



The Prevalence of Human Papillomavirus among Iranian Breast Cancer Patients: A Systematic Review and Meta-analysis

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Abstract

Introduction: Viruses are known to be vital risk factors for several cancers. Various studies have investigated the association between breast cancer and HPV, and they have reported conflicting results. The aim of this study was to evaluate the prevalence of HPV among Iranian breast cancer patients.

Methods: To identify related e-studies published after January 2018, we searched national (SID, Iranmedex, Magiran, and Irondoc) and international (Pubmed, Google Scholar, Scopus, and Science direct) databases. The search strategy was performed using the following keywords and their Persian equivalents: "Prevalence", "Serum Prevalence", "Number", "Seroprevalence", "Odds Ratio", "OR", "Relative Risk", "RR", "Cohort", "Case Control", "Cross-sectional", "Human Papillomavirus, HPV, Breast Cancer, Breast Carcinoma, Genotype, High Risk Genotype, Iran. All statistical analyses were performed using Stata SE, V.11 software.

Results: According to our analysis, a pooled prevalence of HPV among Iranian breast cancer patients among 344 patients was 7.9% (95% CI: 5.1%-10.6%, I^2 : 0.0%).

Conclusion: Although researchers have linked HPV to cervical cancer, the association between breast cancer and HPV is controversial. It is difficult to determine the association between HPV and breast cancer, and further studies with more samples and evaluations of other parameters are required. In this study, the HPV genome was found in 7.9% percent of all breast cancer samples. Further studies are needed to clarify the role of HPV in breast cancer in Iran. If HPV is found to a risk factor for breast cancer, solutions such as antiviral therapy or vaccination prevention would be effective.

Keywords: Human Papillomavirus, HPV, Breast Cancer, Iran

Introduction

Breast cancer is the most common cancer and the leading cause of death in women around the world (1). Also, it is the second and first deadliest cancer in American and European women,

respectively, with an unknown cause in 50 to 80 percent of cases. After uterine and skin cancers, it is the third most common type of cancer and the most common cause of cancer-induced death among Iranian women (2). Several biological factors and risk factors associated with breast

cancer have been identified (3). Viruses are known to be vital risk factors for several cancers. Several studies have investigated the role of herpes virus, Epstein-Barr virus and mouse mammalian tumor virus in breast cancer. Human papillomavirus (HPV) is a sexually transmitted infection that has been linked to certain types of cancer, including cervical cancer (4,5).

There are over 100 different types of HPV. HPV infection is usually asymptomatic and people are often unaware of the infection. In some cases, it causes abnormal and non-cancerous lumps in the skin of different parts of the body and genital warts (6). High-risk types of HPV can cause precancerous and cancerous lesions (7). Reports related to HPV infection in breast cancer samples vary from 1.6% to 86.2% in different countries and ethnicities (8). Although many studies have been conducted on the role of HPV infection in breast cancer, its function is still unclear. However, previous laboratory studies have shown that HPV immortalizes breast epithelial cells through the expression of E6 and E7 oncogenes (9). Various molecular studies have reported conflicting results regarding the presence of HPV DNA in breast cancer tissues (10-12). Based on the studies conducted in China, Australia, Italy, Japan, the United States, Norway, Greece, Korea, Mexico and Taiwan, HPV infection was observed among women with breast cancer (13). A systematic review conducted in Europe, North America, and Australia found an association between HPV and breast cancer (14). Various studies have investigated the association between breast cancer and HPV, and they have reported conflicting results (15-17). The aim of this study was to evaluate the prevalence of HPV among Iranian breast cancer patients.

Methods

To identify related e-studies published after January 2018, we searched national (SID, Iranmedex, Magiran, and Irondoc) and international (Pubmed, Google Scholar, Scopus, and Science direct) databases. The search strategy was performed using the following keywords and their Persian equivalents: "Prevalence", "Serum

Prevalence", "Number", "Seromapidemiology", "Odds Ratio", "OR", "Relative Risk", "RR", "Cohort", "Case Control", "Cross-sectional", "Human Papillomavirus, HPV, Breast Cancer, Breast Carcinoma, Genotype, High Risk Genotype, Iran. We used the "AND" operator to identify articles, including all keywords applied to the search strategy. We also used "OR" to include articles with one of the related keywords. Any initial study with words that did not meet the study goals was excluded from the search results by the "NOT" operator. The search was conducted in May 2022. Also, we reviewed study sources to increase search sensitivity. The two researchers randomly evaluated the search strategy and found that all relevant studies had been identified. In addition, some experts and research centers were interviewed to find any unpublished related studies.

Study selection

Full texts or abstracts of all articles, evidence and other reports were provided during our advanced search. First, we excluded the duplicates. Then, the irrelevant articles were excluded after reviewing their titles, abstracts and full text. We also reviewed the results in detail to identify and exclude duplicate studies to prevent bias.

Inclusion criteria

All studies written in Persian or English and passed through the above evaluation stages and achieved the required quality scores with the following characteristics were considered eligible for the final meta-analysis:

- 1-Cross-sectional studies (descriptive-analytical), case-control or cohort studies after 2016.
2. Studied reported sample size studies according to their design. For example, total sample size in cross-sectional studies, specific case-specific sample size in control case studies, and specific sample size exposed- without exposure in cohort studies.
3. Cross-sectional studies reported the prevalence of HPV infection among breast cancer patients.
4. Case studies have reported the prevalence of HPV among women with and

without breast cancer. 5. Cohort studies have reported breast cancer in women with and without HPV infection.

Exclusion criteria

1. Case report or case series. 2. Studies did not report a specific sample size. Cross-sectional studies did not report HPV infection among women with breast cancer. Case-control studies did not report the prevalence of HPV infection among control subjects. 5. Cohort studies did not report the prevalence of HPV infection among exposed and non-exposed participants. 6. Duplicate studies (only one of them was included). 7. Studies presented in congresses and meetings without full text. 8. Studies did not obtain sufficient quality scores.

Data extraction

The data extracted from case-control and cohort studies included title, name of first author, and date of study, sample size, and frequency of HPV. All extracted data were entered into the Excel spreadsheet.

Data analysis

In cross-sectional studies, the standard error of HPV infection prevalence was calculated using the binomial distribution formula. The sensitivity analysis was performed to diagnose this study, which had a greater effect on heterogeneity. We also designed forest plots to represent points and integrated estimates with 95% confidence intervals (intersecting lines). Each box in these plots showed the weight of the study. Bag test with significance level of less than 0.01 was also performed to evaluate the publication bias. All statistical analyses were performed using Stata SE, V.11 software.

Results

At the beginning of our search, 1132 studies in the area of study question were identified, which were limited to 372 cases after limiting the search strategy and eliminating duplicates. After reviewing the titles and abstracts, 212 unrelated articles were excluded and after reviewing the full texts, 156 articles were excluded. Finally, 5 eligible studies were included in the meta-analysis (Figure 1).

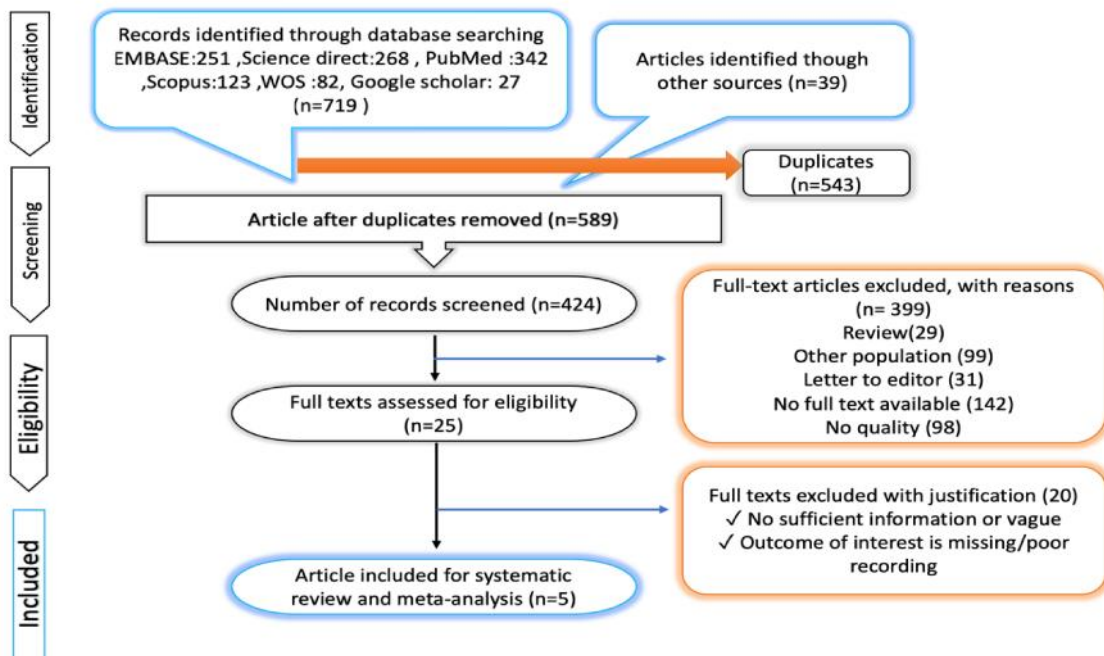


Figure1. Prisma flow diagram

Study Characteristics

A total of 344 breast cancer patients with a mean age of 49.6± 4.7 were enrolled in the study. All

included studies were of prospective design. Out of 5 studies 3 were conducted in Tehran , one in Isfahan and one in Kerman(Table1).

Table1. Characteristics of the included studies regarding the prevalence of HPV

Author	Year	Province	Design	Sample size	Mean age	Prevalence of HPV
Ghaffari	2018	Tehran	Pros	72	52.15 ± 10.63	4/72(5.55%)
Hosseinpouri	2020	Isfahan	Pros	40	N/A	3/40(7.5%)
Aghdam	2019	Tehran	Pros	75	48.2±10.8	0
Mofrad	2021	Tehran	pros	59	50	7/59(11.8%)
Afshar	2018	Kerman	pros	98	48.09±3.5	8/98(8.2%)

Meta-analysis of the prevalence of HPV among Iranian breast cancer patients

According to our analysis a the pooled prevalence of HPV among Iranian breast cancer patients among 344 patients was 7.9%(95%CI:5.1%-10.6%, I²: 0.0%)(Figure 2).

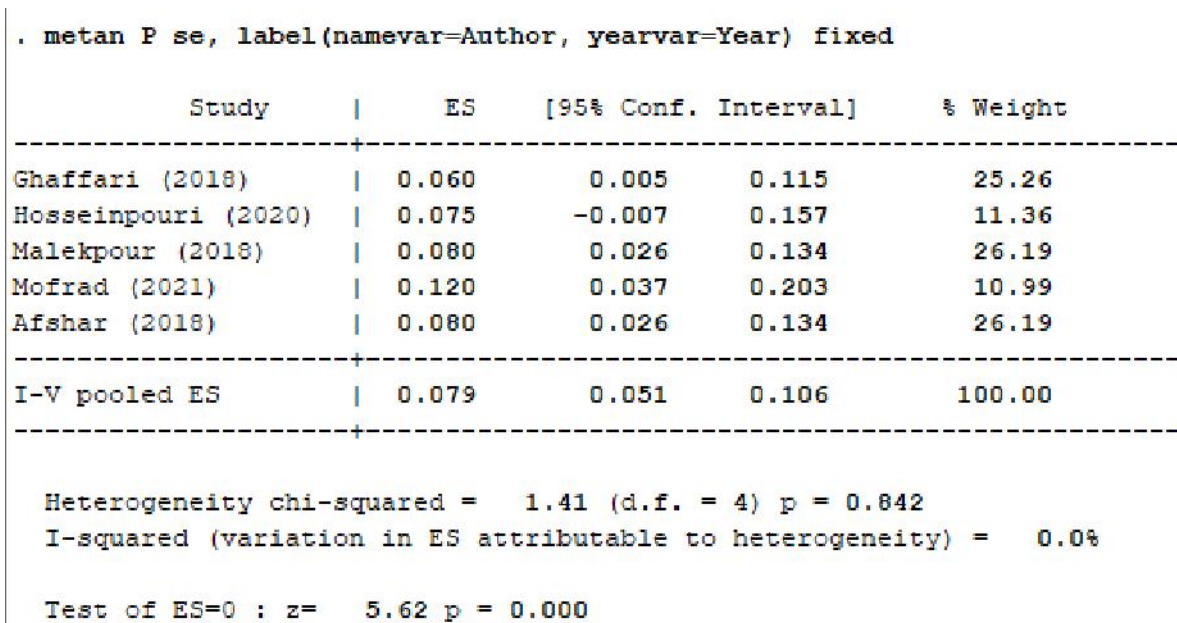


Figure 2. Meta-analysis of the prevalence of HPV among Iranian breast cancer patients

Discussion

The role of infection in causing several cancers has been well proven in recent years. Among the various viral agents, HPV is associated with a variety of cancers in humans, such as cervical cancer, anal cancer, and a number of genital and oral cancers (18). Despite some reports on an association between HPV and breast cancer, the role of HPV infection in breast cancer carcinogenesis is still being debated.

The results of the present study revealed a low prevalence of HPV DNA in breast cancer samples. Our results are in line with the results of other studies from different geographical areas, which reported 4.4% and 3.57% of breast cancer samples in Mexican and Thai women, respectively. Similarly, Choi et al. carried out a study on Korean women with breast cancer and found an HPV diagnosis of 5.6 percent. Past studies investigating the prevalence of HPV in the general population in Iran reported it at a range between 0.6 and 5.7% (18-20). Since the overall prevalence of HPV in breast cancer in our study was ... percent, it is recommended to consider HPV as a vital risk factor for clinical and epidemiological approaches. Our results were in line with the results of other meta-analyses.

In a global meta-analysis conducted by Simoes et al. on 29 studies from 1990 to 2011, the estimated overall prevalence of HPV in breast cancer patients was reported at 23%, ranging from 13% in the European population to 42.9% in the African and Australian populations. They also reported a 5.9 odds ratio for breast cancer in HPV-positive cases compared with control group (21). There are other meta-analyses that identify HPV infection as an effective risk factor for breast cancer and report a high odds ratio of 3.6 to 4.02 (22, 23).

Regarding HPV genotypes, two meta-analyses examined the prevalence of different HPVs, and both reported higher prevalence of high-risk HPVs, including 16, 18, and 33 percent, compared to other HPV strains. In a study conducted by Ni Li et al., the prevalence of these three high-risk HPVs was estimated at 7.04, 7.13, and 14.36 percent, respectively, but other HPVs, including low-risk HPVs, were less than 3 percent (22 and 23). Also, some articles suggest that there is no evidence to consider HPV as a risk factor for breast cancer (24, 25). This discrepancy in the results of different articles may be rooted in different populations studied, insufficient sample size, sexual behaviors of the cases studied and technical issues such as samples and sample quality, sensitivity of techniques used and technical errors.

Large-scale case-control, cross-sectional, and even cohort studies using multiple sample sources and combined detection techniques can result in more reliable and decisive data.

Beyond the epidemiological evidence mentioned, there is biological evidence that HPV may play a role in causing cancers, including breast cancer. Several proteins expressed in high-risk HPV genotypes are thought to act as oncoproteins. These HPV-related oncoproteins are involved in proliferation. In short, by integrating HPV into the host cell genome, it begins to express the E6 gene.

This protein inhibits tumor suppressor p53 protein. E7, as another HPV-related oncoprotein, binds to the tumor suppressor retinoblastoma protein. Other proteins, such as E1 and E2, are also involved in accelerating HPV replication. All of these proteins are accused of damaging and stabilizing DNA, as well as inhibiting tumor suppression mechanisms and apoptosis, and in

turn tumorigenesis. Regarding the breast cancer, certain pathological pathways are thought to be involved in tumorigenesis. Studies have shown that proteins E6 and E7, especially those expressed by high-risk HPVs, reduce the regulation of P53, NFX1, and BRCA1 and lead to the upregulation of protomor signaling pathways (8).

Conclusion

Although researchers have linked HPV to cervical cancer, the association between breast cancer and HPV is controversial. It is difficult to determine the association between HPV and breast cancer, and further studies with more samples and evaluations of other parameters are required. In this study, the HPV genome was found in percent of all breast cancer samples. Further studies are needed to clarify the role of HPV in breast cancer in Iran. If HPV is found to a risk factor for breast cancer, solutions such as antiviral therapy or vaccination prevention would be effective.

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