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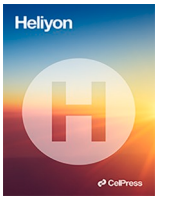

Review article

Correlation between breast cancer and human papillomavirus (HPV) infection

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ABSTRACT

Breast cancer (BC), the most common malignant tumor in women worldwide, has been increasing in incidence and mortality year by year. While significant progress has been made in understanding the pathogenesis of breast cancer, certain aspects remain under investigation. Human papillomavirus (HPV) is known to be closely associated with a variety of cancers, including cervical, vulvar, anal, and head and neck cancers. It is important to note that while HPV is associated with the mentioned cancers, its direct association with breast cancer remains a topic of debate and research. In this paper, we review the research progress on the correlation between breast cancer and HPV infection, and put forward the problems in the current research. This review aims to shed light on the current understanding and controversies surrounding the correlation between HPV infection and breast cancer, providing insights for future research aimed at enhancing prevention and treatment strategies.

1. Introduction

Breast cancer (BC) is one of the most common malignant tumors among women in the world, with its incidence rate and mortality increasing year by year. However, the pathogenesis of breast cancer is still not completely clear. Recent studies have suggested a potential link between human papillomavirus (HPV) infection and breast cancer. However, further research is needed to establish the nature and significance of this association.

Human papillomavirus (HPV) is a small double stranded circular DNA molecule belonging to the family Papillomavirus. Its genome can be divided into three parts: the early region (E) encoding proteins primarily involved in viral DNA replication and cell transformation, the late segment (L) encoding viral structural proteins, and the noncoding region (LCR) [1,2]. At present, it is known that there are no less than 150 types, which can be divided into 5 genera based on differences in L1 gene DNA sequences [3]. And according to the risk of inducing cervical cancer (CC), some subtypes of HPV belonging to the genus of α can be divided into high-risk (HR) HPV and low-risk (LR) HPV [4]. The low-risk types, such as HPV-6 and HPV-11, share a low-risk HPV lifecycle organization and do not typically cause neoplasia [5]. But recently, HPV42, also usually classified as a “low-risk" type, was found to be the main cause of digital papillary adenocarcinoma, an uncommon malignant tumor of the fingers and toes [6]. Among the high-risk types, HPV-16 and HPV-18 are the most prominent, accounting for over 80 % of the global CC burden, while other types are typically associated with cervical cancer as well as anal and genital cancer, including HPV-31, HPV-33, HPV-45, and HPV-58 [7].

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2. Relationship between HPV infection and breast cancer

2.1. Epidemiological relationship between HPV infection and breast cancer

Since Di Lonardo et al. firstly clarified the potential relationship between HPV infection and breast cancer in 1992 [8], there have been increasing studies reporting the detection of HPV DNA in breast cancer tissue, with detection rates ranging from 0 % to 84.38 % [9–40] (Table S1). Simões et al. conducted a comprehensive analysis of several studies and found that the overall detection rate of HPV in breast cancer was 23 %, varying from 13.4 % in Europe to 42.9 % in North America and Australia [41]. It can be seen that there are certain differences in the detection rate among different regions. Sometimes, even within the same region, the reported detection rates can vary significantly.

For example, the detection rates of two studies from Iran were 0 and 48.6 %, respectively [23,35].

Additionally, there are variations in the prevalent HPV types among BC patients in different regions. Most regions are dominated by HPV16, while some regions, such as Australia, have more HPV18. In addition, HPV6 and HPV11 are more prevalent among patients in Morocco, Turkey and Northeast Brazil (Table S1).

Most HPV gene copy numbers detected in breast tissue are very low (0.00054–9.3 copies per cell) [27,28,42–44]. This could be attributed to the scarcity of mature HPV virus particles in terminally differentiated cells. Once cellular transformation occurs, virus replication stops and integrates into the host genome, leading to a sharp decrease in the detectable virus count [41]. However, some researchers also suspect that due to the low virus copy number, HPV might only play an indirect role in these malignant tumors [43, 45].

Studies conducted by Lv et al. indicate that HPV infection does not occur simultaneously in breast and cervical specimens, in other words, HPV infection in breast cancer tissue is more likely to be present in patients without cervical infection [46]. Similar conclusions have been reached by Ngamkham et al., who employed polymerase chain reaction and enzyme immunoassay methods, their findings suggest that HPV infection is not the primary risk factor for the development of breast cancer, and may only contribute to a relatively small proportion of breast cancer or nonmalignant lesions [34]. Some research results even indicate that there is no relationship between HPV infection and the development of breast cancer [35]. The probability of HPV-positive women suffering from breast cancer is 5.9 times higher compared to HPV-negative women [30]. Purrahman et al. insist that HPV infection is associated with a poor prognosis in breast cancer patients [47], because some researches indicate that invasive ductal carcinoma (IDC) exhibits relatively higher incidence of HPV infection [24,37].

The reasons for these inconsistencies may be attributed to variations in sampling and tissue processing procedures, detection methods, primer design, breast cancer subtypes of the sample, and differences among diverse populations. For example, compared to individual polymerase chain reaction (PCR) methods, the detection frequency of HPV through sequencing or in situ hybridization is relatively higher; also, the detection rate of HPV in paraffin embedded specimens is lower than that in fresh frozen tissues [42]; furthermore, among various breast cancer subtypes, Luminal B subtype or ER-positive individuals exhibits relatively higher incidence of HPV infection [29,38].

2.2. Oncogenic mechanisms of HPV infection in breast cancer

2.2.1. HR-HPV in BC

For HPV infection to occur, the virus particles must infect the target cell through microtraumas [48]. After successful entry into the initial outbreak of genome replication, the virus establishes a stable infection, during which the viral genome synchronizes with cellular replication [49]. Subsequently, the lifecycle of the virus depends entirely on the differentiation process of keratinocytes in the stratified epithelium. The virus itself does not have a replication mechanism, so it is entirely dependent on cellular enzymes. Under normal circumstances, the replication cycle is highly controllable; however, for unknown reasons, this control can sometimes be lost, and viral DNA integrate randomly into the host cell genome [7]. Research indicates that the majority (86–100 %) of HPV genomes exist in integrated form in breast tissue, representing a crucial step for HPV in inducing the transformation of normal epithelial cell and carcinogenesis [27,43,50,51]. HPV-driven transformation triggers a germ cell-like transcriptional program that is conserved in all HPV-driven cancers [6].

Two major viral oncoproteins, E6 and E7, originating from the early regions of high-risk HPV genes， are directly involved in the development of HPV-related malignancies by targeting synergistically various cellular pathways involved in the regulation of cell cycle control, apoptosis, and cell polarity control networks as well as host immune response. It has been elucidated that the E6 and E7 oncoproteins are constitutively expressed in malignant lesions, leading to the inactivation of p53 and RB, respectively [52]. E6 facilitates the degradation of p53 by binding to the helper protein E6-AP, which is a component of the ubiquitin-mediated protein degradation pathway [53,54]. Furthermore, the E7 protein of high-risk HPV binds to RB and other pocket proteins, such as p107 and p130, causing dysregulation of the cell cycle [55,56]. This leads to genomic instability and is associated with the progression of normal cells towards malignancy. In addition, Islam et al. has identified two new novel E6/E7 fusion transcripts (E6 ^ E7 *I, E6 ^ E7 * II) in breast tumors, suggesting that the molecular pathogenesis of HPV in breast cancer differs from that in other tumors [42].

The Breast cancer Susceptibility Gene (BRCA1/2) are directly associated with hereditary breast cancer, regulating crucial cellular functions such as cell growth, cell cycle, DNA damage repair and apoptosis, thus exerting tumor suppression effects. Mutations in BRCA1/2 impair the ability of breast epithelial cells to initiate DNA repair processes following damage, significantly increasing the risk of cancer development. Some studies [57] have explored the relationship between BRCA1/2 mutations and HPV infection in breast cancer patients. However, the evidence supporting a direct link between HPV infection and BRCA1/2 mutations remains inconclusive,

requiring further research to establish any potential association. Additionally, while there have been investigations into the impact of virus infections on breast epithelial cells, including increased expression of protooncogenes such as c-jun and c-fos, and the potential activation of downstream cancer-related pathways, enhancing cell metastasis, and leading to the occurrence and development of breast cancer [16]. Furthermore, Ohba et al. found that HPV infection can induce overexpression of A3B, which is a proto-oncogene that is a source of genomic uracil damage and mutation. They concluded that HPV plays an important role mainly at the initial step of breast carcinogenesis. Once the cells undergo critical mutation at certain host genes initially, the persistent effect of A3B and its inducer HPV is no longer required given the mutator role of A3B, or their continued presence in the tissue may be selected against [33]. This view is similar to the "hit and run" theory that HPV initiates or contributes to cancer development, but in some cases vanishes from tumor cells before the disease is diagnosed, as summarized by Kudela et al. [58]. However, this theory is clearly controversial as many studies have found that HPV not only promotes the occurrence of cancer, but is also associated with its progression, metastasis, and prognosis [12,15,18,19].

MicroRNA-124-3p (miR-124-3p) is a member of the microRNA family that can participate in cell differentiation, growth and apoptosis. It is expressed at low levels in breast cancer and plays the role of tumor suppressor genes [59]. Human epidermal growth factor like domain protein 7 (EGFL7) is a secreted protein with increased expression in epithelial ovarian cancer, breast cancer and other malignant tumors, and is closely related to tumor angiogenesis [60]. Xiong et al. found a negative correlation between HPV infection and miR-124-3p expression, while a positive correlation was observed with EGFL7 in breast cancer tissue [17]. Yang et al. observed higher expression levels of Ki-67 and human epidermal growth factor receptor 2 (HER-2) in breast cancer from the HPV positive group compared to the HPV negative group. HPV infection induces high expression of the viral oncogenes E6 and E7, activating proto-oncogenes, and inactivating suppressor genes. This leads to dysregulated cell proliferation and apoptosis. Moreover, the upregulation of Ki-67 and HER-2 contributes to uncontrolled cell proliferation and malignant transformation [14]. In addition, HPV infection may also promote the progress of breast cancer and lead to poor prognosis of patients by promoting HER-2/c-erbB-2 and p53 expression and inhibiting Bcl-2 expression [15,61]. The regulation of Bcl-2 expression may be achieved by affecting he expression of NF-κ B p50 and NF-κ B p65, key components of the NF- κB signaling pathways [12]. However, according to Wang et al., HPV primarily influences breast cancer progression through the regulation of β-catenin and P16 proteins, with less significant association with p53 [19].

In addition, HPV may also work synergistically with the estrogen receptor (ER) signaling pathway. Wu et al. demonstrated that HPV E2 protein interacts with nuclear receptor co-activators, enhancing the transcriptional activity of ER α [62]. Therefore, high estrogen signal caused by ER gene overexpression may lead to overexpression of HPV genes E6 and E7 in HPV positive breast cancer cells, thus accelerating the progress of breast cancer [63].

HPV infection can also elicit immune response in breast cancer cells, including mechanisms such as tumor immune escape and immunosuppression. These reactions can affect the development and prognosis of breast cancer. Research results show that compared to breast cancer patients without HPV infection, HPV-positive breast cancer patients exhibit higher level of survivin, and its expression level is related to HPV and tumor metastasis, suggesting that HPV infection may accelerate the process of local autophagy and have an impact on breast cancer metastasis [18]. Ma et al. concluded, through research and analysis, that individuals infected with HPV16 exhibit elevated expression levels of programmed death receptor 1 (PD-1) and programmed cell death ligand 1 (PD-L1), which promotes immune escape in virus infected cells or tumor cells [13]. Santos et al. found that the main role of HPV in MDA-MB-231 was to regulate the immune response by increasing regulatory T cells and decreasing CD8 and CD56 T lymphocytes. In addition, the E6 and E7 oncogenes of HPV16 significantly reduced the expression of monocytes and even activated the M1 macrophages [64].

2.2.2. LR-HPV in BC

Previous studies have found that LR-HPV types, such as HPV6 and 11, do not display transforming activities in vitro assays and have rarely been detected in malignancies [65]. LR-HPVs can alter cell proliferation, apoptosis, and immortalization, but their carcinogenic potential is lower than that of HR-HPVs [66,67]. Even LR-HPVs may slow down the spread of cervical cancer to the invasive stage [68]. Thus, the role of LR-HPVs in BC receives far less attention. However, the recent discovery of HPV42 as an exception undoubtedly sounded the alarm for us. Leiendecker et al. have found that the cellular context in which HPV42 is present may determine the full oncogenic potential of HPV42. Specifically, HPV42, which is currently classified as a"low-risk" HPV type, can only lead to warts in the keratinocyte cell lineage of the mucosal, but it causes oncogenic transformation leading to DPAs in the eccrine lineage [6]. Considering that LR-HPV accounts for the majority of breast cancer patients in some regions [10,37,40], and the role of HPV in breast cancer is still unclear, it is necessary to deeply study the role of low-risk HPV in it, whether it is the "mastermind" or "accomplice", or just a "passer-by"?

3. Detection of HPV in breast cancer

At present, the detection of HPV in breast cancer tissue mainly uses flow cytometry fluorescence hybridization technology, next generation hybridization capture technology, immunohistochemistry and in situ hybridization. Flow cytometry fluorescence hybridization technology, also known as liquid phase chip technology or microsphere suspension chip, is a new type of biochip technology based on the xMAP technology developed by Luminex in the United States. It has the advantages of high throughput, high sensitivity, and fast response, but the disadvantage is that it requires the use of bead hybridization for PCR amplification products, which has a certain risk of contamination, and requires flow cytometry detection. The advantage of next-generation hybridization capture technology lies in the fact that there is no risk of PCR amplification product contamination, samples do not require DNA extraction, can detect the entire HPV genome, provide HPV viral load information, and have low detection equipment requirements for

HPV. The disadvantage is that most HR-HPV subtypes cannot be distinguished, the operation steps are slightly cumbersome, and some HPV subtypes have potential cross-reactivity with other HPV subtypes [69]. Immunohistochemical techniques, which rely on antigen-antibody reactions to visualize HPV16 E6 and HPV18 E7 proteins within tissues or cells, offer a straightforward and cost-effective approach. However, it is important to recognize that the techniques can be influenced by various factors, leading to potential false positive and false negative results. In situ hybridization technology generally provides superior detection capability for HPV when used on paraffin embedded samples compared to conventional HPV detection technology, However, it is worth considering that the sensitivity, simplicity, and detection flux of HPV in situ hybridization targeting DNA may not be as efficient as conventional HPV detection technology. In recent years, there has been increasing research on HPV E6/E7 mRNA in situ hybridization detection, with RNAscope [70] being the most widely utilized technique. In addition to the four mainly used methods mentioned above, HPV can also be genotyped by using next-generation sequencing (NGS). NGS is reported to be more sensitive than the conventional HPV genotyping methods. Moreover, for rare HPV variants, accurate results can only be obtained through NGS analysis, which is meaningful for epidemiological monitoring of HPV and HPV vaccination [71–74]. With the continuous improvement of sequencing technology and bioinformatics tools, NGS is expected to become the best choice for further exploring the carcinogenic mechanism of HPV and finding new-generation treatment methods in the future, which can not only promote scientific discoveries but also benefit other applications with significant economic and health impacts [71–73].

Sample types commonly used to test for HPV include fresh tissue, frozen tissue, and formalin-fixed, paraffin-embedded (FFPE), with the most commonly used being FFPE [11,18,25,26,28–30,32,35,37–39] (Table S1). Kudela et al. summarized all possible factors affecting HPV diagnostics in breast tissue. Sample size, samples age and samples type among the relevant factors. A low sample size affects the statistical power of the research; significant degradation of DNA occurs in 4–6 years of storage; the formaldehyde fixed tissue dewaxing process may damage or degrade the HPV virus within the tissue, potentially resulting in undetectable HPV in paraffin embedded specimens [57]. In addition, sampling errors and HPV contamination can also affect the accuracy of the results. Therefore, fresh tissue samples generally exhibit higher detection rates for HPV when compared with paraffin embedded specimens.

4. The problems

While the role of HPV in breast cancer remains uncertain, research is ongoing to understand its potential mechanisms of involvement. For example, the mechanism by which HPV infects the breast and enters breast cells is currently unclear. Although various hypotheses have been proposed, definitive evidence supporting these hypotheses is lacking. The first hypothesis regarding HPV infection in the breast is that HPV can be transmitted from cervical infection to the breast through lymphatic or blood circulation [75]. One hypothesis, proposed by De Villiers et al., suggests the 'anterograde catheter model,' which posits that HPV may infect the breast tissue through the skin of the nipple [76]. Some proponents of this hypothesis suggest that practicing healthy sexual behavior may reduce the risk of HPV transmission to the breast, and can help assess the risk of breast cancer and facilitate early diagnosis through HPV detection in breast duct lavage, nipple discharge and breast milk [24].

In addition, it is not clear how HPV enters breast cells, and there are currently two views. The first viewpoint is based on the relationship with the complex mechanisms of endocytosis and cell transport related to the alpha genus HPV types [membrane associated proteins, integrins, related membrane-associated proteins and transmembrane complexes, and epidermal growth factor receptor (EGFR)] [77]. Integrin α6 is considered a primary receptor for HPV16 in cervical cells [78]. And in breast tissue, integrin α6 and laminin-322 play crucial roles in maintaining normal breast morphology. It can also act as an HPV receptor during infection and promote tumor progression [79,80]. Another viewpoint suggests that extracellular vesicles (EVs) including exosomes, microbubbles, and apoptotic bodies, play a role in HPV transmission and tumor progression in breast cancer. HPV positive EVs generated from the primary site of infection can transfer to cells lacking HPV receptors, such as breast epithelial cells, and locally induce tumor cell proliferation [81]. Presence of HPV was also detected in the serum-derived extracellular vesicles [82].

Among the three systematic reviews on HPV infection and breast cancer published in the past two years, one carried out a meta-analysis of 23 studies from all over the world in the past 20 years, and found that the HPV DNA detection rate of 3243 BCE patients was 21.95 % (8.96 % in the control group), the other analyzed 74 studies in the past 30 years, and the HPV DNA detection rate of 7156 BCE patients was 25.6 %. The third analyzed 33 studies in the past 15 years, and the HPV DNA infection rate of 1890 BCE patients was 24 % (8 % in the control group) [83–85]. All three have confirmed the involvement of HPV in breast tumorigenesis, although one think that caution should be taken when analyzing the data due to the lack of scientifically rigorous and unified study design [85]. And without exception, HPV vaccines are thought to help prevent breast cancer. Studies with larger sample sizes or extensive epidemiological studies are needed to advance the knowledge in this area [83,85]. It is necessary to improve the methodological quality of HPV detection, such as a more uniform test selection [85] and detection of both integrated and free viral DNA [84]. In addition, one review suggested that the potential role of LR-HPVs in breast carcinogenesis should be investigated [83].

In theory, HPV vaccine should be able to prevent HPV related breast cancer. However, with the popularity of HPV vaccine, the burden of breast cancer is increasing globally [86–88]. Whether this phenomenon contradicts the Bradford Hill criteria for assessing causal relationships may require further clarification through longer-term clinical follow-up studies. The analysis of big data appears to simplify research on this topic. Guo et al. utilized data from the USCS database to assess the incidence of HPV-related cancers before and after the introduction of the HPV vaccine [89]. Although it does not include breast cancer, it provides one workable track. And the application of big data analysis in HPV carcinogenesis research goes far beyond this [90,91].

5. Conclusions

Primary prevention is a highly effective way to control cancer. Certain strains of HPV have been linked to the occurrence and progression of breast cancer. Thus, further elucidation is required regarding the mechanisms by which HPV infects the breast tissue and penetrates breast cells and how it enters breast cells in order to achieve effective disease prevention and risk assessment. WHO has launched a global initiative to scale up prevention, screening, and treatment interventions to eliminate cervical cancer as a public health problem in the 21st century [92]. The HPV vaccine used in this initiative should be equally beneficial to prevent breast cancer. To prove that HPV vaccine can reduce the incidence rate of BC can not only provide prevention and immunotherapy strategies for BC, but also confirm the correlation between them in turn. In addition, further in-depth research is needed to understand the role of LR-HPV infection in breast carcinogenesis for vaccine development and diagnostic targets.

Data availability statement

Data availability is not applicable to this article as no new data were created or analyzed in this study.

CRediT authorship contribution statement

Guimei Zhao: Writing – review & editing, Writing – original draft, Visualization, Supervision, Conceptualization. **Jinchun Chang:** Writing – review & editing. **Kaipeng Wei:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e37027.

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