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Human Papillomavirus Infection and Risk of Breast Cancer in Iran: A Meta-Analysis

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Abstract

Background: Breast cancer is the most common malignancy and a leading cause of death in women. Viruses are known to be the risk factors for breast cancer.
Objectives: This systematic review and meta-analysis aimed to evaluate the association between human papillomavirus (HPV) and the development of breast cancer in Iranian women.
Methods: The international databases, including Web of Science, Embase, PubMed, Cochrane, and Scopus, were searched in this study. Furthermore, relevant studies published on the association between HPV and breast cancer were identified using the appropriate keywords. The data were analyzed in Stata software (version 14) using the random-effects model.
Results: In total, 18 studies were found eligible to be included in this study. The total sample size was determined at 2466 cases with the mean ages of 47.25 and 39.9 years for experimental and control groups. The overall findings showed a significant relationship between developing breast cancer and HPV infection. The results also revealed that the HPV infection increased the risk of breast cancer in women 5.02 fold more than those without HPV infection (95% CI: 3.46-7.29, I2=65.2%, P=0.003). In addition, the prevalence of HPV infection among women with breast cancer was estimated at 25.66% (95% CI: 17.34-34.95, I2=86%, P=0.000).
Conclusion: HPV infections, especially high-risk HPVs, are significantly frequent in breast cancer samples and should be considered an important risk factor for developing breast cancer.

Keywords: Breast cancer, Human papillomavirus, Meta-analysis

1. Background

Breast cancer is the most frequent cancer and the leading cause of death among women worldwide (1). Furthermore, it is the second and first deadliest cancer among American and European women, respectively, with unknown etiology in 50%-80% of cases. After uterine and skin cancers, breast cancer is the third most common type of cancer and the most common cause of cancer-related death among Iranian women (2). Several biological factors and risk factors have been introduced to be associated with breast cancer (3).

Viruses are known as critical risk factors for several cancers. Numerous studies have examined the role of Herpes Virus, Epstein-Barr virus, and Mouse Mammalian Tumor virus in breast cancer. Human papillomavirus (HPV) is a sexually transmitted infection, the association of which with certain types of cancers, including cervical cancer, has been well established (4,5)

There are more than 100 different strains of HPV. The HPV infection is asymptomatic in most cases, and people are often unaware of the infection. In some cases, it causes abnormal and non-cancerous masses (tumors) on 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 on HPV infection in breast cancer samples vary from 1.6% to 86.2 % in different countries and ethnicities (8). Despite many studies on the role of HPV infection in the development of breast cancer, its function is still unclear. However, previous *in vitro* studies have shown that HPV makes the breast epithelial cells immortal through the expression of oncogenes E6 and E7 (9). Different molecular studies have reported conflicting results on the presence of HPV DNA in breast cancer tissues (10-12).

2. Objectives

This systematic review and meta-analysis aimed to evaluate the association between HPV and breast cancer among Iranian women.

3. Methods

This systematic review and meta-analysis study was conducted according to the PRISMA statement (13).

3.1. Search strategies

In order to find published studies regarding the prevalence of HPV infection in Iranian patients with breast cancer, a comprehensive search was performed. The keywords included "breast cancer", "breast carcinoma", "breast neoplasm", "HPV", "Human papillomavirus", "Human papilloma virus", "frequency", "prevalence", "genotype", and "Iran" that were used in certain combinations and search strategies using OR and AND on international databases, such as ISI, PubMed, Embase, Scopus, as well as Iranian national databases, including SID and Magiran. The keywords were also checked on Google scholar's search engine to find uncovered articles. Furthermore, the references of selected articles were checked for relevant articles. All records were then imported into Endnote software and duplicated records were deleted.

3.2. Study selection

After deleting the duplicated records, the titles and abstracts of the remained records were checked to find the eligible studies using the inclusion and exclusion criteria. The inclusion criteria were: 1) original case-control and cross-sectional studies investigating the association of HPV infection with breast cancer in Iranian patients, 2) the presence of extractable intended data, and 3) accessibility of articles in full texts. On the other hand, the review articles, meta-analysis, animal and other preclinical studies, congress abstracts, articles in other languages than English and Persian, and retracted articles were excluded from the research procedure. Following that, the eligible studies were selected by two authors independently using the above-mentioned criteria, and the selected studies were checked and confirmed by all authors.

3.3. Data extraction and quality assessment

The data of the selected studies, such as authors' names, design of the study, publication date, age, number of cases and controls, number of HPV positive and HPV negative cases, and frequency of low- and high-risk HPV genotypes were extracted by two different authors. For genotype analysis, the genotypes were categorized into groups, including high-risk HPV genotypes (16, 18, 31, 33, 34, 35, 39, 45, 51, 52, 56, and 58) and low-risk HPV genotypes (6, 11, 42, and 43). The mentioned data were checked for potential mistakes by other authors and confirmed by all authors. The Newcastle-Ottawa Scale was used to evaluate the methodology and quality of the studies. In this regard, studies were scored and classified into three groups of low (scores 0-3), moderate (scores 4-6), and high (scores 7-9). It should be mentioned that none of the articles received a score of less than 4.

3.4. Data synthesis and analysis

Variables, including sample size and mean±SD of the intended data, were compared in this study. The weight of each study was determined according to its inverse variance. In order to check out the test heterogeneity of the included studies, the Q test and I^2 index were performed at an α-level error of less than 10% significance. Furthermore, the random-effect model was used to analyze the heterogeneous data. All data were analyzed in Stata software (Version 14).

4. Results

The present study investigated 18 eligible original articles (case-control=6 and cross-sectional=5) on the association of HPV with breast cancer in Iran (Tables 1, 2).

Table 1. Characteristics of the articles (case-control) reviewed in this study

First Author (reference)	Publication language	Year	Case (N)		Control (N)		Mean age±SD		Quality assessment score	OR (95% CI)
			Event (High-risk genotypes frequency)	Total	Event (High-risk genotypes frequency)	Total	Case	Control		
Bakhtyarizadeh (15)	EN	2017	0	150	0	150	35.2±12.15	45±9.46	5	-
Doosti (26)	Persian	2016	20 (10)	87	0	84	47.7±12.5		5	9.14 (3.61-23.17)
Malekpour Afshar (17)	EN	2018	8 (6)	98	0	40	48.09±3.5	41.22±3.48	5	4.41 (0.92-21.16)
Ahangar-Oskouee (27)	EN	2014	21 (3)	65	0	65			5	10.67 (4.21-27.05)
Khodabandehlou (28)	EN	2019	35 (31)	72	5 (5)	31	48.86±10.95	48.97±9.22	6	3.87 (1.64-9.15)
Sigaroodi (2)	EN	2011	15 (8)	58	1	41	47.77±12.55	34.20±9.70	7	5.54 (1.88-16.32)
Alavi (29)	Persian	2009	24 (16)	50	0	29	49.8		5	9.40 (3.50-25.26)
Kazemi Aghdam (30)	EN	2019	0	75	0	75	48.2	38.9	6	-
Manzouri (31)	EN	2014	10 (7)	55	7 (3)	51			5	1.39 (0.49-3.90)
Eslamifar (32)	EN	2015	0	100	0	50			6	-
Karimi (33)	EN	2016	2 (2)	70	0	70	47.8±10.1	31.5±10.4	7	7.50 (0.46-121.06)
tahmasebi fard (34)	Persian	2013	0	64	3	53	_		5	0.11 (0.01-1.05)
Total			135	944	16	739				5.02 (3.46-7.29)

EN: English

Table 2. Characteristics of the articles (cross-sectional) reviewed in this study

First Author (reference)	Publication language	Year	Sample size	Quality assessment score	Prevalence of HPV infection (%)
Ghaffari (16)	EN	2018	72	4	5.56
Rassi (35)	EN	2013	150	4	34.67
Mohtasebi (36)	EN	2016	84	5	32.14
Rezaei (37)	EN	2017	84	4	34.52
Ghaffari (38)	EN	2011	67	5	29.85
Salehpour (39)	EN	2015	326	5	22.70
Total			783		25.66

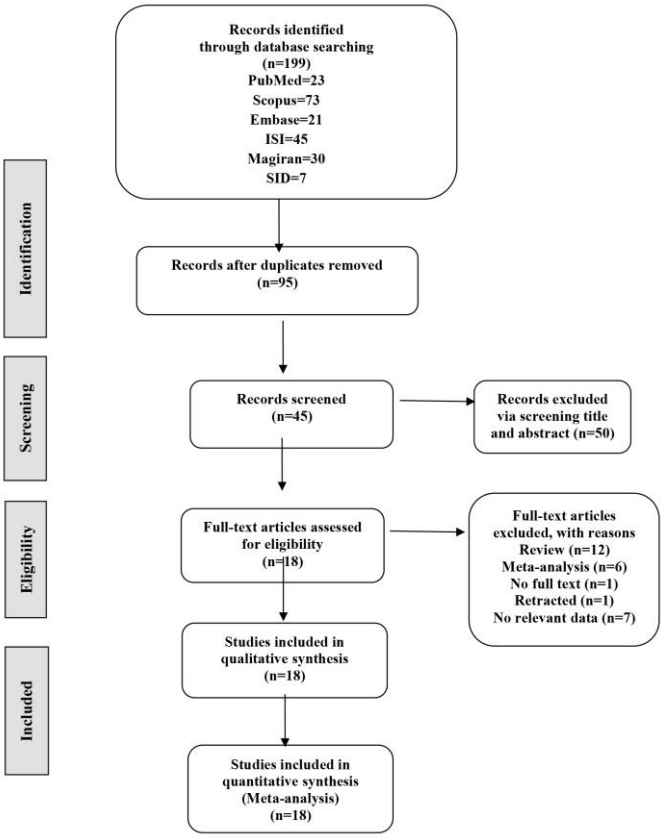

Figure1. PRISMA flow diagram illustrating the selection of articles

Figure 1 illustrates the steps for selecting studies. The total sample size was 2466 individuals with mean ages of 47.25 and 39.9 years for cases and controls, respectively. The overall estimate for odds ratio based on the random-effects model in a case-control study with peto analysis method was determined at 5.02 (95% CI:3.46-7.29, I^2=65.2%, P=0.003) (Figure 2). This result shows a significant relationship between developing breast cancer and HPV infection among subjected women; moreover, the HPV infection increases the risk of breast cancer in women 5.02 fold more than those without this infection.

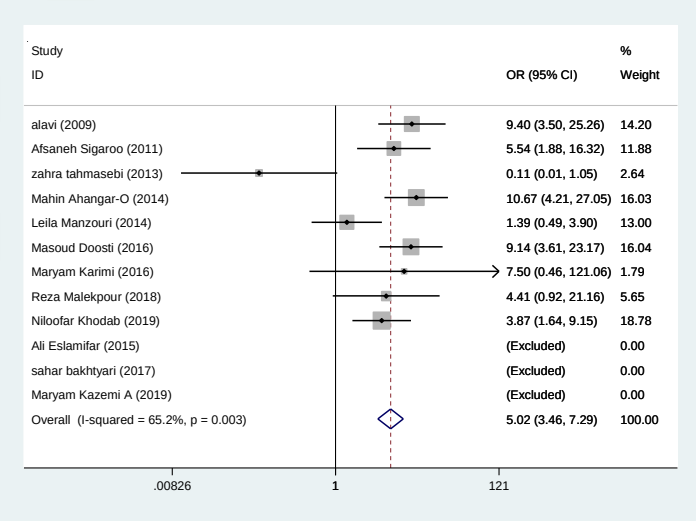

Figure 2. Forest plots for case-control studies investigating the relationship between the variables of human papillomavirus and breast cancer in Iran. Studies are stored in order of publication year and authors based on a random effects model. Square represents effect estimate of individual studies with more than 95% confidence intervals with the size of squares proportional to the weight assigned to the study in the meta-analysis.

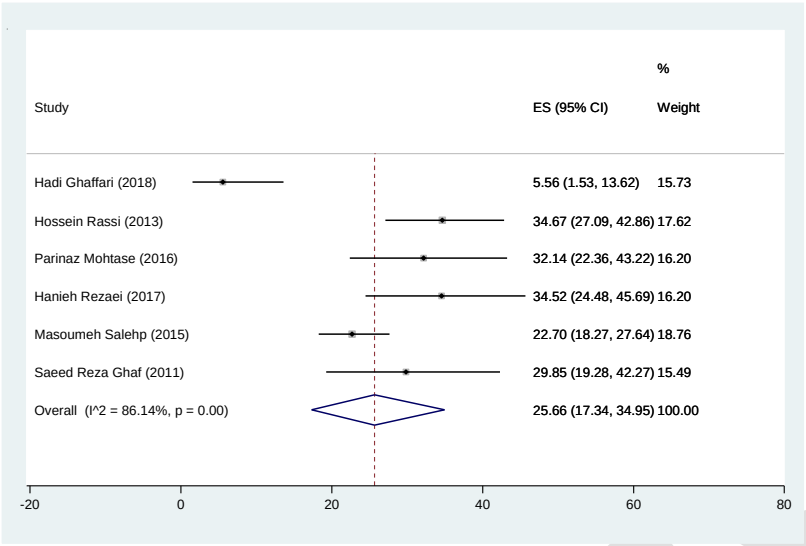

Figure 3. Forest plots for cross-sectional studies investigating the relationship between the variables of human papillomavirus and breast cancer in Iran. Studies are stored in order of publication year and authors based on a random effects model. Square represents effect estimate of individual studies with more than 95% confidence intervals with the size of squares proportional to the weight assigned to the study in the meta-analysis.

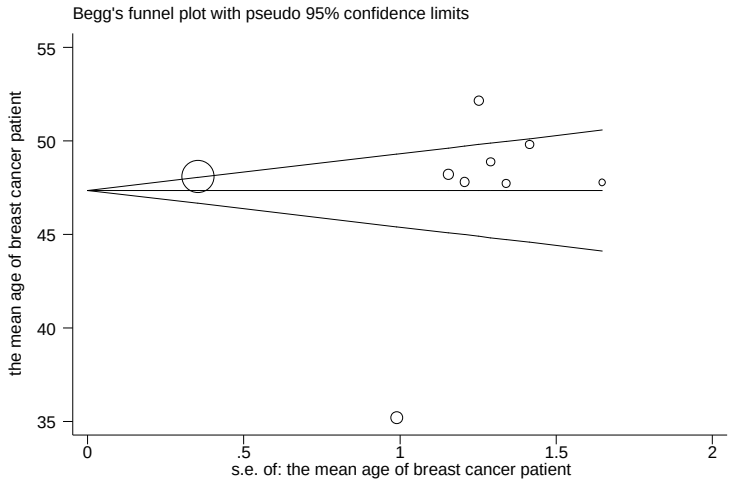

Figure 4. Begg's funnel plot for publication bias representing a pseudo 95% confidence limit.

Furthermore, the pooled estimate for a cross-sectional study based on the random-effects model with Meta probe command (exact method) was calculated at 25.66 (95% CI: 17.34-34.95, I^2=86%, P=0.000) (Figure 3). This result shows that the total prevalence of HPV infection among women with breast cancer was estimated at 25.66% (17.34-34.95).

Regarding the frequency of different HPV genotypes in the case-control studies, the results showed that high- and low-risk genotype estimated frequencies of HPV in case subjects were 18.63% (95% CI: 11.90-26.41, I^2=87.71%, P=0.000) and 8.72% (95% CI: 5.67-12.30, I^2=72.77%, P=0.000), respectively. In addition, these corresponding values in the controls were obtained at 5.15% (95% CI: 0.00-17.27, I^2=77.51%, P=0.001) and 2.92% (95% CI: 0.01-8.84, I^2=43.39%, P=.17), respectively. The Begg's funnel plot results showed no publication bias (P=0.677) (Figure 4).

5. Discussion

The current meta-analysis was performed to answer the controversy on the potential association of HPV infection with developing breast cancer in the Iranian population. In brief, our results indicated a significant association between previous or current HPV infection and breast cancer development. This study is the second meta-analysis investigating this potential association in the Iranian population. The first meta-analysis was conducted by Hagshenas et al. covering 11 published studies until 2015 (14). There

were two main reasons to conduct a new study on the same subject. First, from 2015, there have been new studies investigating the presence of HPV DNA in breast cancer samples in the Iranian population with controversial data and results (15-17). Second, one of the studies included in the previous meta-analysis is now retracted (18). Furthermore, the current meta-analysis included the frequency of high and low genotypes to address the association of different HPV genotypes with breast cancer development. Together, the current study was performed to provide updated and more reliable results on the risk of breast cancer in individuals with HPV infection. Our results were consistent with the findings of a study conducted by Haghshenas et al. and confirmed the significantly higher prevalence of HPV DNA in breast cancer samples, compared to benign breast samples. Additionally, the results showed that the high-risk HPV genotypes were more frequent, compared to low-risk HPVs.

Previous studies investigating the prevalence of HPV in the general population in Iran reported a range between 0.6% and 5.7% (19-21). Considering that the estimated overall prevalence of HPV in breast cancer in our study was 25%, the importance of HPV as a critical risk factor is suggested to be taken into consideration for clinical and epidemiological approaches. Our results were also in line with the findings of other meta-analyses. In a global meta-analysis carried out by Simoes et al. on 29 studies from 1990 to 2011, the overall estimated prevalence of HPV in patients with breast cancer was reported to be 23% ranging from 13% in the European population to 42.9% in African and Australian populations. They also reported an odds ratio of 5.9 for developing breast cancer in cases with positive HPV, compared to controls (22). There are other meta-analyses introducing HPV infection as an effective risk factor for developing breast cancer and reporting high odds ratios ranging from 3.6 to 4.02 (23,24). In case of HPV genotypes, two meta-analyses surveyed the frequency of different HPVs, and both reported a higher prevalence of high-risk HPVs including 16, 18, and 33, compared to other HPV strains. In a study performed by Ni Li et al., the frequencies of these three high-risk HPVs were estimated at 7.04%, 7.13%, and 14.36%, respectively, while other HPVs including low-risk HPVs were all less than 3% (23, 24).

On the other hand, there are original articles (including articles that were included in the current meta-analysis) suggesting the absence of evidence to accuse HPV as a risk factor for breast cancer (15,25). This controversy and discrepancy in the results of different original articles may root in different investigated populations, insufficient sample size, sexual behaviors of studied cases, and technical issues, such as the samples and quality of samples, sensitivity of utilized techniques, and technical errors. Large-scale case-control, cross-sectional, and even cohort studies using multiple sample sources and combined detection techniques could lead to more reliable and conclusive data. Beyond the abovementioned epidemiological evidence, there is biological evidence to be mentioned to spotlight the role of HPV in developing cancers, including breast cancers. Several proteins expressed in high-risk HPV genotypes are thought to act as oncoproteins. These HPV-related oncoproteins are involved in replication processes. Briefly, as HPV is integrated into the host cell genome, it starts to express gene E6. This protein inhibits tumor suppressor protein p53. E7, another HPV related oncoprotein, binds to tumor suppressor retinoblastoma protein. Other proteins, such as E1 and E2, also play roles in accelerated HPV replication. All these proteins are accused to be involved in damaging and stabilizing DNA, as well as inhibiting tumor suppressors mechanisms and apoptosis, and in turn tumorigenesis. In case of breast cancer, some specific pathological pathways are thought to be involved in tumorigenesis. Studies revealed that E6 and E7 protein, especially those expressed by high-risk HPVs, induced downregulation in P53, NFX1, and BRCA1 and resulted in the up-regulation of pro-tumor signaling pathways (8).

Our meta-analysis had its limitations that could be considered in further original and meta-analysis studies. First, not all the included articles investigated the frequency of HPV genotypes, and the results of high- and low-risk HPV frequency need more confirming data. Second, due to the lack of sufficient data regarding the forms and stages of breast cancers in the investigated studies, there is still an unanswered question about the role of HPV in the prognosis of breast cancer. Large-scale studies are recommended to fulfill the mentioned gaps.

6. Conclusion

Considering all aspects, the evidence seems to be sufficient to consider HPV infection, especially the high-risk genotypes, as an important risk factor for breast cancer.

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Footnotes

Authors' Contribution: HN and KK designed the conception of the study; HN, SY, and AGH focused on the statistical analysis; MGH, LJ, and KK were responsible for technical support and conceptual advice. All authors contributed to the drafted manuscript, revised it critically, and approved the final version.

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