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Human papillomavirus and breast cancer in Iran: a meta- analysis

Mohammad Reza Haghshenas [1], Tahoora Mousavi [2], Mahmood Moosazadeh [3]*, Mahdi Afshari [4]

[1] Department of Microbiology, Molecular and Cell-Biology Research Center, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran
[2] Student Research Committee, Molecular and Cell Biology Research Center, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran
[3] Health Sciences Research Center, Faculty of Health, Mazandaran University of Medical Sciences, Sari, Iran
[4] Department of Community Medicine, Zabol University of Medical Sciences, Zabol, Iran

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ABSTRACT

Objective(s): This study aims to investigate the relationship between human papillomavirus (HPV) and breast cancer using meta- analysis.

Materials and Methods: Relevant studies were identified reviewing the national and international databases. We also increased the search sensitivity by investigating the references as well as interview with research centers and experts. Finally, quality assessment and implementation of inclusion/exclusion criteria determined the eligible articles for meta-analysis. Based on the heterogeneity observed among the results of the primary studies, random effects model was used to estimate the pooled prevalence of HPV infection and also pooled odds ratio between HPV and developing breast cancer using Stata SE V. 11 software.

Results: This meta- analysis included 11 primary studies investigating the HPV infection prevalence among 1539 Iranian women. Pooled prevalence (95% confidence interval) of HPV infection among Iranian women with breast cancer was estimated as of 23.6% (6.7- 40.5), while, the odds ratio (95% confidence interval) between HPV infection and developing breast cancer was estimated as of 5.7% (0.7- 46.8).

Conclusion: This meta- analysis showed a high prevalence of HPV infection among women with breast cancer. We also found that the odds of developing breast cancer among women with breast cancer was more than that of women without breast cancer.

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Introduction

Breast cancer, is the second most common cancer in the world. It is considered as a serious problem in many developed countries. Among 30 million women, almost 6000 are infected by human papillomavirus (HPV) (1, 2). The breast cancer mortality among women is much more than the mortalities due to lung and colorectal cancers (3).

Several studies have reported that some viruses such as Epstein-Barr virus (EBV), Mouse mammary tumor virus (MMTV) and HPV have important roles in developing breast cancer (4, 5). The association between HPV and breast cancer have been shown in 1992. The prevalence of HPV infection among women with breast cancer have been reported from zero to 86.2% (6). On the other hand, some studies did not report any relationship between HPV and breast cancer (7-9). It was found in other studies that the pathogenicity of HPV is depends on its genotypes (10) so that HPV 16, HPV18 and HPV33 –the high risk types- are responsible for 70% of breast cancer cases worldwide (5, 10). In addition, some factors including viral infection, familial history, environmental polutions, hormones, obesity and alcohol drinking can be attributed with breast cancer. However, 50%- 80% of risk factors have not been yet identified (6, 11).

According to studies carried out in China, Australia, Italy, Japan, the USA, Norway, Greece, Korea, Mexico and Taiwan, HPV infection was found among women with breast cancer (4). In a systematic review conducted in Europe, North America and Australia, a correlation was found between HPV and breast cancer (3).

Different studies have assessed the relationship between breast cancer and HPV whose results are not the same (8, 12-13). Combining the results of these primary studies using systematic review and

**Corresponding author:* Mahmood Moosazadeh. Health Sciences Research Center, Faculty of Health, Mazandaran University of Medical Sciences, Sari, Iran. T el: +98-911-3555367; email:mmoosazadeh1351@gmail.com

meta- analysis methods can solve such controversies (14-15). This study aims to assess the association between HPV infection and breast cancer among the Iranian studies.

Materials and Methods

Search strategy

To identify the relevant electronic studies published from January 2000 to April 2015, we searched national (SID, Iranmedex, Magiran and Irondoc) and international (Pubmed, Google scholar, Scopus and Science direct) databases. Search strategy was performed using the following keywords and their Farsi equivalents:

"Prevalence", "Seroprevalence", "Ferequency", "Seroepidemiology", "Odds Ratio", "OR", "Relative Risk", "RR", "Cohort", "Case Control", "Cross Sectional", "Human papillomavirus", "HPV", " Breast Cancer", "Breast Carcinoma", "Genotype", "High risk genotypes", "Iran"

We used "AND" operator to identify articles including all keywords applied in the search strategy. We also used "OR" for including papers with either one of the relevant keywords. Any primary study with words did not meet the study aims was removed from the search results by "NOT" operator.

The search was conducted during May 2015. Moreover, we investigated the references of the studies to increase the search sensitivity. Two researchers randomly evaluated the search strategy and found that all relevant studies had been identified. Moreover, we were interviewed with some experts and research centers to find any unpublished relevant study.

Study selection

Full texts or abstracts of all papers, evidences and other reports were provided during our advanced search. At first, we excluded the duplicates. Then, irrelevant articles were removed after reviewing the titles, abstracts and full texts respectively. We also investigated details of the results to identify and exclude the repeated studies in order to prevent from re-publish bias.

Quality assessment

To assess the quality of the studies selected after title and content review, we used a previously applied checklist (16). This checklist included 12 questions using the contents of the STROBE checklist (17). These questions addressed all aspects of methodology such as sample size estimation and selection, type of the study, data collection methods and tools, definition of the variables and methods of dealing with samples, study population, study objectives, statistical analysis tests, and presentation of the results. Each question was assigned one score and studies achieved at least eight scores were entered into the final meta- analysis (16).

Inclusion criteria

All studies written in Farsi or English passing the above assessment phases and achieved required quality scores provided by having the following characteristics were considered eligible for final meta- analysis:

1. Cross sectional (descriptive- analytic) studies, case-control or cohort studies. 2. Studies reported sample size according to their design. For example, total sample size in cross sectional studies, case- control specific sample size in case control studies and exposed-unexposed specific sample size in cohort studies. 3. Cross sectional studies reported HPV infection prevalence among breast cancer patients. 4. Case control studies reported HPV prevalence among women with and without breast cancer. 5. Cohort studies reported the incidence of breast cancer among women with and without exposure to HPV infection.

Exclusion criteria

1. Case report or case series. 2. Studies did not report a specific sample size. 3. Cross sectional studies did not report HPV infection rate among women with breast cancer. 4. Case- control studies did not report HPV infection prevalence among cases and controls. 5. Cohort studies did not report the HPV infection prevalence among exposed and unexposed participants. 6. Duplicated studies (only one of them were entered). 7. Studies presented in congresses and meetings without full texts. 8. Studies did not get enough quality scores.

Data extraction

Of the cross sectional studies, title, first author name, date and place of study conduction, sample size and sampling method, total infection prevalence among women with breast cancer, study language and mean age of women were extracted. Information extracted from the case control and cohort studies included: title, first author name, date of the study conduction, sample sizes of case/ control groups (in case- control studies) or exposed/ unexposed groups (in cohort studies), frequencies of HPV among cases and controls (case- control studies), number of women developed breast cancer among exposed and unexposed (cohort studies) and type of matching in case- control studies. All extracted data were entered into Excel spreadsheet.

Statistical analysis

In cross sectional studies, standard error of HPV infection prevalence was calculated using binomial distribution formula. According to the degree of heterogeneity among the results of the studies,

Table 1. Distribution of primary studies (case-control) included to meta-analysis

References	First author	Publication year	Publication language	Score of quality assessment	Case(N)		Control (N)		OR (95% CI)
					Event	Total	Event	Total	
13	Ahangar-Oskouee	2014	EN	11	22	65	0	65	67.7 (4-1146.5)
24	Alavi	2009	EN	11	24	50	0	29	54.5 (3.1-941.7)
12	Eslamifar	2015	EN	10	0	100	0	50	-
23	Manzouri	2014	EN	11	10	55	7	51	1.4 (0.5-3.9)
22	Sigaroodi	2012	EN	10	15	79	1	51	13.9 (1.8-110.5)
8	Tahmasebi Fard	2013	Persian	9	0	64	3	53	0.1 (0.006-2.2)
Pooled estimate (random model)					21	321	11	278	5.7 (0.7-48.8)

random effects model was applied to estimate the HPV infection prevalence among cancerous women or odds ratio between HPV infection and breast cancer. The degree of heterogeneity among the studies was assessed using Cochrane test (Q) and I^2 index. In addition, sensitivity analysis was performed to detect the study mostly influenced the heterogeneity. We also designed forest plots to illustrate the point and pooled estimates with 95% confidence intervals (crossed lines). Each box in these plots indicated the weight of the study. Moreover, begg test with significance level less than 0.01 was conducted to assess the publication bias. All statistical analyses were performed using Stata SE, V.11 software.

Results

At the beginning of our search, 4121 studies in the field of the study question were identified restricted to 219 after limiting the search strategy and exclusion of duplicates. After review of titles and abstracts, 151 irrelevant papers were removed and after review of full texts, 58 articles were omitted. We also identified one relevant study during investigating the references and finally, 11 eligible studies (8, 9, 12, 13, 18-24) were entered into the meta- analysis (Figure 1, Tables 1 and 2).

Of 11 studies selected for the current systematic review/ meta- analysis, six were case- control and five were cross sectional. No cohort study was identified regarding the study subject. HPV infection prevalence was assessed among 858 women with breast cancer in cross sectional studies. Our case control studies, recruited 681 women 321 of which had breast cancer (cases).

Prevalence of HPV infection in the case- control study carried out by Eslamifar (12) was zero in both case and control groups. In Tahmasebi Fard and coworker study (8), although HPV infection rate was more common in controls than cases, these differences were not statistically significant. The remained case-control studies reported higher rates of HPV infection among cases than among controls (Table 1). In five cross sectional studies, HPV infection prevalences among women with breast cancer varied from zero in Moradi study (9) to 34.7% in Rassi study (21).

Based on the significant heterogeneity observed among the results (Q=19.3, *P-value*=0.001 and I-Squared=79.2%), pooled odds ratios (95% confidence interval) of developing breast cancer between women with and without HPV infection using random and fixed models were estimated as 5.7 (0.7- 46.8) and 5.4 (2.9-9.9) respectively. Non significant Begg test (*P-value*= 0.3) showed no publication bias. Total prevalence of HPV infection among women with breast cancer was estimated as 23.6% (6.7-40.5). Sensitivity analysis showed that the study conducted by Moradi *et al* (9) influenced the heterogeneity. Excluding this study from the meta-analysis, considerably decreased the heterogeneity (Q=8.6, *P-value*=0.03 and I-squared=65.3%) and the HPV infection prevalence (95% confidence interval) was changed to 29.2 (22.5-35.29).

Table 2. Distribution of primary studies (cross sectional) included to Meta-analysis

Reference	First author	Publication year	Publication language	Score of quality assessment	Sample size	Prevalence of HPV infection (%)
18	Rassi	2013	EN	10	150	34.7
9	Moradi	2009	Persian	9	231	0
21	Rassi	2014	EN	8	84	32.1
20	Salehpour	2015	EN	10	326	22.7
19	Ghaffari	2011	EN	8	67	30
Pooled estimate (random model)					858	23.6 (6.7-40.5)

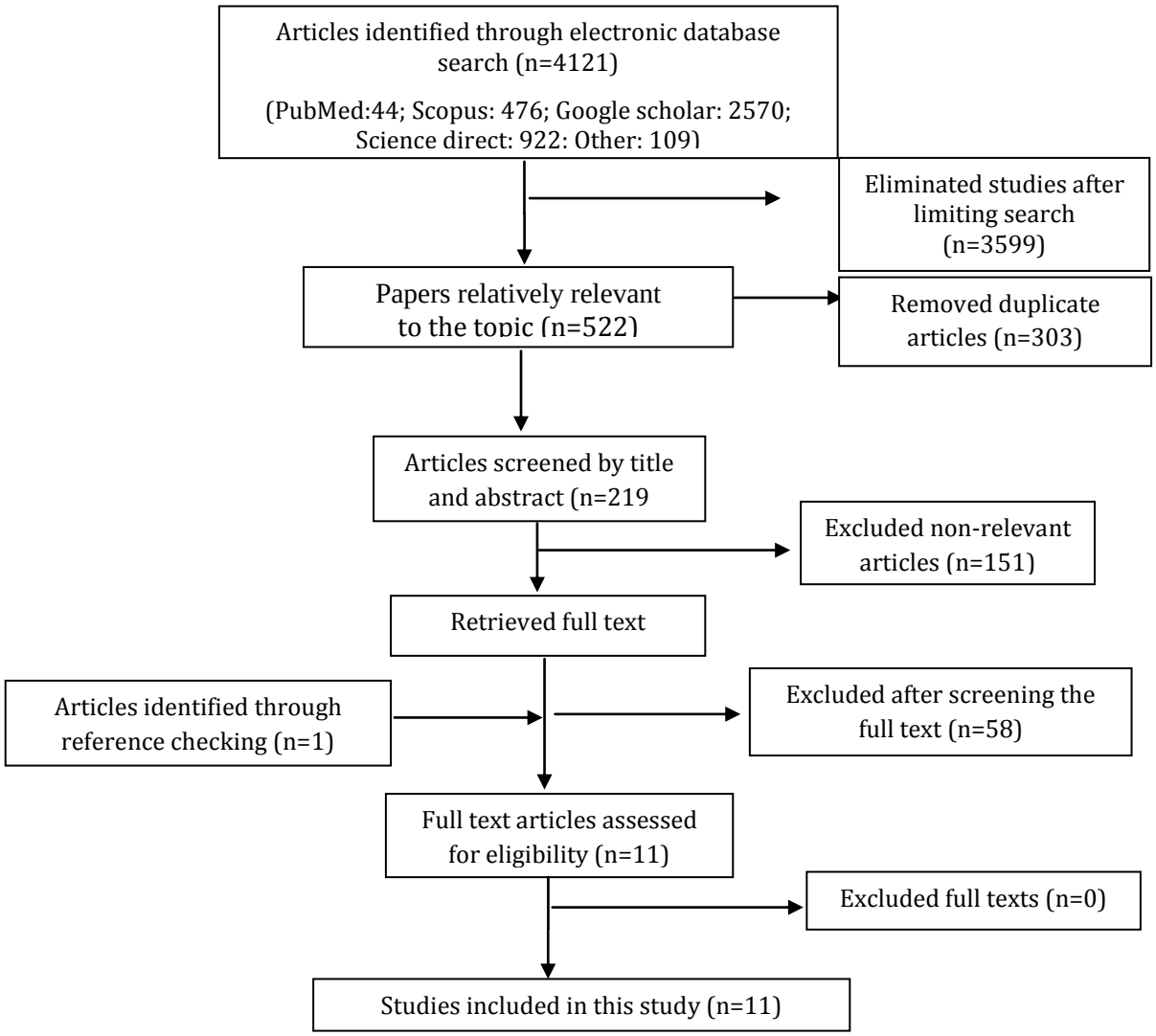

Figure 1. Literature search and review flowchart for selection of primary studies

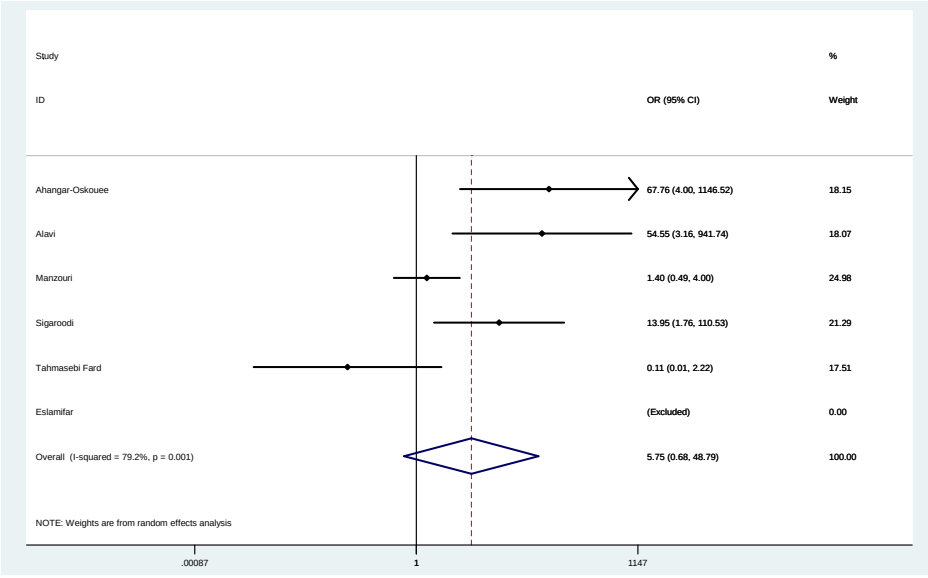

Figure 2. Estimation of Odds ratio of Breast cancer in positive human papillomavirus women

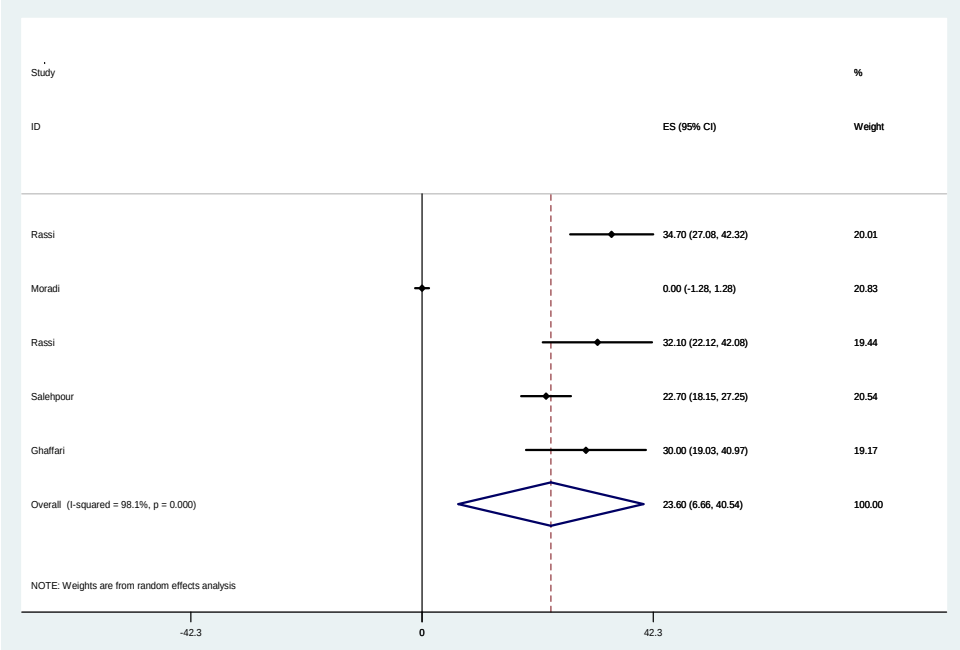

Figure 3. Estimation of human papillomavirus prevalence in women infected breast cancer

Discussion

Our study showed that among 1539 pregnant women investigated in 11 cross sectional and case control studies, 1119 women had developed breast cancer. According to our meta- analysis of the results of cross sectional studies, total HPV infection prevalence among women was estimated as of 23.6%. In addition, the odds ratio of developing breast cancer between women with and without HPV infection was estimated as of 5.7%.

A meta-analysis carried out by Simoes *et al* in Europe (3), North America and Australia, HPV infection prevalence among 2211 breast cancer patients was 23% (European countries: 13.4% and North America and Australia:42.9%). They also combined the results of nine case-control studies and found an association between breast cancer and HPV infection (odds ratio: 5.9; 95% CI: 3.26-10.67). Based on the above findings, HPV infection among Iranian breast cancer women was more common than among European women and lower than that of North American and Australian women. Therefore, we can expect that almost one-fourth of women with breast cancer, are simultaneously infected with HPV infection (25).

In a study conducted by Eghbali *et al* in Booshehr (South-west of Iran) among 799 randomly selected women, HPV infection prevalence was reported as 0.63% (26). HPV infection prevalence among women living in Tehran (Capital of Iran) and Shiraz (south of Iran) were 5.7% and 5.5% respectively (27, 28). Zandi *et al* reported that HPV infection prevalence among 200 Iranian women was 5.5% (29).

Similar studies have been carried out in Brazil, Germany, London and France, did not report HPV infection prevalence among women with breast cancer (30-33), while, the infection rate among women with breast cancer in Mexico and Greece was reported lower than 16% (33, 34). On the other hand, the corresponding figures for Australia, Syrian and Turkey were between 20.9% and 86.2% (36-38). Another study conducted in Iraq among 129 breast cancer patients, estimated the HPV prevalence as of 46.5% (39). Primary studies entered in the current systematic review showed a zero prevalence of HPV infection in some areas of Iran in 2009 and then a considerable increase during 2011 and 2013 in other regions. During 2014 and 2015, HPV infection rate was decreased in another area of Iran. Such variability in different parts of Iran might be due to various HPV genotypes and different types of high risk behaviors (3). Prevalence of HPV among patients with breast cancer is different in various parts. Some probable factors can be related to false positive results such as different diagnostic methodologies. PCR primers been used since 2000 were more useful in the diagnosis of HPV infection in cervical cancers but have not been effective in viral infection diagnosis among patients with breast cancer. It might be due to the higher concentration of HPV in the cervical cancer specimens. Other factors such as condition of specimen storage in the lab, PCR condition and histopathologic quality of samples could be associated with the diagnostic sensitivity (25).

Ahangar-Oskuee *et al* (13) study showed that HPV6 was the most common type of this virus among their samples (26%). That was similar to the results of the study carried out by Villiers *et al (*40) reported

HPV6 and HPV11 as the prominent types but was in contrast to those reported by Alavi *et al* (24), Rassi *et al* (18, 21) observed HPV16-18 (26%), HPV16 (37.03%) and HPV16-18(34%) respectively as the most common types. It might indicate that these types of HPV are more common among Iranian women with breast cancer. Moreover, during HPV analysis, presence of DNA can be reported but that may not necessarily indicative of infection or viral activity. Investigation of E6 and E7 proteins has a major role in the HPV cellular cycle and can be an important marker for detecting breast cancer development (5, 41). During a study conducted in Italy on nine samples, genes attributed to the E6 and E7 proteins were negative, indicating lack of infectiousness of high risk types of HPV in the study samples (42).

None of the primary studies used in our systematic review/meta-analysis, investigated different genotypes of HPV, therefore, we could not assess the relationship between these genotypes and breast cancer. The small number of evidences was another limitation of the current study.

Conclusion

Our meta- analysis showed that women with HPV infection compared to those without HPV, had more chance of developing breast cancer. We also found a high prevalence of HPV infection among women with breast cancer.

Declaration of interest

The authors declare no conflict of interest.

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