Segundo Editorial

The Possible Involvement of HPV in Breast Cancer

ABSTRACT
The exact role that viruses play in tumorigenesis is unclear, but it seems they are responsible for causing one of a series of steps required for the development of cancer. The first step for infering whether a particular cancer is caused by this virus is showing the virus in tissue degradation. Molecular techniques, in comparison with the evaluation of antibodies in immunohistochemistry, are the most effective techiniques to establish the presence of the virus. Human papillomavirus (HPV) and Epstein-Barr virus (EBV) have been found in breast carcinomas worldwide. The high-risk human papillomavirus may be an important risk factor for breast carcinogenesis and metastasis. The role of human papillomavirus in breast carcinogenesis is still unclear and may ultimately be determined by monitoring the incidence of future breast cancer among women vaccinated for human papillomavirus types as high-risk.
Keywords: molecular evidence, breast cancer, carcinogenesis, **etiopathogenesis,** human papillomavirus, HPV, STD.

INTRODUCTION

Breast cancer is one of the main health problems in developed countries, and earned it a ranking of second place (15%) in incidence in the world, after the lung cancer (25% to 50%), with the exception of skin tumours. In Brazil, breast cancer is the most letal among women. According to the National Institute of Cancer, the estimated risk is of 52 cases per 100 thousand women. Early detection of this neoplasia it still not entirely possible, due to the variations in risk factors and genetic characteristics that are involved in its etiology[1].

It is well-known there are risk factors associated with the development of breast cancer. However, in 50% to 80% of cases, the known risk factors are not identified, and this situation led to the attempt to identify new factors related to this neoplasia as viral infections[2].

Despite decades of research, no etiologic factor for human breast cancer has been identified. More than 60 years ago it was shown that breast tumors in rats are caused by a mammary tumor virus, the oncornavirus (MMTV or Bittner virus)[3]. The MMTV genetic material was identified in human breast tumors, but there is no conclusive evidence if MMTV is causal, and not mereley an innocuous infection in human beings[4].

The three most studied virus that could possibly cause breast cancer in humans are: MMTV, the Epstein-Barr (EBV or gamma herpes virus), and the human papilloma (HPV)[5]. MMTV and EBV occur in 37% and 50% of breast cancer cases, respectively[6].

The HPV are accepted as carcinogenic in human cervical and anogenital cancer. The suspicion that HPV may also play a role in human breast cancer is based on the identification of HPN of high oncogenic risk (16, 18, 31, 33, and 35) in these tumors, and in the immortalization of the human breast normal cells. The controversy surrounding the HPV involvement with breast cancer can occur due to the difficulty to find the virus in the specimens, contrasting with the facility for detecting cervical cancer[7].

Potential mechanism of transmission

The scientific challenge is to determine if the HPV are etiological agents and not just passengers or parasites. The potential mechanism of transmission of HPV for the breast remains unknown, and opinions are divided between the direct contact with the genital region and the breast, and the hematological spread. Although HPV transmission route is not yet determined, some types of HPV are found in both tumors (cervical and breast)[8].

The oral-genital HPV transmission can occur in the varied sexual conduct. HPV has been detected in the oral cavity of infants and also in breast cancer tissue, suggesting its vertical transmission through breast milk, however rare, around 2.5% according to Yoshida *et al*. (2011)[9], and 4%, according to Sarkola *et al.* (2008)[10]. The oral HPV infection of a partner between the 6th and 12th postpartum months was statistically associated with breast cancer[10].

Sensibility and specificity of the chosen method are important factors in the HPV detection. However, most studies utilizes the polymerase chain reaction (PCR) from de DNA of positive control, but affected by the vulnerability to contamination in the laboratory, and the inability to locate *in situ* the signal to a specific type of cell. To overcome these disadvantages, methods of molecular biology are used, as they are resistant to contamination, like the *in situ* hybridization (ISH) with specific probes for the identification of the viral type in positive cell in the capsid region of the malignant mammary tissue. Based on these findings, it is obvious saying that PCR is more sensitive than the *in situ* hybridization or the *southern blot*, although hybridization *in situ* is more specific, as it shows the virus location[11].

De Villiers *et al.* (2005)[12] investigated through PCR and ISH the occurrence of HPV in breast and nipple/areola carcinoma of these patients, finding 69% and 86%, respectively, and postulate a ductular retrograde pattern of viral propagation. The authors relate that HPV-11 was the most prevalent in both, followed by HPV-6. Other types detected were: HPV 16, 23, 27 and 57 (nipples and carcinomas), HPV 20, 21, 32, 37, 38, 66 and GA3-1 (only nipples), HPV 3, 15, 24, 87, DL473 (only carcinomas), and several types were shown in seven carcinomas and ten nipple samples.

Any viral hipothesis as a cause of breast cancer should take into account the most striking epidemiological characteristic of human breast cancer, whose mortality is three to six times greater than other cancers, and its incidence is up to eight times higher in some Asian and Western populations. These differences dramatically decreases two to three times within one or two generations, when immigrants from countries with low-risk to high-risk of breast cancer change their patterns of food consumption, raising the levels of circulating hormones, reinforced by gender, promoting the MMTV and HPV hormone-dependent viral replication, and the beginning of the breast oncogenesis[13].

Some work suggest that high-risk infections by HPV are associated with breast cancer

The first breast HPV investigation report is from 1992, in Italy, when Di Lonardo *et al.* [14] detected the sequence of HPV-16 DNA through PCR in 29% of the 40 breast cancer specimens embedded in paraffin, and in 17% of lymph nodes containing metastatic breast cancer. Few studies have convincingly demonstrated the presence of oncogenic HPV in the human mammary epithelium using more than one method and careful methodology[11,14-20].

Akil *et al*. (2008)[21] investigated 113 invasive breast cancers and found 69 (61%) positive cases of high-risk HPV, as follows: HPV-16 (9%), HPV-18 (10%), HPV-31 (77%), HPV-33 (56%) and HPV-35 (37%); and 24 tissues (34,78%) amongst these specimens have been coinfected with more than one HPV type.

A solution for the detection of low levels of HPV copies or viral loads, such as 5.4 copies per ten cells, is to use the *in situ* PCR technique. Antonsson *et al.* (2011)[22] reported the prevalence of HPV-18 DNA by PCR of 50% (27/54) in slightly younger female patients, when compared to olders ones, with less T staging, and less nodal involvement, but *in situ* hybridization revealed negative. However, Baltzell *et al.* (2011)[11] used PCR-IS and observed HPV-16 in 3% (2/70), and 6% by ISH (4/70), justifying the little agreement between the methods due to few positive specimens, sensibility differences, and specific HPV types.

De León *et al.* (2009)[23] found 29% (15/51) of HPV DNA by PCR in breast carcinomas within an average age of 53 years and average tumor size of 9 cm, of which ten of the cases (66,6%) were positive to HPV-16, three (20%) to HPV-18, and two cases (13,4%) positive to both of them. In the benign conditions group (43 cases), all were negative to HPV-DNA.

Between 1992 and 2012 the worldwide systematic revision of a number of studies about HPV relation in breast cancer, showed that prevalence varies between 4% (3/67) in Mexico to 86% (25/29) in the USA (**Table 1**)[8,11,12-14,19,21,24-36]. These variations are based in different geographic regions, and can be attributed to distinct susceptibility of the population to the various detection methods of HPV types or to the *primer* type of PCR used (Simões *et al.* 2012) [37]. Damin *et al.* (2004)[25] Brazilian study found 25% (25/101) of DNA sequence of HPV in breast carcinoma, and detected HPV-16 in 56% (16/25), HPV-18 in 40% (10/25), and HPV-16 and 18 in 4% (1/25). The study did not observe HPV DNA in benign mammary

Table 1 – Authors who have detected HPV DNA in cancer and in the normal breast tissue.

Authors	Year	*HPV-Positive/Number of Cases (%)*		*Technique*
		Tumor	*Normal Tissue or Nipple*	
Di Lonardo *et al.*[14]	1992	7 / 70 (10)	-	PCR/ISH
Hennig *et al.*[15]	1999	19 / 41 (43)	-	PCR/ISH
Yu *et al.*[16]	1999	19 / 72 (26)	-	PCR/ *Southern blot*
Yu *et al.*[17]	2000	14 / 32 (43)	-	PCR/ *Southern blot*
Liu *et al.*[18]	2001	6 / 17 (35)	-	PCR/ *Dot blot hybridization*
Li *et al.*[24]	2002	19 / 28 (68)	-	PCR
Damian *et al.*[25]	2004	25 /101 (25)	0 /41 (0)	PCR
Widschwendter *et al.*[8]	2004	7 / 11 (64)	-	PCR
De Villiers *et al.*[12]	2005	25 / 29 (86)	20 / 29 (69)	PCR
Kan *et al.*[26]	2005	24 (48)	-	PCR
Tsai *et al.*[27]	2005	8 / 62 (13)	2 /44 (5)	PCR
Kroupis *et al.*[28]	2006	17 / 107 (16)	-	PCR
Gumus *et al.*[29]	2006	37 / 50 (74)	16/50 (32	PCR
Choi *et al.*[30]	2007	8 / 123 (7)	0 / 31 (0)	PCR
Akil *et al.*[21]	2008	69 / 113 (61)	-	PCR
Khan *et al.*[31]	2008	26 / 124 (21)	-	PCR
He *et al.*[32]	2009	20 / 24 (60)	1/20 (5)	PCR
De León *et al.*[23]	2009	15 / 51 (29)	0/43 (0)	PCR
Mendizabul-Ruiz *et al.*[33]	2009	3 / 67 (4)	0/40 (0)	PCR
Heng *et al.*[19]	2009	8 /26 (20)	3/17 (18	PCR
Aceto *et al.*[34]	2010	3 /5 (60)	-	PCR
Aguayo *et al.*[35]	2011	4 /46 (9)	-	PCR
Antonsson *et al.*[22]	2011	27 /50 (50)	-	PCR *in situ*
Silva & Silva[20]	2011	12/90 (13)	-	PCR/ISH
Baltzell *et al.*[11]	2012	4/70 (6)	-	PCR *in situ*/ISH
Joshi & Buehring[36]	2012	3 / 29 (10)	-	PCR

PCR: polymerase chain reaction; ISH: *in situ* hybridization..

tissue. In some studies, high-risk HPV was detected in normal tissue and in low levels of cancer[19,23,25,27,29,30,33]. The definition of normal tissue is important, as non-malignant areas can contain atypia with high-risk of cancer recorrence.

High-risk HPV anchors a series of proteins, appointed as early (E1-E7) or late (L1 and L2)[38]. Furthermore, HPV E5 and E6 act early in the transformation, before the integration, and are known for breaking cytokeratin, thus causing the remarkable perinuclear halo in the citoplasm and the increase of nuclear volume, leading to the aspect known as koilocyte[19,39,40]. Koilocytosis is accepted as pathognomonic or characteristic of infection by HPV. HPV in koilocytes was detected by PCR-IS in 22% (4/18) in normal skin and breast lobes in 33% (4/12) of ductal carcinomas *in situ* (CDIS)[41].

CerbB-2 receptor is abundant in approximately 30% of human breast cancers. Recently, Yasmeen *et al.* (2007)[42] reported that CerbB-2 cooperates with the oncoproteins E6/E7 of HPV type 16 to induce breast tumorigenesis via beta-catenin activation[43]. Disagreeing with the authors, HPV-18 genes sequences were present in the DNA extracted by PCR of breast tumors in 48% (24/50) of Australian women samples. Neither correlation with the degree of tumor, nor patient's survival, nor steroid receptor status, nor CerbB-2, nor expression of p53, nor mutation was observed[26].

The *following authors* reported the absence of detection of HPV DNA in breast cancer and suggested it is improbable that integrated HPV is etiologically associated with the development of breast carcinomas: Bratthauer *et al.* (1992)[44], Wrede *et al.* (1992)[45], Czerwenka *et al.* (1996)[46], Gopalkrishna *et al.* (1996)[47], Lindel *et al.* (2007)[7], de Cremoux *et al.* (2008)[48], Subhawong *et al.* (2009)[49], Hachana *et al.* (2010)[50], Chang *et al.* (2011)[51], and Hedau *et al.* (2011)[52]. Among them, six studies showed the absence of oncogenic HPV in its specimens (Bratthauer *et al.*, 1992[44]; Wrede *et al.*, 1992[45]; Czerwenka *et al.*, 1996[46]; Gopalkrishna *et al.*, 1996[47]; Chang et al., 2011[51]; Hedau *et al.*, 2011[52]), confirming the use of positive controls and ISH to avoid contamination (**Table 2**).

HPV has been proposed as the causal agent of breast cancer based in several reports of oncogenic high-risk of HPV in these tissues. Although the expectation of the presence of high-risk HPV is not enough for the tumorigenic transformation, it is expected to become an early event, and also that cumulative changes over the years become the starting step, similar to cervical carcinogenesis.

Finally, there is an urgent need for obtaining additional evidences in order to evaluate the possibility of breast cancer prevention with vaccines against HPV[53].

Table 2 – Authors who did not detect HPV DNA in breast cancer.

Authors	Year	*Nº Cases*	*HPV (%)*	*Technique*
Bratthauer *et al.*[44]	1992	43	0	PCR/ISH
Wrede *et al.*[45]	1992	92	0	PCR
Czerwenka *et al.*[46]	1996	20	0	PCR/ISH
Gopalkrishna *et al.*[47]	1996	30	0	PCR/ISH
Lindel *et al.*[7]	1992	81	0	PCR
de Cremoux *et al.*[48]	2008	50	0	PCR
Subhawong *et al.*[49]	2009	33	0	ISH
Hachana *et al.*[50]	2010	123	0	PCR/ISH
Chang *et al.*[51]	2011	48	0	PCR/ISH
Hedau *et al.*[52]	2011	252	0	PCR/ISH

PCR: polymerase chain reaction; ISH: *in situ* hybridization.

Conflict of interest

There is no conflict of interest to declare.

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