, 1.2	PET	PCR

Table 1 (*continued*)

Table 1 (*continued*)

Country	Breast tumour						Adjacent normal breast	Tissue preservation type	Methods of detection
	Benign	Malignant							
	HPV (%)	HPV (%)	HPV16 (%)	HPV18 (%)	HPV33 (%)	Other HPV (%)	HPV (%)		
China [Li *et al*. 2015] (7)		3/187, 1.6	–	–	–	–	0/92, 0.0	PET	PCR/Seq
Australia [Lawson *et al*. 2015] (35)	29/40, 72.5	29/40, 72.5	4/40, 10.0	22/40, 55.0	8/40, 20.0	–	6/20, 30.0	PET	PCR/Seq
Australia [Ngan *et al*. 2015] (36)	23/31, 74.1	24/31, 77.4	3/31, 9.6	21/31, 67.7	4/31, 12.9	–	–	PET	PCR/Seq
UK [Salman *et al*. 2017] (37)	6/36, 16.6	35/74, 47.2	7/35, 20.0	8/35, 22.8	3/35, 8.5	25/35, 71.4	–	CPT	PCR/Seq
India [Islam *et al*. 2017] (38)	5/7, 71	203/213, 64.8	120/174, 69	61/174, 35.0	5/174, 2.9	–	2/21, 9.5	CPT	PCR/Southern
Spain [Delgado-García *et al*. 2017] (39)		130/251, 51.8	–	–	–	–	49/186. 26.3	PET	PCR
Iran [Khodabandehlou *et al*. 2019] (40)		35/72, 48.6	–	–	–	–	5/36, 16.1	CPT	PCR
UK [Wrede *et al*. 1992] (41)	–	0/80, 0.0	0/80, 0.0	0/80, 0.0	0/80, 0.0	–	–	PET	PCR
USA [Bratthauer *et al*. 1992] (42)	–	0/13, 0.0	0/13, 0.0	0/13, 0.0	0/13, 0.0	0/13, 0.0	0/15, 0.0	PET	PCR
India [Gopalkrishna *et al*. 1996] (43)	–	0/25, 0.0	0/25, 0.0	0/25, 0.0	–	–	0/5, 0.0	FNAC	PCR
Switzerland [Lindel *et al*. 2007] (44)	–	0/81, 0.0	0/81, 0.0	0/81, 0.0	0/81, 0.0	0/81, 0.0	–	PET	PCR
France [de Cremoux *et al*. 2008] (45)	–	0/50, 0.0	0/50, 0.0	0/50, 0.0	0/50, 0.0	0/50, 0.0	–	CPT	PCR
China [Chang *et al*. 2012] (46)	–	0/48, 0.0	–	–	–	–	3/30, 10.0	PET	PCR

PCR, polymerase chain reaction; PCR/Seq, polymerase chain reaction followed by sequencing; PCR/southern, polymerase chain reaction followed by Southern blot; PCR/in-situ, PCR followed by in-situ hybridisation; MS-PCR, mutagenically separated PCR; HC2, hybrid capture 2; PET, paraffin-embedment tissue; CPT, cryo preserve tissue.

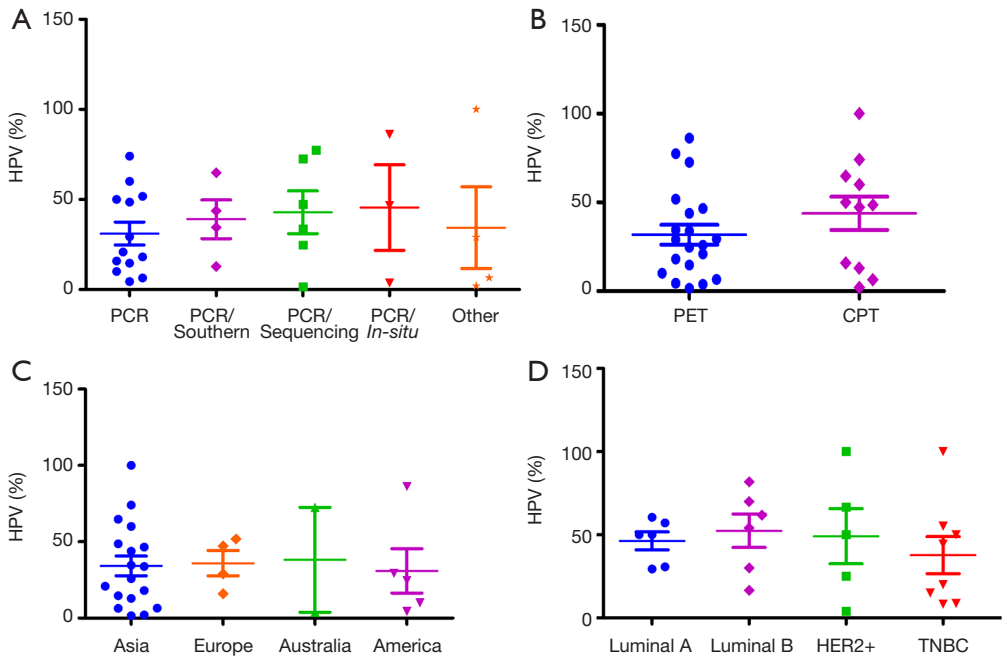

Figure 1 HPV prevalence in breast cancer in worldwide. (A) Frequency of HPV among the methods of detection. (B) Frequency of HPV among the preservation type of tissue samples. (C) Distribution of HPV among different continents of the world. (D) Frequency of HPV among different subtypes of breast cancer (BC). PET, paraffin-embedded tissue; CPT, cryo preserved tissue.

Molecular profiles of HPV in BC

The persistent high-risk (hr) HPV infection are well known prerequisite factor for clinical progression and the development of Cervical intraepithelial neoplasia III (CIN III) and CACX (77-79). The persistent infections with hrHPVs have been identified as an essential but not sufficient factor in the pathogenesis of anogenital and other epithelial carcinomas (80). It was evident that sequential changes in the molecular profiles (genetic/epigenetic expression) of HPV occurred during development of tumour. Recent studies have shown that the majority (86–100%) of HPV genome present in breast tissue in an integrated form, an important step of HPV induced normal epithelial cell transformation as well as carcinogenesis (*Table 3*) (85). On the other hand, low copy number of HPV genome with range 0.00054–9.3 copies/cell in breast tumor was reported by different investigators including our group (*Table 3*). Based on sequence variation of the HPV genome, four naturally occurring lineages have been characterized like European-Asian (A), African-1(Af-1) (B) African-2(Af-2) (C) and Asian-American-North American (D) (86). Among these, American-North American (D) lineage was associated with the virulence property (87). Our previous sequence variation analysis of E6-E7 and LCR regions of HPV16 genome revealed that "A" lineage was frequent in BC (64.2%, 36/56) followed by D (33.9%) and B (1.78%) (38). Among these, frequent variants such as 7521 G > A at LCR and 350T > G at E6 regions indicated their importance in the process of carcinogenesis (88). HPV genome is functionally subdivided into three regions: early, late and the regulatory-long control region (LCR) or non-coding region (NCR), each are separated by two polyadenylation (pA) sites: early pA (pAE) and late pA (pAL) sites (*Figure 3*) (89). After HPV infection and capsid uncoating, P97 promoter derived early poly-cistronic mRNA transcript is responsible for production of early response proteins i.e., E1, E2, E4, E5, E6 and E7 by differential splicing (90). On the other hand, the poly-cistronic mRNA transcript from the late promoter P670 through differential splicing could produce E1, E2, E4, L1 and L2 proteins. Our previous study showed high methylation in p97 promoter (97%) and enhancer (51%) at LCR region of HPV16 genome, indicating the importance of this epigenetic modification in regulation of the viral genome expression (38) (*Table 3*).

The expression of E6 and E7 oncogenes have their significant biological implications in HPV induced carcinogenesis. The E6/E7 transcripts were detected in

Table 2 Worldwide prevalence of HPV infection in different subtypes of breast cancer

Country	TNBC			Her2+			Luminal B			Luminal A		
	HPV (%)	HPV16/18/33 (%)	Other HPV (%)	HPV (%)	HPV16/18/33 (%)	Other HPV (%)	HPV (%)	HPV16/18/33 (%)	Other HPV (%)	HPV (%)	HPV16/18/33 (%)	Other HPV (%)
Algeria [Corbex *et al.* 2014] (50)	5/25, 20.0	4/25, 16.0	1/25, 4.0	–	–	–	–	–	–	–	–	–
Italy [Piana *et al.* 2014] (51)	6/40, 15.0	28.6	14.3	0/2, 0.0	–	–	–	–	–	0/38, 0.0	–	–
Australia [Lawson *et al.* 2015] (35)	1/2, 50.0	1/2, 50.0	–	2/2, 100.0	2/2, 100.0	–	18/22, 81.8	14/22, 81.8	4/22, 18.1	3/6, 50.0	3/6, 50.0	–
Spain [Vernet-Tomas *et al.* 2015] (52)	0/16, 0.0	–	–	–	–	–		–	–		–	–
Venezuela [Fernandes *et al.* 2015] (53)	2/2, 100	–	–	0	–	–	4/7, 54.1	–	–	4/13, 30.7	–	–
India [Islam *et al.* 2017] (38)	37/67, 55.2	–	–	56/84, 66.6	–	–	58/83, 69.9	–	–	23/38, 60.5	–	–
Spain [Delgado-García *et al.* 2017] (39)	11/24, 8.7	–	–	5/12, 4.0	–	–	73/118, 61.8	–	–	37/88, 29.4	–	–
Morocco [Habyarimana *et al.* 2018] (54)	4\9, 44.4	2\2, 100.0	2\2, 100.0	3\6, 50.0	2\3, 66.6	1\3, 33.3	3\10, 30.0	2\3, 66.6	1\3, 33.3	12\21, 57.1	11\12, 91.6	1\12, 8.3

TNBC, triple negative breast cancer.

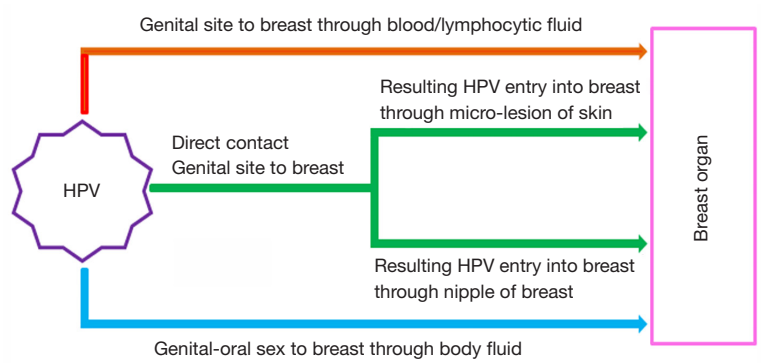

Figure 2 Representative diagram showing possible route of HPV transmission to breast tissue. There are mainly three possible mechanisms: (I) infected genital site to breast through blood/body fluid, (II) direct contact between genital and breast due abnormal sexual activity and (III) oral to breast due to oral sex activity.

24–100% of BC samples by different researchers including our group (*Table 3*). Apart from the existing transcripts of E6/E7, two novel fusion transcripts of E6/E7 (E6^E7*I, E6^E7*II) in breast tumour were detected by us suggesting the underlying differences in molecular pathogenesis of HPV in BC compared to other cancers (*Figure 3*) (38).

Going further, different investigators including our group detected the E6/E7 protein expression in 24–76% breast samples indicating functional relevance of HPV in breast tumour tissue (*Table 3*) (35). In addition, E6 and E7 expression was also evident in adjacent normal tissue, nipple tissue and epithelial layer of normal breast skin (8,38,71).

Table 3 Molecular profiles of HPV in breast cancer

References	Molecular profiles	Description		
	Physical Status	Integrated (%)	Mix (%)	Episomal (%)
Khodabandehlou *et al.* 2019 (40)		86 (30/35)	14 (5/35)	--
Khan *et al.* 2008 (18)		96 (25/26)	--	4 (1/26)
Islam *et al.* 2017 (38)		87.5 (105/120)	8.3 (9/120)	4.2 (5/120)
Aguayo *et al.* 2011 (81)		100.0 (4/4)	--	--
Herrera-Goepfert *et al.* 2013 (82)	Viral Load	0.20892 copies/cell		
Lawson *et al.* 2016 (71,83)		0.00054–0.0021 copies/cell		
Khan *et al.* 2008 (18)		5.4 copies/cell		
Islam *et al.* 2017 (38)		9.3 copies/50 ng gDNA		
Islam *et al.* 2017 (38)	Sequence variants	70.8% (34/48)		
Islam *et al.* 2017 (38)	Methylation status	P97 promoter: 96.7%, (30/31), Enhancer: 51.6%, (16/31)		
Lawson *et al.* 2015 (35)	E6 expression (mRNA/protein)	76% (16/21)		
Islam *et al.* 2017 (38)		53.3% (16/30)		
Suarez *et al.* 2013 (84)		56.2 (9/16)		
Lawson *et al.* 2015 (35)	E7 expression (mRNA/protein)	24% (5/21)		
Islam *et al.* 2017 (38)		53.3% (16/30)		
Suarez *et al.* 2013 (84)		56.2 (9/16)		
Ngan *et al.* 2015 (36)		62.5% (20/32)		

Molecular pathogenesis of HPV associated BC

The molecular mechanism of HPV infection in promoting cervical cancer development and progression has been studied comprehensively (91). However, the exact mechanism by which HPV induces or promotes breast carcinogenesis is not well defined yet. It was evident that the E6 and E7 oncoproteins of HPV16 could immortalize human mammary epithelial cells through inactivation of p53 and RB respectively indicating their importance in cellular transformation (55,92). Different in-vitro studies showed association of E6/E7 with multiple cellular pathways in transformation of mammary epithelial cells (*Figure 4*) (5). Among these pathways, E6/E7 could down regulate P53, NFX1 and BRCA1 resulting up regulation of CoX2, NF-κβ and ER associated pathways (72,93-97). On the other hand, E6/E7 could stabilize HER2 receptor resulting in the activation of beta-catenin and thus enhance cellular proliferation (*Figure 3*) (55,98). Al Moustafa *et al.* observed co-over expression of E6/E7 and HER-2 in 40% of HPV16 positive BC (99). Ohba *et al.* showed association of the APOBEC3B pathway with the ER-positive breast tumors in presence of HPV (56). The association of E6 with these pathways in breast carcinogenesis has been validated in murine model systems (100).

Future management of HPV associated BC

In this review, it is evident that HPV is associated with a sub set of BC irrespective of different molecular subtypes. As HPV infects the breast through nipple and micro-lesions on the breast skin due to genetial-breast sex activity, hygienic sexual practice could prevent HPV infection to the breast. In conventional cervical cancer screening, cervical swab is used for HPV test followed by Pap test leading to early diagnosis of cervical cancer (101). Likewise, it is pertinent to detect HPV in breast ductal lavage, breast nipple discharge and breast milk which will be useful for determination of risk of BC as well as early diagnosis of BC. Apart from these, detection of HPV in breast tissue will be powerful biomarker for specific treatment protocol of the

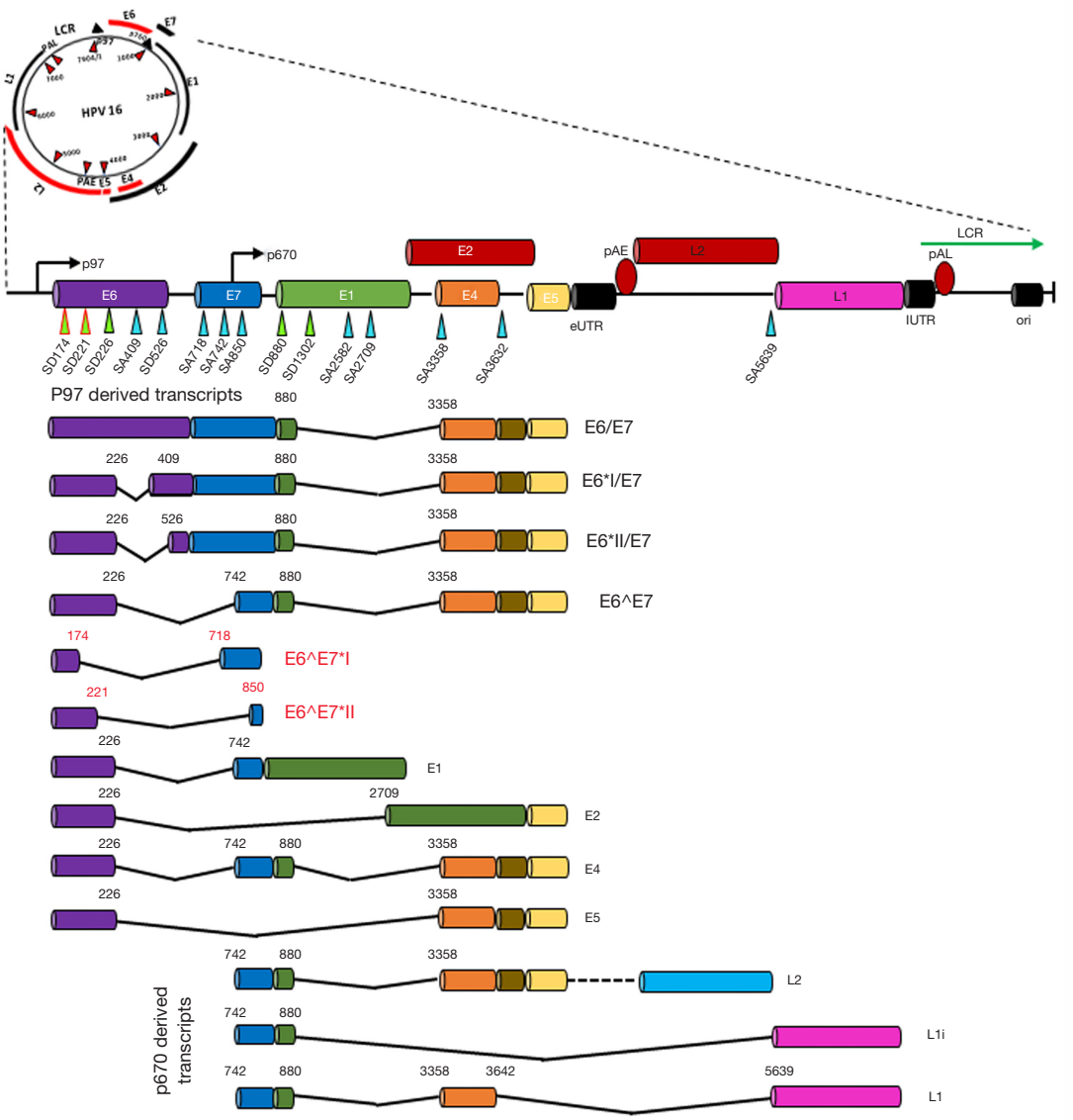

Figure 3 Schematic representation of molecular portrait of human papillomavirus 16 (HPV16) genome. The ~8 kb human papillomavirus genome may be found as an episomal or linear integrated form in the nucleus of the infected cell. The viral genome harbours two polyadenylation signals such as early polyadenylation signal (pAE) and late polyadenylation signal (pAL). The pAE signal terminates the transcription of early (E) genes such as E1–E7, whereas pAL signal terminate transcription of late (L) genes L1 and L2. The LCR of the genome contains the origin of DNA replication (ori) and the early viral promoter, p97 while the late promoter, p670, is located in the E7 coding region. eUTR and lUTR represent the early and late 3'UTR respectively. Known 5' splice donor site (SD) like SD226, SD880, SD1302 and SD3632 are shown as green circle with black border whereas 3' splice acceptors (SA) SA409, SA526, SA742, SA2582, SA2709, SA3358 and SA5639 are shown as blue circle with black border. Apart from these, two novel splice donor sites SD174 & SD221 and accepter sites SA718 & SA850 are depicted as green circle with red border and blue circle with red border respectively. Alternative splicing among these splice sites are produce two sets of mRNA transcripts from respective promoter p97 and p670. Red colour E6^E7*I & E6^E7*II represent the novel transcripts. Each transcript represents the most likely candidate mRNA for production of the corresponding proteins.

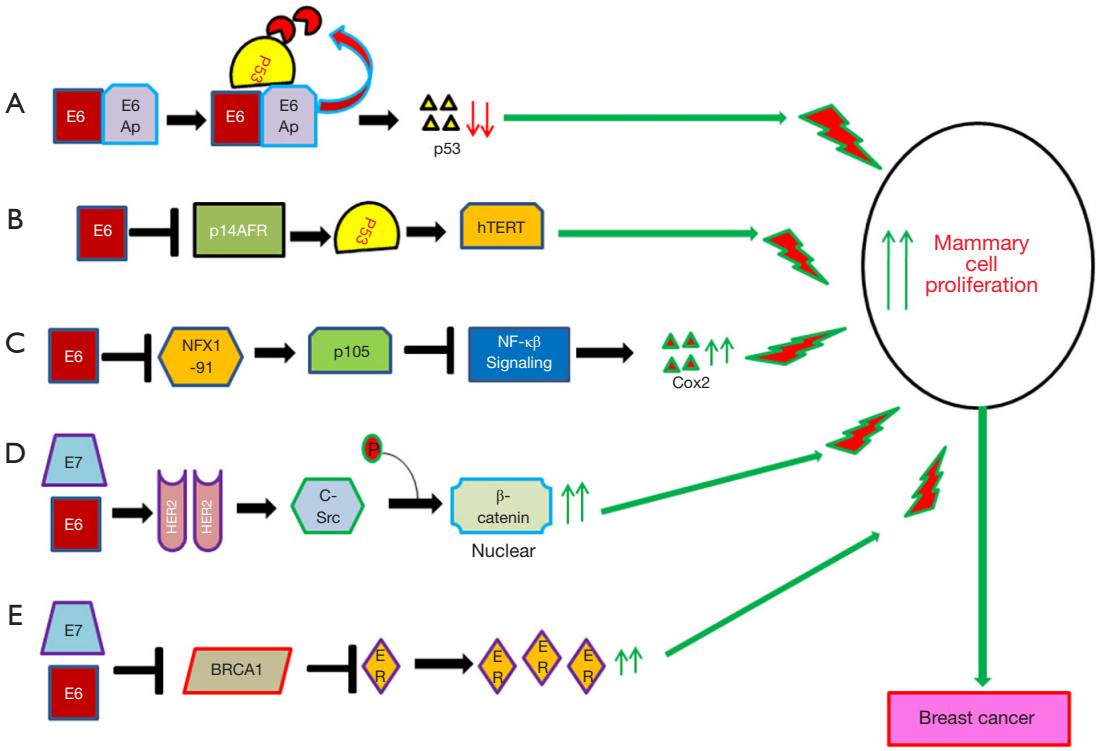

Figure 4 Schematic diagram represent the Putative mechanism of HPV in breast carcinogenesis. (A) Interaction of E6 with E6-AP leads to the degradation of p53 resulting in increased cellular proliferation eventually transforming into immortalized mammary epithelial cells (MEC). (B) E6 linked with hTERT can mediate immortalization of MEC through inactivation of p14ARF-p53 pathway (V) E6 could increase the mammary cell proliferation through up regulation of Cox2. This occurs due to E6 mediated degradation of NFX1 resulting in p105 down regulation and stabilizing NF-κβ which can now activate transcription of COX2. (D) E6/E7 interaction with HER2 results in its activation. HER2 in-turn activates c-Src which leads to the phoshorylation of beta-catenin at its C-terminal end as a result of which beta-catenin translocates to nucleus and activates different proliferation associated genes. (E) E6/E7 inhibits the function of BRCA1 resulting in restoration of expression of ER. High expression of ER leads to increased proliferation of mammary cell due to modulation of different proliferation associated genes.

HPV infected BC. Moreover, the presence of HPV in blood plasma of BC patients can be the indicator of dissemination of tumour cells from the primary site which can serve as a useful prognostic tool of the disease. The prevalence of HPV in BC indicates that prophylactic vaccination against HPV is needed to restrict the disease in women (102).

Conclusions

In this review, we suggest that HPV is an important etiological factor in the development of a sub-set of BC and also HPV associated BC has some distinct molecular profile than other HPV associated cancers like cervical cancer (CACX), head and neck squamous cell carcinoma (HNSCC). Thus an in-depth understanding and analysis of the molecular profile of BC in the light of HPV is essentially needed for the proper management of the disease.

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Footnote

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