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REVIEW ARTICLE

Human Papilloma Virus infection and breast cancer development: Challenging theories and controversies with regard to their potential association

Aikaterini Mastoraki[1], Dimitrios Schizas[2], Anastasia Gkiala[1], Vasiliki Ntella[1], Natasha Hasemaki[2], Ioanna Pentara[1], Vasileia Ntomi[3], Alkistis Kapelouzou[2], Theodore Liakakos[2]

[1]4th Department of Surgery, National and Kapodistrian University of Athens, 1 Rimini str., 12462, Chaidari, Athens, Greece. [2]1st Department of Surgery, National and Kapodistrian University of Athens, Laikon General Hospital, 17 Ag.Thoma str., Athens, Greece.

Summary

Breast cancer (BC) remains the most frequently diagnosed malignancy among women worldwide. Recognized predisposing factors may be absent in the majority of affected patients, which has aroused a stronger interest in identifying risk parameters that contribute to BC pathogenesis. Human papilloma virus (HPV) infection is strongly associated with malignancies, such as cervical cancer, oropharyngeal cancer and anal cancer. Various surveys have linked HPV to the development of BC. Relevant variations in HPV identification among BC samples may be attributed to differences in study design, the populations involved and the HPV detection techniques applied, which are still controversial with conflicting opinions and results that deny the causative association between HPV infection and BC development. Furthermore, the role of HPV, a potential cause of human BC, has recently received more attention because of the possible restriction of disease progression using an HPV vaccine.

The aim of this review was to evaluate both the aspects supporting and those against the theory of BC related to HPV infection. Recent literature has been also assessed in order to provide an update on the current concepts of relevant association.

Key words: *breast cancer, HPV infection, causative relation, controversies, therapeutic targets*

Introduction

Breast cancer (BC) remains the most frequently diagnosed malignancy among women in many populations [1]. In nearly all cases, the etiology is unknown [2]. It has been generally accepted that BC represents a complex multistep process in which age, familial or previous history of breast surgical intervention, genetic changes and environmental factors, such as viruses, carcinogens, radiation and dietary components, may alter common cellular pathways, resulting in uncontrolled cell proliferation [2]. However, recognized predisposing factors may be absent in 50-80% of affected patients, which has aroused a stronger interest in identifying new risk parameters that contribute to the pathogenesis of this nosologic entity [3,4]. In addition, HPV infection has been strongly associated with malignancies, such as cervical cancer, oropharyngeal cancer and anal cancer [5,6]. Papillomaviruses can be grouped according to tissue tropism with HPV types found in mucosal lesions being referred to as mucosal or genital types and those detected in skin called cutaneous types. High-risk HPV infec-

Corresponding author: Aikaterini Mastoraki, MD, PhD. 4th Department of Surgery, Athens University, Medical School, Attikon University Hospital, 1 Rimini str., 12462, Chaidari, Athens, Greece.
Tel: +30 6932 577710, Fax: +30 210 5326412, Email: dr_kamast@yahoo.gr
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tions have been suggested as the causative agent in 99.7% of cervical cancers and have also been detected in more than 50% of other anogenital malignancies [7,8]. The most prevalent high-risk HPV types are HPV-16 and HPV-18, which account for 70% of the cancer cases, with another 10 types making up the other 30%.

Various studies have linked HPV virus to the development of BC. Since Di Lonardo first elucidated the potential relationship between HPV infection and BC in 1992, a growing number of studies have reported the detection of HPV DNA in BC tissues, with the prevalence ranging from 0 to 86.2% [9-11]. Relevant variations in HPV identification among BC samples may be attributed to differences in study design, the populations involved and the HPV detection techniques applied which is still controversial with conflicting opinions and results that deny the causative association between HPV infection and BC development [12,13]. Furthermore, the role of HPV as a potential cause of human BC has recently received more attention because of the possible restriction of disease progression using an HPV vaccine, which is now administered in the primary prevention of human cervical cancer [14]. The aim of this review was to evaluate both the aspects supporting and those against the theory of BC related to HPV infection. Recent literature has also been assessed in order to provide an update on the current concepts of relevant association.

HPV oncogenesis

Papillomaviruses are small, double-stranded DNA molecules belonging to the Papillomaviridae family. Until today, over 110 different HPV types have been fully characterized and are generally categorized according to tissue tropism [11]. With regard to their molecular biological data and epidemiological association with cancer, mucosal HPV subtypes are further divided into high- and low-risk entities. Mucosal high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82) are responsible for the development of different kinds of malignancies, such as cervical, vaginal, penile, anal, head/neck and oral neoplastic disorders [15,16]. They have been implied in the etiology of 99.7% of cervical and more than 50% of other anogenital cancers [8,17]. Furthermore, benign anogenital lesions as well as low-grade squamous intraepithelial lesions of the cervix are commonly attributed to low-risk HPV detection, whereas HPV types 6 and 11 are also responsible for the development of papillomas in the oral/nasal cavity or the larynx. Finally, cutaneous HPV genotypes are responsible for the development of the rare hereditary dermatological disease epidermodysplasia verruciformis (EV) and HPV 5 and 8 are the most frequently encountered types [18].

The HPV genome is a double-stranded circular DNA of 8,000 bases that is further divided into three portions: (1) an approximately 4,000 kb early region (E) that encodes proteins primarily involved in viral DNA replication and cell transformation, (2) an approximately 3,000 kb late section (L) that encodes the structural proteins of the virus particles, and (3) an approximately 1,000 kb noncoding region (LCR) that contains the origin of viral DNA replication and transcriptional regulatory elements [19,20]. It has been elucidated that E6 and E7 oncoproteins derived from relevant E6 and E7 genes located in the early region of high-risk HPV genomes are constitutively expressed in malignant lesions inactivating p53 and pRb tumor suppressors respectively [21]. E6 facilitates the degradation of p53 based on its association with an accessory protein, E6-AP, a component of the ubiquitin proteolytic pathway [22,23]. Moreover, E7 proteins of high-risk HPVs bind to Rb as well as to other pocket proteins, such as p107 and p130 leading to cell cycle deregulation [24,25]. This results in genomic instability and has been implicated in the progression of normal cells into malignant transformation.

Research supporting the relationship between HPV and breast cancer

Since Di Lonardo first described a potential causative relationship between HPV and BC, many researchers supported this opinion [9]. A number of recent studies have demonstrated that approximately 29% of human BCs are positive for high-risk HPV subtypes, especially 16, 18, and 33 [26]. The increased interest can be attributed to the scientific importance of establishing viral causes of malignancy. Antonsson et al analyzed 54 BC samples using PCR, cloning and sequencing, *in situ* hybridization and statistical analysis of the data in 2011, and the results suggested that HPV DNA prevalence in tissue samples was 50% and HPV-18 type was detected in each case [27]. However, with regard to tumor size, HPV-positive lesions were remarkably smaller. Therefore, a statistically significant (p=0.03) correlation has been suggested among HPV negative BCs and advanced tumor size as well as T stage. In addition, Kroupis et al found from the meticulous investigation of 107 frozen BC specimens that HPV-positive BC patients were younger with a lower ER positive rate and higher proliferative index [28].

In 2009 Lawson et al described that putative HPV-associated koilocytes were present in nor-

mal breast skin and lobules as well as in relevant tissue structures of patients affected with Ductal Carcinoma *In Situ* (DCIS) and Invasive Ductal Carcinoma (IDC) [29]. HPV 18 was also identified by *in situ* PCR in the breast lobules and koilocytes of the same specimen. Moreover, HPV oncoprotein E6 is detected in the basal layer of breast skin, the intercellular space and cytoplasm of koilocytes, normal breast epithelial and malignant cells as well. Nevertheless, E6 nuclear staining was weak. In accordance with the above-mentioned evidence, Heng et al identified high-risk HPV DNA sequences in the nuclei of BC epithelial cells in 5 among 13 DCIS (39%) and 3 among 13 IDCs (23%) [30]. Unexpectedly, HPV-containing cells were apparent in the surrounding normal tissue of several samples. The presence of HPV in normal breast tissue is consistent with the requirement for HPV infection in the breast before HPV-induced tumourigenic transformation of a single clone is established.

Recently, Wang et al studied 81 fresh BC tissues to elucidate potential association between HPV presence by hybrid capture 2 (HC2) assay and the expression of BCL2, p21, p53 and Rb oncogenes by immunohistochemistry [31]. They concluded that HPV infection demonstrated no significant correlation with the clinicopathological characteristics of BC. Furthermore, HPV-positive tumors presented significantly higher BCL2 expression and lower p53 expression compared witg HPV-negative lesions. On the contrary, the expressions of p21 and Rb genes and disease survival was irrelevant with HPV status. Overall results suggest a possible role of HR-HPV in BC carcinogenesis, in which BCL2 and p53 may be involved. Similarly, Delgado-García et al studied 251 BC cases and 186 benign breast tumors using three different molecular techniques with PCR and reported that HPV DNA was evidenced in 51.8% of the affected patients and in 26.3% of the control group ($p<0.001$) [32]. HPV-16 revealed the most prevalent serotype. Therefore, the researchers suggested a potential causal relationship between HPV and BC.

Additionally, ElAmrania et al studied 76 BC and 12 control samples and evaluated the presence of 62 HPV types using highly sensitive assays combining multiplex PCR and bead-based Luminex technology [33]. Results were indicative of HPV DNA detection in 25% of BC lesions and only 8.3% of control specimens. High-risk mucosal types HPV16 and 18 were not confirmed in the subjects, but other probable/possible high-risk HPV types (51, 52, 58, 59 and 66) were found in 5.3% of BC tumors. Subsequent statistical analysis showed no significant difference between controls, BC cases and relevant inflammatory status ($p>0.05$). Overall, the proportion of HPV DNA in the BC tumors was 3 times that in the control group and HPV DNAs belong to different genera in BC samples [34]. Final conclusion remains that, given the complexity involved and the relatively low prevalence of HPV infection in BC lesions, studies with a large sample size are required to better understand the role of HPV infection in human BC etiology.

Finally, in a recent survey among 103 BC and 95 normal breast samples, as the non-malignant controls, DNA extraction was verified by human beta-globin gene amplification and PCR was conducted based on HPV L1-specific consensus primers MY09/MY11 and GP5+/GP6+, followed by nested multiplex polymerase chain reaction with type-specific primers for the E6/E7 consensus region. HPV DNA was detected in 49.5% BC samples and 15.8% normal breast samples ($p\leq0.0001$). Therefore, high frequency of HPV infection in BC samples indicates a potential role of this virus in breast carcinogenesis [35].

Research against the relationship between HPV infection and breast cancer

It is common knowledge that inconsistencies in the published surveys regarding the prevalence of HPV in human BC can be partially attributed to variable sampling and tissue processing protocols, assay methods, designed primers, sample size and variable HPV identification in different populations. More specifically, variations in the examination of paraffin-embedded specimens and fresh tissues, low sensitivity and accuracy of HPV detection techniques as well as geographic differentiation in the prevalence of HPV types in BC cases remain major contributors to the conflicting results [36].

In 2011 Herrera-Romano et al evaluated 118 BC tissues and two paraffin-embedded tissues of lesions of the nipple of Mexican patients for HPV sequences [37]. No BC samples exhibited koilocytosis, in contrast to lesions of the nipple. Besides, DNAs were purified via PCR using two HPV16/E6 or GP5/6 primer set oligonucleotides. Results were indicative of HPV DNA absence in BC tissues failing to support an association between HPV infection and this cancer. The same period, Mou et al obtained tumor and noncancerous breast tissue samples from 62 female BC patients; normal breast tissues were also available from 46 women without malignancy [38]. HPV was detected, using nested PCR, in 6.5% among BC tumor specimens, while no HPV DNA was confirmed in either the noncancerous samples from BC patients or normal breast tissue control group. Therefore, low frequency of

HPV detection in the above-mentioned investigation suggested that HPV infection is not considered a major risk factor in BC development.

In accordance with previous surveys, Baltzell et al initiated *in situ* hybridization and PCR with primers specific for the capsid region of HPV-16 and resistant to molecular contamination to examine malignant tissue specimens from 70 BC patients at The University of Texas [39]. HPV was observed in 4 out of 70 specimens (5.7%) using ISH and only 2 of 70 specimens (2.9%) of samples tested with PCR. Concordance between the 2 methods was high for negative specimens; both methods yielded negative results in 66 of 70 specimens (94.3%). However, there was no concordance for the few positive specimens, probably because of differences in sensitivity and the targeted HPV types. The results showed that oncogenic (high-risk) HPV types were present in malignant breast epithelium very infrequently and, thus, may be causative agents of only a relatively small proportion of all BC lesions.

A different approach proposed by Lv et al supported the idea that high-risk HPV types were detected in both BC tissues and cervical cells among 56 BC patients [40]. Relevant results suggested that HPV infection did not coexist in breast and cervical samples. Therefore, HPV infection of BC tissues is more likely to occur in patients without cervical infection. Similar findings have been reported by Ngamkham et al using PCR and enzyme immunoassay [41]. Researchers detected HPV DNA in 25/700 (3.57%) samples, in which 10/350 (2.857%) from benign breast lesions/tumor samples and 15/350 (4.285%) among BC cellular structures were all collected from Thai women. HPV 16 remains the predominant type in this study, followed by HPV 33, 18, 35 and 52. Subsequent demographic and histopathological correlation analysis of all studied parameters failed to prove statistically significant association between BC history or hormone receptor status and HPV infection (P>0.05). They concluded that HPV can cause only a relatively small proportion of all BC or non-malignant breast lesions.

More recently, Bakhtiyrizadeh et al studied 150 BC fixed paraffin-embedded tissue specimens and equal number of non-malignant breast lesions [42]. All samples were first deparaffinized and then subjected to commercial DNA extraction. The pres-

Table 1. Analytical results of the studied articles

First author	*Number of samples*	*Type of samples*	*Breast cancer samples*	*% of HPV presence*	*Benign samples*	*% of HPV presence*	*Prevalent HPV type*	*Positive correlation p<0.05*
Antonsson A.	58	Fresh frozen	54	50%	4	25%	HPV-18	No
Kroupis C.	107	Fresh frozen	107	15,9%	-	-	HPV-16	Yes
Lawson JS.	32	FFPE	14	50%	18	22%	HPV-16,18	No
Heng B.	43	FFPE	26	30,7%	17	18%	HPV-18	No
Wang YW.	81	Fresh frozen	81	17,3%	-	-	-	No
Delgado-García S.	437	FFPE	251	51,8%	186	26,3%	HPV-16	Yes
ElAmrani A.	88	Fresh frozen	76	25%	12	8,3%	HPV-11	No
Herrera-Romano L.	130	FFPE and fresh frozen (10)	130	0%	-	-	-	No
Mou X.	108	Fresh frozen	62	6,5%	46	0%	HPV-16	No
Baltzell K.	70	FFPE	70	8,6%	-	-	-	No
Ngamkham J.	700	Fresh frozen	350	4,29%	350	2,86%	HPV-16	No
Bakhtiyrizadeh S.	300	FFPE	150	0%	150	0%	-	No
Fernandes A.	74	Fresh frozen	48	25%	26	7,69%	HPV-18	No
Kouloura A.	402	liquid storage medium (Thin-Prep)	201	0%	201	0%	-	No
Khodabandehlou N.	103	Fresh frozen	72	48,6%	31	16,1%	HPV-18	Yes
Afshar RM.	138	FFPE	98	8,2%	40	0%	HPV-16,18	No
Calvacante JR.	198	FFPE	103	49,5%	95	15,8%	HPV-6,11	Yes
Carolis S.	51	Nipple discharge	29	24%	22	5%	HPV-16	No
Bonlokke S.	193	FFPE	93	1,08-2,15%	100	0-1%	HPV-16	No
Naushad W.	350	FFPE	250	18,1%	100	0%	-	No

FFPE; Formalin-fixed and paraffin-embedded

ence of HPV genomic DNA was determined using PCR and Real time PCR techniques, respectively. No HPV genomic DNA was present in either malignant or benign cases, so the results of this study indicated no relationship between HPV infection and BC development. Results were summarized in Table 1.

Potential etiology of conflicting observations

As mentioned above previous surveys suggested that HPV prevalence in BC worldwide ranges from 0 to 86% [13]. Potential explanations include difficulties in detection due to limited viral verification and low prevalence of HPV in BC specimens, differences between fresh samples and paraffin-embedded specimens, variations in detection methods and different histological types of breast tumors. After taking into consideration the previously presented evidence, an inconsistency in the results of different surveys can be underlined. The reasons for these conflicting elements remain unclear and need further elucidation. Nevertheless, there are some valuable points in the research process that can alter the expected finding and influence the conclusions of the study.

One of the most frequent controversial elements in HPV detection process, with regard to PCR procedure, is the establishment of international standards and well-trained physicians. These parameters can create defects in the way the investigation is conducted. Furthermore, the use of correct PCR primers is of vital significance. Some studies have suggested different detection rates for any given HPV subtype when multiple PCR primers are initiated, while a few studies have documented differential amplification when comparing various primer pairs. All these factors have a negative impact on the sensitivity and accuracy of the PCR procedure. Moreover, the majority of published surveys used techniques restricted to the detection of specific, single or combinations of HPV types. The use of type-specific primers may increase the number of positive samples but is biased with regard to the HPV types involved as several HPV structures cannot be confirmed [11]. Finally, primers designed against E6 and E7 areas can reflect the actual HPV infection rate more accurately. Relevant drawbacks include their expense and inability to detect unknown virus categories.

Controversy regarding the relationship between HPV infection and BC is also attributed to the difference between paraffin-embedded specimens and fresh tissues. HPV virions can usually be destroyed during sample fixation and processing. It is impossible to detect HPV in paraffin-embedded specimens submitted to extended preservation. In addition, sampling error or contamination with HPV is often encountered. Therefore, the detection rate of HPV is higher in fresh tissues relative to that in paraffin-embedded specimens. Finally, variations based on different geographic areas could be caused by the differential susceptibility of relevant populations or various HPV detection modalities indicated in the assays.

Another important contributor is the threshold that HPV levels must reach in order to be detected by PCR. Generally, the HPV detection templates contain 10–20 copies per cell. The HPV structure is integrated in the host genome only in mature cells after viral replication stops. Through this procedure the quantity of HPV viral load is sharply decreased in terminally transformed cells. Therefore, it is obvious that the choice of detection method and associated sensitivity of the selected technique are important factors affecting the HPV identification process [43]. Real-time PCR as well as real-time fluorescent quantitative technologies will improve the appropriate assays for HPV verification.

The lack of ability of the PCR method to detect the exact kind of cells infected with HPV is also of upmost importance. In this way PCR may overestimate the relationship between the virus and BC [44]. False positive results may also occur through amplicon contamination, antibody cross-reactivity with unintended antigens and high background staining in a detection system. On the other hand, false-negative results can be attributed to test insensitivity, inadequate antigen retrieval procedures or problems with tissue fixation and preparation. In conclusion, there has been substantial evidence presented in this review that suggests HPV as a causative BC agent. Nevertheless, data remain contradictory resulting in a lack of consensus [18]. With respect to its possible role in BC development, HPV meets virtually all the criteria verified to test the validity of viral implication of this nosologic entity.

Conflict of interests

The authors declare no conflict of interests.

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