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Exploring The Association Between Human Papillomavirus (HPV) And Breast Carcinoma: A Review

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ABSTRACT
Anal, cervical, and oropharyngeal malignancies are all known to be caused by the human papillomavirus (HPV). However, its exact function in Breast Cancer (BC) is still up for debate. Findings from a systematic literature search shed light on the possible link between HPV and BC. There could be a connection amongst HPV infection and the development of BC, as several works have shown HPV DNA in breast carcinoma tissues. There has been some conflicting evidence on the nature of the link between HPV and BC; some research has found the virus, while others have not. Different studies have shown different patterns of HPV genotypes in BC tissue; some have identified high-risk genotypes like HPV-16 and HPV-18, while others have shown a broad range of genotypes without any discernible pattern. To explain the significance of HPV in BC cases, better-designed research with bigger sample numbers and rigorous methodology are required.

Keywords: Human Papillomavirus (HPV); Breast carcinoma; Cancer; HPV DNA.

INTRODUCTION

Globally, Breast Cancer (BC) is the most common disease to be diagnosed and the primary cause of cancer-related deaths in women (1). Several risk factors are linked for breast carcinoma such as age, weight, family history, physical activity, contraceptive use, and consumption of alcohol (2). Breast lumps, bloody discharges from the nipple, and changes in breast size or form are common signs of BC. Human papilloma viruses are small, circular DNA viruses which belong to the family papillomaviridae, containing between 7,200 and 8,000 base pairs (bp) with a diameter of 55 nm. They consist of a 72 capsomere capsid containing the viral genome (3).

The relationship between HPV infection and cervical and oropharyngeal cancer is well recognized. However, the role of HPV in BC remains a topic of debate and ongoing research. Sexually transmitted viruses, such as HPV, cause genital warts to appear on infected people (4). Due to the production of oncogenic proteins, HPV might induce inflammation and this can make HPV a strong suspect for development of BC (5). The initial link between Human Papilloma Virus and BC was first identified by

Lonardo and his colleagues in 1992, marking a significant discovery in the field of oncology (6). BC's devastating impact is evident in the stark statistics: one woman losses her life every minute, and over 1,400 women succumb to the disease daily. There were over 680,000 deaths in 2020 due to BC, which impacted 2.3 million women globally. If left unchecked, the situation is projected to worsen dramatically with new cases potentially reaching 2.7million and deaths soaring to 870,000 by 2030 (7). This alarming trajectory underscores the urgent need for immediate attention, action and collective efforts to combat this growing health crisis and mitigate its devastating consequences. This comprehensive review summarizes the current evidence on the potential relationship amongst HPV infection and BC development, exploring the recognition of HPV in BC tissue, the prevalence of HPV subtypes, proposed mechanisms of HPV-induced carcinogenesis, epidemiological studies investigating the association, clinical implications, and future research directions.

Classification of BC

Nearly all BCs (90–95%) are adenocarcinomas, which develop from cells that line the milk ducts or lobular glands. While invasive ductal carcinomas (IDC) make up 75-80% of them, invasive lobular carcinomas (ILC) only make up 5-10%. Other types of invasive BC include mixed (ductal and lobular), inflammatory, metaplastic, adenoid cystic, cribriform, medullary, papillary, tubular, and mucinous carcinomas (8,9).. Based on the epidermal growth factor receptor type-2 (HER2), progesterone (PgR), and estrogen (ER) immunohistochemistry expression, BC is classified into four molecular subtypes, each with a unique treatment strategy and prognosis (10). The different subtypes include HER2-enriched (ER-, PgR-, HER2+), triple negative BC (TNBC) (ER-, PgR-, HER2-), Luminal A (ER+and/or PgR+, HER2-, Ki-67 <14%), Luminal B (ER+and/or PgR+, HER2-, Ki-67 high or ER+and/or PgR+, HER2+, Ki-67 any) (11). Molecular subtype could vary in the same people with 25% of BCs as tumors develop. A change to a more aggressive BC subtype (e.g., from Luminal A to TNBC) is indicated by an increase in Ki-67 and a decrease in ER and PgR when recurrences are compared to original tumors (12, 13).

HPV Subtypes

- The identification of over 200 distinct forms of HPV has been made possible by genetic variations revealed by DNA sequence data (14).
- There are 12 high-risk HPV types: HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59. HPV 16 and 18 genotypes are considered as two of the most common virus genotypes that has been found associated with cancers worldwide (15,16).
- For the first time, Yu *et al*., reported HPV-33 in 43.8% IDC patients in China (17).
- Sigaroodi *et al.,* detected HPV-16 and HPV-18 in 53.34% of BC cases, respectively, while Balci *et al.,* (18) reported 23% prevalence of HPV-16 in breast tumors.
- HPV -16 was the most prevalent serotype studied by Garcia *et al.,(19)*
- 5–12.6% of patients in Iran and Spain had HPV6/HPV11 (20), 1.5–11.5% of patients in Brazil and the UK had HPV31, 16–19.2% of patients in Thailand and the UK had HPV35, 23% of UK BC patients had HPV45 and 1.5–11% of patients in Brazil, the UK, and Thailand had HPV52 (21).
- According to a PCR cohort study, HPV type 18 was found in 55% of the 40 BC specimens, making it the most frequent type. HPV type 16 was found in 13% of the cases. 15 individuals had the same HPV type found in both benign and malignant cases. In 72% of benign breast specimens and 59% of invasive BC specimens, HPV E7 proteins were found (22).

The presence of high-risk HPV subtypes raises questions about their potential oncogenic role in breast carcinogenesis and requires further investigation into their specific mechanism of action (23).

Proposed mechanisms of HPV-induced carcinogenesis

A number of theories have been proposed to explain how HPV infection could play a role in the emergence of BC. Two basic theories have been put forward regarding how HPV might infect mammary gland cells, nevertheless, the precise mechanism is still unknown. The first theory states that women who have cervical dysplasias have mononuclear white blood cells in their lymphatic or circulatory systems, which allow HPV to enter the mammary glands. When a primary tumor is malignant, plasma flow can be used to transfer the tumor cells. Furthermore, HPV virions might spread to different organs from the original infection site (24). Since the HPV lifecycle takes place in the epithelial layers, some scientists contend that the likelihood of HPV viremia is low (16). One more theory is predicated on extracellular vesicle activity. There is still a lot of debate on the increasing trend of HPV infection spread. Patients with HPV DNA-positive squamous cell carcinoma of the middle rectum and BC patients had HPV DNA in serum-derived extracellular vesicle activity (25). However, experimental evidence suggests potential mechanisms by which HPV may contribute to breast carcinogenesis through interactions with hormonal, immune, and genetic factors (26).

HPV viral proteins, such as E6 and E7, have been shown to interfere with cellular pathways involved in cell cycle regulation, apoptosis, and DNA repair, potentially promoting cellular transformation and genomic instability (27).

BRCA1 and BRCA2, two crucial biological components that interact with HPV proteins, are the susceptibility genes for breast and ovarian cancer. These genes are well-known for producing tumour suppressors, which stop the growth of tumours by repairing DNA damage (28). Any decrease or disruption of the expression of BRCA1 or BRCA2, which are important in the repair process of damaged DNA, may result in cancer. Mutations of this gene can be responsible for more than 80% of inherited ovarian and BCs (20). In addition, HPV infection can induce chronic inflammation and immune dysregulation in breast tissue, creating a tumour-promoting microenvironment (29).

Detection of HPV in breast tissue

Various viruses including bovine leukemia virus, EBV, MMTV(Mouse Mammary Tumor Virus) and HPV have been investigated as potential contributors to BC development. The 1944 discovery of MMTV induced BC in mice sparked research into viral links to human BC. In 1990, HPVs were shown to immortalize mammary cells, reducing their growth factor dependence. A large number of studies have shown HPV DNA in breast cancer patients since Di Leonardo's 1992 discovery of 30% of breast and lymph node samples containing HPV-16 DNA, indicating a potential link between HPV infection and BC (30).

A systematic review of 23 studies from 9 countries, covering 6 continents, analysed 3,243 breast tissue samples for HPV presence. The studies conducted between 2004 to 2022 had a mean patient’s age of 51.34 years, ranging from 35.2 to 59.0 years. Various specimen types were used including formalin-fixed paraffin-embedded (FFPE) tissues (47.83%), fresh/frozen tissues (30.44%), and paraffin-embedded (PE) tissues (17.39%). The review found an overall HPV prevalence of 17.08% (554/3,243) with 21.95% (445/2,027) in BC patients and 8.96% (109/1,216) in controls. IDC was the most common BC type, reported in 74% of studies, with a prevalence range of 31.08-97.33%. This comprehensive rev-

ew provides valuable insights into HPVs presence in breast tissue samples worldwide (30).

Another systematic review of 74 studies, comprising 7,156 BC biopsies revealed a significant presence of Human Papilloma Virus(HPV). The study conducted from 1990 to June 2022.The overall prevalence of HPV was 25.6%, with a slightly higher rate of 26.2% observed in case-control studies, indicating a 5.55-fold increased risk. Subtype analysis showed HPV-16 to be the most prevalent accounting for 9.6% of cases. Geographical variations were noted with Europe reporting the highest HPV prevalence at 39.2%, while Australia showed a higher frequency of HPV-18. These findings highlight the substantial burden of HPV in BC, emphasizing the need for further investigation and consideration of HPV's role in BC development (31).

Many investigations have found HPV DNA in BC tissue samples using PCR and in-situ hybridization methods (32, 33). Using polymerase chain reaction (PCR) analysis, *Rodriguez et al.* found HPV DNA in 20.3% of the breast tissues from Mexican women (33). Using a PCR-based approach, *Carolis et al.* also found HPV DNA in 30.4% of BCs in Italy (34). There could be a connection between infection with HPV and the development of BC, as many investigations have found HPV DNA in certain breast carcinoma samples. Using the same subjects, Lawson et al. found the same high-risk HPV genotypes in cervical squamous intraepithelial lesions (SILs) and BC tissues (34). Women who tested positive for HPV in their cervical SILs also had HPV infection in their BC samples (35). Based on these results, the scientists hypothesized that HPV could reach breast tissue in HPV-positive cervical cancer patients via the lymphatic or blood circulation. One competing idea suggests that oral-breast or genital sexual contact can induce small wounds or micro-lesions on the areola or nipple, which might then infect breast tissue (36).

Out of 251 cases, 186 BC specimens showed HPV DNA in 51.8% of the cases and benign in 26.3% as reported by Garcia *et al.*, in Spain (19). Villiers *et al.*, identified HPV DNA in 20% of breast samples using PCR-based techniques in Europe (2). Similarly, Cavalcante *et al*., identified HPV DNA in 49.5% of BC from women in the northeast region of Brazil by PCR analysis (37). In a meta-analysis by Haghshenas *et al.*, which included 11 studies of 1539 Iranian women with BC, described an HPV prevalence of 23.6%, and developing BC was estimated 5.7%. This study showed a high prevalence of HPV infection among women with BC (38). Meta-analysis showed an increased risk of breast carcinoma with HPV. Subgroup analysis showed a positive association of three high risk HPV types HPV16, 18 and 33 (39). Nationwide population study conducted by Lin *et al.*, using Taiwan's centralized health data, managed by the Ministry of Health and Wealth fare and Taiwan Cancer Registry showed the risk of BC was higher when compared to head and neck cancer and cervical cancer which are established to have causal connections with HPV (4).

A study of 56 BC patients in north-eastern Brazil revealed notable characteristics. Consistent with national trends, over 50% of patients were above 56 years old, with 80% of BC cases in Brazil affecting women over 50. The majority of patient's experienced early menarche (11-14 years) and late menopause (45-50 years), potentially increasing their risk due to prolonged estrogen exposure. However, this research found no significant correlation between these reproductive factors and BC development. Interestingly, oral contraceptive use, previously linked to BC, had minimal impact in the patient group, as most did not use hormonal contraception. This study also found that most patients had between one and three children, and over half of them breastfed. Surprisingly, breastfeeding which is often considered protective against BC, did not appear to have a protective effect in most of the patients. This suggests that multiple risk factors contribute to BC development and breastfeeding may not be enough to

counterbalance other risk factors in many cases. Nearly 79% of patients had no family history of BC, suggesting that factors beyond genetics played a significant role in the development of BC in these individuals. Contrary to expectations, their study found that most BC patients in the Al-Dhahira population were aware of and practised self-examination and mammography, unlike the general population, which showed a concerning lack of knowledge about screening methods. They showed that the predominant BC types were IDC and triple-negative BC. Notably, IDC, which accounts for 50-80% of all BC diagnoses, was the most common type observed in their patient population. The analysis revealed a single case of invasive lobular carcinoma that tested positive for HPV, which was also characterized as triple-negative, highlighting a rare occurrence of HPV association with this specific BC subtype. Findings indicated that most samples had an E2/E6 ratio of less than 1, implying a mixed HPV status, characterized by a combination of episomal and integrated viral DNA. HPV 16 has been detected primarily in advanced stage BCs (grade II and III), implying a connection to more aggressive tumor behaviour which may impact treatment outcomes and patient survival. Authors recommended additional investigations with larger cohorts and broader regional representation, fostering a more comprehensive understanding between the association of HPV and breast carcinoma (40).

HPV DNA was detected in 25.2% of BC tissues, mainly in advanced stage III cases (54.4%). The study proposed a novel link between HPV gene products and chemoresistance is, potentially through interference with crucial cellular genes. While HPV's involvement in tumor development is supported, its precise contribution to chemoresistance requires additional research to understand its mechanisms (41).

However, other studies have failed to replicate these findings which cast doubt on the role of HPV in the pathogenesis of breast carcinoma (42). Some researchers have failed to detect significant HPV DNA in BC samples, casting doubt on a direct causal relationship. The prevalence of HPV in BC varies extensively across studies, ranging from 10% to 80%, subject on factors such as sample size, geographical location, and HPV detection methods (43). One of the case–control studies examined in 193 Danish women diagnosed with BC showed no etiological correlation with HPV and breast carcinoma (44). One more study examined for the occurrence of HPV DNA in fresh frozen BC and normal breast tissue specimens achieved from patients in Australia. It showed no suggestion of HPV DNA with the BC (45).

Epidemiological studies

Research on the link between HPV infection and the likelihood of developing BC in nationally representative samples has shown conflicting findings. The mechanism of virus-induced oncogenesis in breast tissue remains a mystery, and more molecular investigations are needed to fill this knowledge gap (4). While some studies have shown a link between HPV infection and an increased risk of BC, other investigations have failed to find any such link even after controlling for other possible variables (46). Methodological differences, geographic variations, and study design limitations can lead inconsistencies in study results and hinder the interpretation of epidemiological data (47).

Clinical effect

Important implications for BC prevention, diagnosis, and treatment techniques might arise from the discovery of a causal connection between HPV infection and the disease. Treatment and prevention of HPV-associated BC are possible with the use of antiviral drugs and HPV vaccinations (48).

Future directions

The involvement of HPV in the development and progression of BC needs more investigation. To further understand the link amongst infected by HPV and the risk of BC, large-scale studies with long-term follow-ups are necessary. In order to find effective ways to treat HPV-associated BC and discover possible therapeutic targets, molecular investigations are necessary.

CONCLUSION

A relationship between HPV infection and BC has been suggested in certain studies, while other publications have failed to find any such relationship. Therefore, further research is required to conclude the specific clinical consequences of HPV infection and BC. They must do more clinical, molecular, and epidemiological studies on HPV-associated BC if it is possible to find better ways to detect it, prevent it, and treat it.

CONFLICT OF INTEREST

No conflicts of interest declared.

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