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REVIEW

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Association between human papillomavirus infection and prostate cancer: A global systematic review and meta-analysis

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Abstract

Although an increasing number of studies have been conducted to evaluate the association between human papillomavirus (HPV) infections and distribution of HPV types worldwide with the risk of prostate cancer (PC), the results remain inadequate. Hence, we investigated the association between HPV infection and PC risk using a meta-analysis. Relevant studies from January 1990 to December 2016 were searched in PubMed, Web of sciences, and Scopus databases. Pooled odds ratio (OR) and their corresponding 95% confidence interval (CI) were calculated to find the association between the prevalence of HPV and prostate cancer risk. To do so, data from 24 studies with 5546 prostate cancer cases were pooled in order to evaluate the heterogeneity of chief parameters including study region, specimen type, HPV DNA source, detection technique, publication calendar period, and Gleason score. All statistical analyses were performed using STATA 11 and MedCalc 13. A significant positive association was found between HPV infection and PC risk (OR = 1.281; $P = 0.026$). The genotype 16 was more frequently found in patients with PC which significantly increased the cancer risk (OR = 1.60; $P < 0.001$). Age 65 and older could significantly escalate PC risk (OR = 3.564; $P < 0.001$). Our results clearly favor the potential pathogenetic link between HPV infection and increased risk of PC affirming that HPV infections could play a part in the risk of PC.

KEYWORDS

HPV, human papillomavirus, meta-analysis, prostate cancer

1 | INTRODUCTION

Prostate cancer (PC) is the second prevalent cancer in men worldwide.[1] Not much evidence exists on the development of PC and the precise mechanisms involved in this process. Certain aspects might affect a man's risk of getting PC including age >50 years, ethnicity, acquired/inherited genetic mutations, and sexually transmitted infections (STIs).[2,3] Previous studies have shown that HPV could be among the STD culprits' involved in PC.

HPV is a small epitheliotropic, non-enveloped, double-stranded DNA virus that belongs to *Papillomaviridae* family.[4–6] Having over 150 fully sequenced types, one-third of HPV types infect the genital tract.[7,8] Zur Husaen discovered the participation of HPV infection in cancer in 1977.[9,10] Later in 1990, McNicol and Dodd first identified HPV DNA in prostatic tissues using polymerase chain reaction assay (PCR).[11] Further investigations revealed that viral infections could affect PC development by activating the chronic inflammatory processes leading to DNA damage and cancer.[12–14] Above and beyond (moreover, on the other hand, etc.), the E6/E7 oncoproteins of HPV types 16 and 18 have been described to eternize prostate epithelial cells.[15] Surprisingly, several epidemiological and biological studies have displayed the presence of HPV in both healthy and cancerous prostate tissues.[15,16] Therefore, the association between the PC development and HPV infections is still controversial.

Because the validity of these contrary views is not clear, we undertook this study and intended to investigate any possible association between HPV infection and prostate cancer risk using a meta-analysis.

2 | MATERIALS AND METHODS

2.1 | Study selection

In this meta-analysis, relevant previous studies from January 1990 to December 2016 were searched in PubMed, Web of sciences and

Scopus databases. These searches were performed using the following keywords: "Papillomavirus/HPV," "Risk factor," "Human" and "Prostate cancer OR prostate tumor" with "OR" and "AND" and "NOT" Boolean operators in the Title/Abstract/Keywords fields. Also, we screened citations manually in retrieved articles to identify additional eligible studies. Literature published in English and human population studies were included in the current meta-analysis.

2.2 | Inclusion and exclusion criteria

Inclusion criteria were:[1] publication time between 1990 and 2016,[2] detection of HPV DNA in biopsy tissues,[3] detection of antibodies in serological studies,[4] case–control studies.

The subsequent studies were ruled out:

(i) Studies on immunosuppressive patients

(ii) Congress abstracts, case report articles, and review articles

(iii) Investigations published in languages other than English

(iv) Studies with no extractable data

(v) Meta-analysis or systematic reviews and duplicate publication of the same survey (or published both in English and other languages). The exception was duplicate studied in which sample sizes and detailed results were provided.

2.3 | Data extraction and quality assessment

The obtained information from each study consisted of the following items: first author, year of publication, the location of study, sample sizes, specimens' type (tissue or serum), sources of controls, HPV detection method, HPV genotype, the age of patients and Gleason score of prostate cancer. The Newcastle–Ottawa Scale was used for assessing the methodological quality. Studies were graded as low, moderate or high-quality according to the scores of 0–3, 4–6 and 7–9, respectively. Two independent investigators without knowledge of existing scores examined the selected studies based on the criteria described above to resolve any discrepancies.

2.4 | Statistical methods

We used pooled ORs and their corresponding 95% confidence intervals (CIs) to evaluate the association of HPV infection and prostate cancer risk. Cochran's Q test was used to assess heterogeneity and the I^2 index was employed for calculating the variation in the pooled estimations. For the latter analysis, significance was considered at $P < 0.05$.[17,18] The meta-analysis was performed with a random-effects model when the heterogeneity of the individual studies was statistically significant. Otherwise, a fixed-effects model was used. Meanwhile, a sensitivity analysis was done by consecutively eliminating a particular study or group of them (if any) with maximum impact on the heterogeneity test. A funnel plot was established for checking the existence of publication bias and symmetric assumption. The funnel plot asymmetry was measured by Egger's linear regression test and Begg's test ($P < 0.05$ was considered representative of statistically significant publication bias).[19] Subgroup analysis was performed based on the year of publication, age of the patients, biological sample, HPV detection method, HPV genotype and studied Continents by using the available individual data. All statistical analyses were conducted using statistical software (STATA; version 11.0; Stata Corporation, College Station, TX, USA) and MedCalc version 13.

3 | RESULTS

3.1 | Characteristics of the included studies

The assortment process shown in Figure 1 was designed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[20] Based on the exclusion/inclusion criteria, 24 case–control studies were included in the final meta-analysis among which 13 and 11 had reported HPV prevalence in tissue and serum, respectively. These studies included 5576 cases and 7946 healthy subjects. Among 24 case–control studies, 13 were carried out in American people, six were done in European people, three were from Asians, one from Africans and one study was done in Oceania people. Publication year of these studies was ranged from 1992 to 2016. More information on the studies is shown in Table 1.

3.2 | Main results of this meta-analysis

According to Table 2, a significant positive association was found between HPV infection and prostate cancer risk. The pooled odds ratio (OR) was 1.281 (95% CI, 1.030–1.594; $P = 0.026$) for the association between HPV infection and occurrence of prostate cancer (Figure 2). According to the subgroup analysis, the genotype 16 was more frequently found in patients with prostate cancer and significantly increased the cancer risk (OR = 1.60; 95% CI, 1.231–2.081; $P < 0.001$). Age > 65 years old significantly increased prostate cancer risk (OR = 3.564; 95% CI, 1.806–6.962; $P < 0.001$) and the dominant detection method was PCR (OR = 2.794; 95% CI, 1.432–5.453; $P = 0.003$). Based on the studies in Oceania and Asia, the association between HPV infection and prostate cancer risk was the highest (OR = 21; 95% CI, 1.777–248.1; $P = 0.016$) and (OR = 14.697; 95% CI, 2.787–77.50; $P = 0.002$), respectively. For the studies in Europe, the association between HPV infection and prostate cancer risk was the lowest (OR = 1.095; 95% CI, 0.912–1.313; $P = 0.331$). The association between HPV infection and prostate cancer was more frequently found in a biological tissue sample (OR = 3.622; 95% CI, 2.197–5.971; $P < 0.001$). According to Lowess smoothing analysis, the OR for the association between HPV infection and risk of PC was decreased over time until 2003 while increased afterwards (Figure 3).

3.3 | Sensitivity analysis

A sensitivity analysis was performed by sequential omission of individual and groups of studies. The pooled OR did not significantly deviate from the consecutive exclusion of any participants or group of studies, indicating that our results were statistically robust (Figure 4).

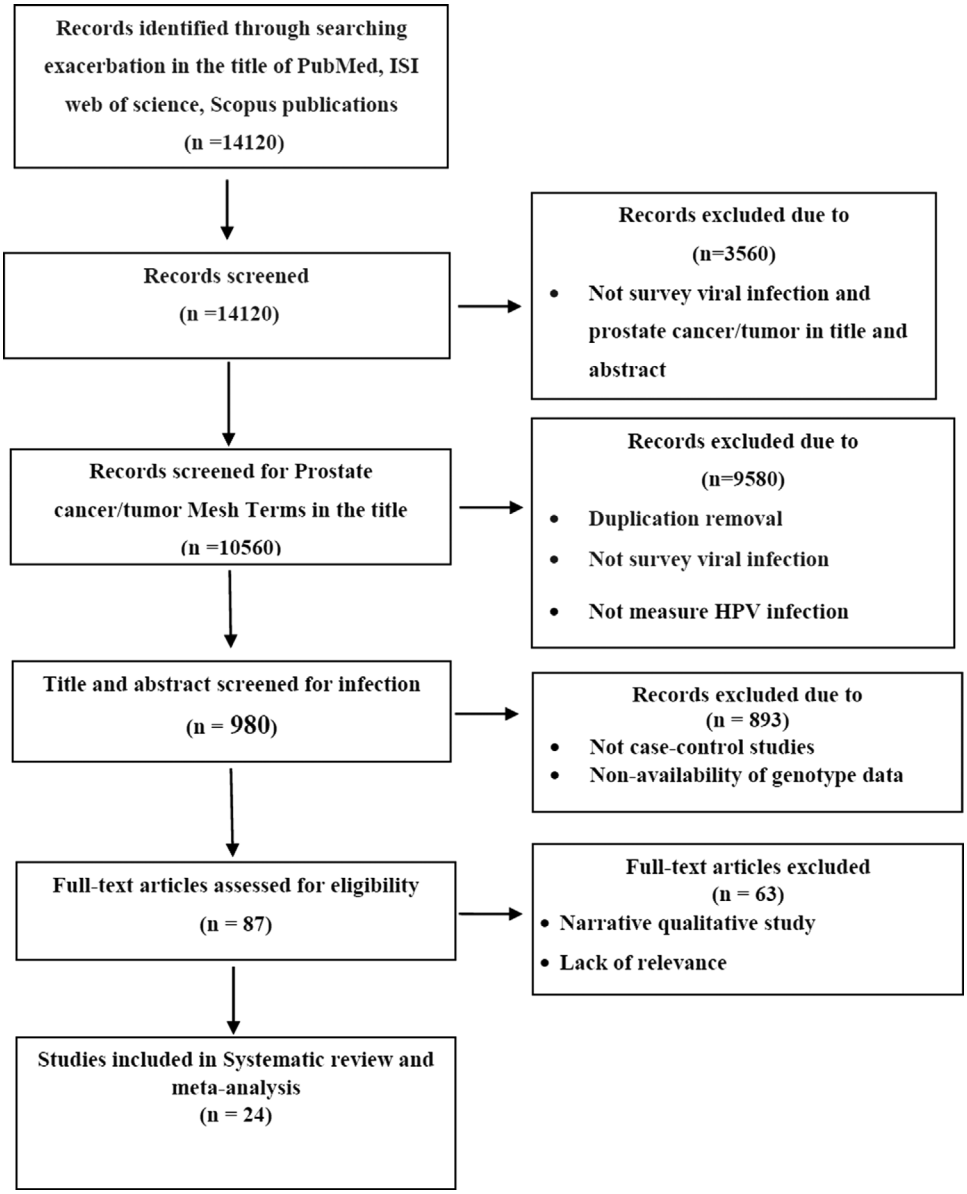

FIGURE 1 Flow-chart of the selected studies

3.4 | Heterogeneity and publication bias

The heterogeneity analysis was conducted using Cochran's *Q* test and the I^2 index. Significance for the heterogeneity results was considered with an $I^2 > 50\%$ and *P*-value heterogeneity <0.05. Heterogeneity between studies was observed ($I^2 = 61.23\%$; $P < 0.001$; Table 2 & Figure 5). Publication bias was examined by a funnel plot and Egger's and Begg's tests. In most cases, significant publication bias was identified (Table 2).

4 | DISCUSSION

There are several factors with clear/less clear effect on PC risk such as the age (>50), geographical region, mutations in some cellular genes, inflammation and infectious agents.[12,21] Several previous studies, both epidemiological and biological, have proposed some infectious agents as major causes of cancers worldwide.[22] Viral infections are important risk factors involved in initiation and development of approximately 18–20% of cancers.[23]

Few meta-analyses have investigated the correlation between the risk of prostate cancer and HPV infections.[15] In a study in 2005, HPV infection, found either in sera or tissue, was shown to be a risk factor of prostate cancer (OR = 1.39; 95% CI, 1.12–2.06).[24] In other studies, the most common oncogenic virus types (HPV 16 and/or HPV 18) were evaluated and it was claimed that "the overall risk of prostate cancer was not significantly increased by either HPV 16 (OR = 1.09; 95% CI, 0.97–1.23) or HPV 18 (OR = 1.05; 95% CI, 0.89–1.24) infections in sera and tissue combined while it was significantly increased when HPV DNA was detected in prostate tissues."[2,25] In the newest meta-analysis, HPV infection of each type was significantly associated with an increased risk of prostate cancer (OR = 1.32; 95% CI,

TABLE 1 Characteristics of the incorporated studies in this meta-analysis

Study	Location	Year	Number of case	Number of control	Type of control	Case positive	Control positive	Sample	HPV detection method	HPV genotype	Age patients: mean (range)	Age healthy: mean (range)	Histological grade
Ibrahim et al.	USA	1992	48	16	Healthy	6	2	Tissue	PCR, ISH	16	64 (43–84)	59(25–69)	6
Tu et al.	USA	1994	60	1	Healthy	3	0	Tissue	PCR	16,18	NA	NA	3–9
Wideroff et al.	USA	1996	56	42	Hyperplastic	7	4	Tissue	PCR	6,11,16,18,31,33,45	(64–65)	(63–65)	NA
Terris et al.	USA	1997	73	37	Healthy	18	6	Tissue	PCR	16	66.1(44–76)	66.1 (44–76)	1–4
Hisada et al.	USA	2000	48	63	Healthy	20	19	Serum	ELISA	16	NA	NA	NA
Hayes et al.	USA	2000	276	295	Healthy	19	15	Serum	ELISA	16	(40–79)		NA
Rosenblatt et al.	USA	2003	642	570	Healthy	81	64	Serum	ELISA	16,18	(40–64)	(40–64)	NA
Sutcliffe et al.	USA	2007	584	577	Healthy	107	114	Serum	ELISA	16,18,33	65(40–75)	65(40–75)	<7≥
Huang et al.	USA	2008	868	1283	Healthy	154	310	Serum	ELISA	16,18	65(60–69)	65(60–69)	≥7
Dennis et al.	USA	2009	267	267	Healthy	50	45	Serum	ELISA	NA	NA	NA	NA
Sutcliffe et al.	USA	2010	616	616	Healthy	23	22	Serum	ELISA	16,18,31	NA	NA	<7≥
Bergh et al.	Sweden	2007	201	201	Healthy	0	0	Tissue	NA	NA	64 (51–71)	64 (51–71)	NA
Korodi et al.	Sweden	2005	799	2596	Healthy	107	363	serum	ELISA	16,18,33	(40–65)	(40–65)	NA
Adami et al.	Sweden	2003	238	210	Healthy	69	48	Serum	ELISA	16,18,33	NA	NA	NA
Dillner et al.	Finland	1998	165	290	Healthy	40	60	Serum	PCR	11, 16, 18, 33	58.6(18–78)	58.3(18–78)	NA
Michopoulou et al.	Greece	2014	50	30	Healthy	8	1	Tissue	PCR	16,18,31	65.5	65.5	2–3
Anwar et al.	Japan	1992	68	10	Healthy	28	0	Tissue	PCR	16,18, 33	69(53–88)	63(53–88)	2–9
Suzuki et al.	Japan	1996	51	51	Healthy	8	0	Tissue	PCR	16	NA	NA	1–5
Hassanein et al.	Saudi Arabia	2016	85	15	Healthy	22	0	Tissue	PCR	16,18,31,33	63.3±10.5	59.2±10.7	NA
Smelov et al.	Russia	2016	13	13	Healthy	2	0	Tissue	NGS	NA	70(55–79)	68(42–78)	NA
Whitaker et al.	Australia	2013	10	10	Healthy	7	1	Tissue	PCR	18	NA	NA	NA
McNicol et al.	Canada	1990	4	5	Healthy	4	1	Tissue	PCR	16,18	NA	NA	NA
Fierro et al.	Mexico	2010	55	75	Healthy	11	4	Tissue	PCR	NA	71(36–88)	66(50–88)	6–10
Sitas et al.	Africa	2007	205	673	Healthy	139	390	Serum	ELISA	16	NA	NA	NA

TABLE 2 Subgroup analysis for the association between HPV infection and prostate cancer risk

Characteristics	Categories	No. of studies	*P*-value	Pooled OR (95% CI)	Heterogeneity test (Q, I^2 %, *P*)	Publication bias (Begg's test, *P*; Egger's test, *P*)	Model
All studies	–	24	**0.026**	1.281 (1.030, 1.594)	(56.74, 61.23%; $P < 0.001$)	(Begg's test, 0.04; Egger's test, 0.001)	Random
Year of publication	≤2004	12	**0.001**	1.387 (1.137, 1.692)	(12.08, 8.95%; $P = 0.35$)	(Begg's test, 0.016; Egger's test, 0.015)	Fixed
	>2005	12	0.234	1.204 (0.887, 1.635)	(37.34, 73.22%; $P < 0.001$)	(Begg's test, 0.005; Egger's test, 0.003)	Random
Age of patient	≤65 years old	7	**0.017**	0.824 (0.703, 0.966)	(10.33, 51.6%; $P = 0.06$)	(Begg's test, 0.26; Egger's test, 0.10)	Fixed
	>65 years old	5	**<0.001**	3.564 (1.806, 6.962)	(3.35, 0.08%; $P = 0.50$)	(Begg's test, 0.22; Egger's test, 0.11)	Fixed
Biological sample	Tissue	13	**<0.001**	3.622 (2.197, 5.971)	(15.95, 31%; $P = 0.14$)	(Begg's Test, 0.03; Egger's test, 0.01)	Fixed
	Serum	11	0.369	1.088 (0.906, 1.306)	(25.63, 61%; $P = 0.004$)	(Begg's test, 0.12; Egger's test, 0.02)	Random
HPV detection Method	PCR	12	**0.003**	2.794 (1.432, 5.453)	(21.77, 50%; $P = 0.02$)	(Begg's test, 0.007; Egger's test, 0.005)	Random
	Elisa	10	0.449	1.079 (0.887, 1.312)	(24.78, 63.4%; $P = 0.003$)	(Begg's test, 0.15; Egger's test, 0.05)	Random
HPV genotype	unknown	4	0.096	1.411 (0.941, 2.115)	(5.17, 61%; $P = 0.07$)	(Begg's test, 0.99; Egger's test, 0.29)	Fixed
	16	6	**<0.001**	1.60 (1.231, 2.081)	(3.52, 0.0%; $P = 0.62$)	(Begg's Test, 0.06; Egger's test, 0.23)	Fixed
	16, 18	4	0.760	0.912 (0.505, 1.646)	(10.96, 72.65%; $P = 0.001$)	(Begg's test, 0.31; Egger's test, 0.30)	Random
	16, 18, 31, 33	7	0.492	1.057 (0.903, 1.237)	(11.38, 47.28%; $P = 0.07$)	(Begg's test, 0.007; Egger's test, 0.005)	Fixed
Continent	America	13	0.371	1.125 (0.869, 1.457)	(26.51, 54.75%; $P = 0.009$)	(Begg's test, 0.16; Egger's test, 0.03)	Random
	Asia	3	**0.002**	14.697 (2.787, 77.50)	(0.08, 0.0%; $P = 0.95$)	(Begg's test, 0.29; Egger's test, 0.31)	Fixed
	Africa	1	**0.012**	1.528 (1.098, 2.127)	(0, 0.0%; *NA*)	(Begg's test, NA; Egger's test, NA)	NA
	Oceania	1	**0.016**	21 (1.777, 248.1)	(0, 0.0%; *NA*)	(Begg's test, NA; Egger's test, NA)	NA
	European	6	0.331	1.095 (0.912, 1.313)	(6.08, 34.24%; $P = 0.19$)	(Begg's test, 0.22; Egger's test, 0.04)	Fixed

Bold font *P*-values indicate statistical significance with $P < 0.05$.

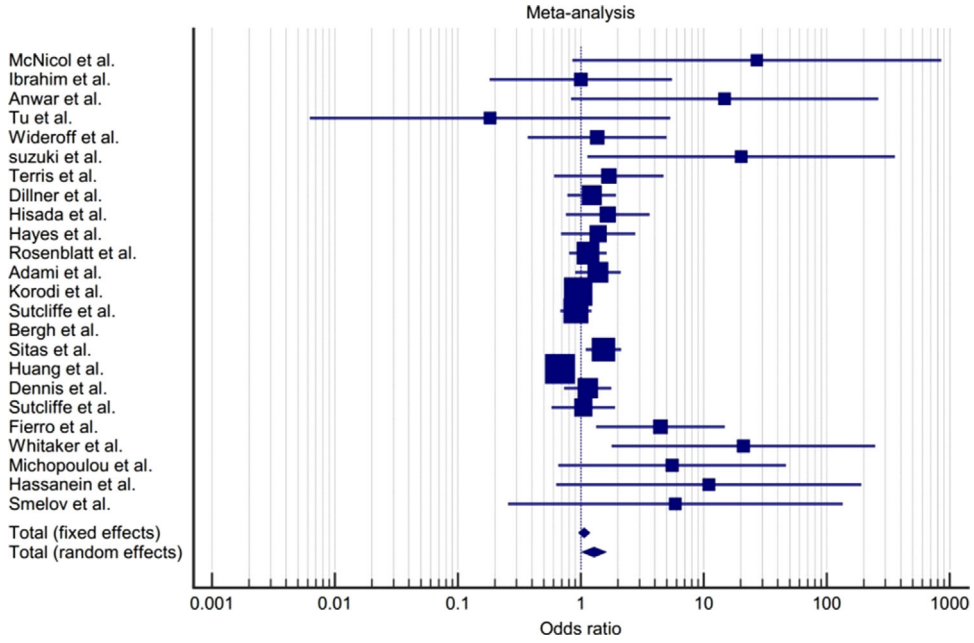

FIGURE 2 Forest plot displaying the association between HPV infection and risk of prostate cancer [Colour figure can be viewed at wileyonlinelibrary.com]

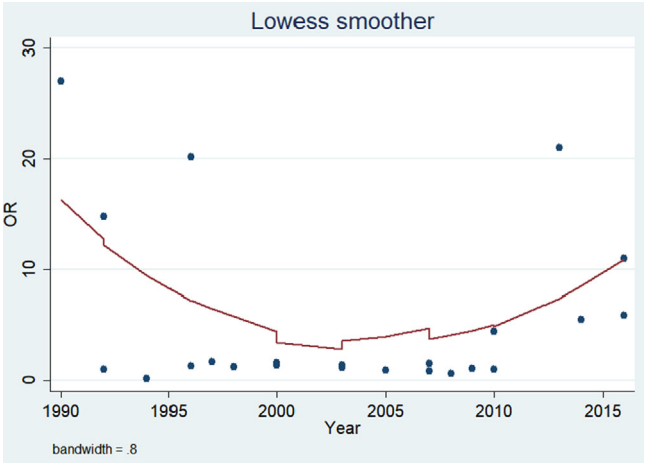

FIGURE 3 The odds ratio of HPV infection with prostate cancer over time of publication [Colour figure can be viewed at wileyonlinelibrary.com]

1.12–1.55). Also, they demonstrated that "the statistically significant association was absent for studies performed on sera (OR = 1.03; 95% CI, 0.95–1.12) while persisted in studies on tissues (OR = 1.79; 95% CI, 1.29–2.49)."[15] In this study, we found a significant positive association between HPV infection and prostate cancer risk. The pooled OR was 1.281 (95% CI, 1.030–1.594; $P = 0.026$). According to the heterogeneity assessing results, the divergence of HPV infection occurrence globally indicates the impact of demographic aspects like geographical area, ethnicity, and lifestyle on the prevalence of HPV infection in PC.

Viruses could elevate cancer risk through cellular transformation, interrupting the cell-cycle control, amplifying cell turnover rates, and immune suppression.[26] One of the most important of these aspects is chronic inflammation.[27] Previous studies have been shown chronic inflammation related to viral infection is involved in different cancers such as thyroid, breast, and prostate cancer.[12,28]

So far, a linkage has been described between HPV and various malignancies that involve the anogenital tract and those involving the head and neck cancers. The two possible ways introduced HPV employs to participate in PC, immortalization, and inflammation.[29]

The persistent infection of HPV and the association with tumor development was approved in some cancers such as cervical cancer and head and neck cancers.[30,31] Although, HPV infection can be cleared by the immune system in the majority of individuals, but in some cases the HPV infection can become to persist infection. Patients with persistent HPV infection is high risk for acquiring abnormalities for some reasons such as chronic inflammation and reasons mentioned earlier.[32]

Its prevalence was 14% for PC and 27% for nodular hyperplasia; and HPV-18 was the only type identified[13] whereas the significantly prevalent genotype of the 24 case–control studies was HPV16 which can exacerbate the cancer risk ($P < 0.001$). Several studies confirm the current result.[15] The most frequently detected high-risk HPVs in prostate cancers are types 16, 18, 31, 33, and 58,[25] which is consistent with our results. A prior study has also described high-risk-HPV type 16 positivity in 53.8% of malignant and in 20.0% of benign prostate biopsies. Low-risk HPV types such as HPV6 and HPV11 presented in benign controls in a higher proportion suggesting the formation of benign and precancerous lesions in prostate cancer.[33] There could be several hypotheses addressing this difference, prevalence and genotypes distribution of HPV, including geographical, sample size, sampling and methodological differences.

The PC is less frequent in Asia, Africa, Central and South America than North America, northwestern Europe and Australia. It occurs more frequent in African-American men and less regular in Asian-American and Hispanic/Latino men than in non-Hispanic whites.

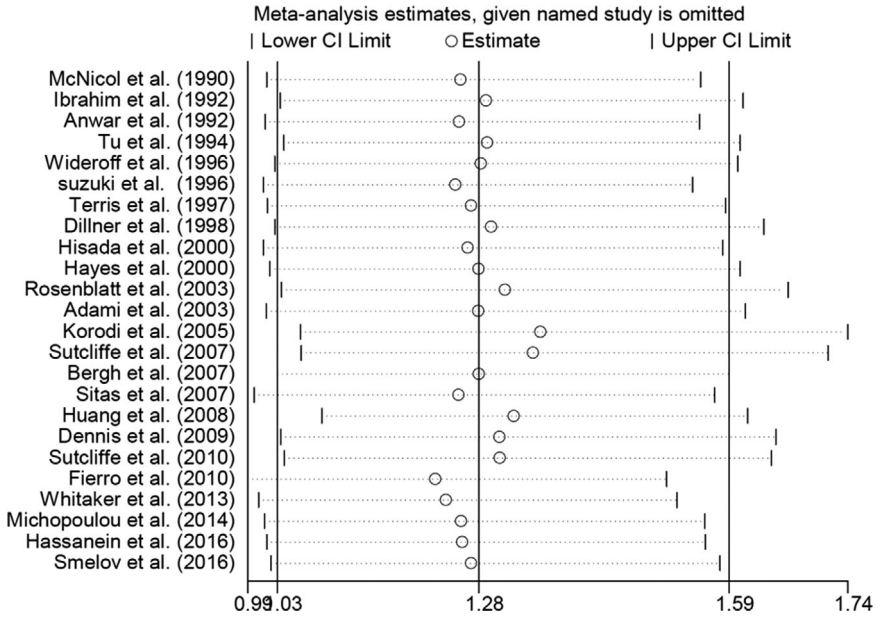

FIGURE 4 A sensitivity analysis plot for single studies on the summary effect size

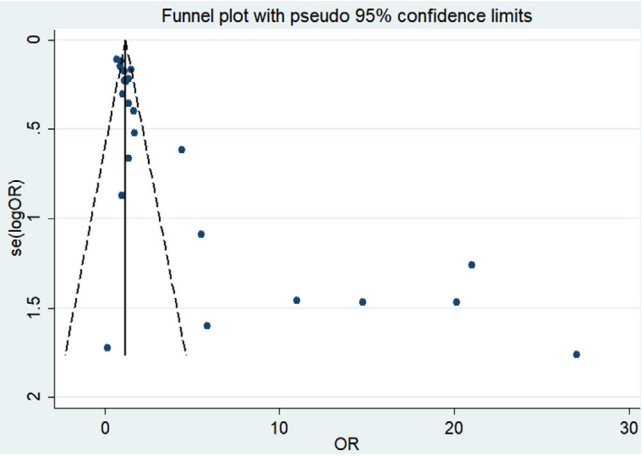

FIGURE 5 Begg's funnel plot with pseudo 95% CL for publication bias of the association between human papillomavirus infection and PC risk [Colour figure can be viewed at wileyonlinelibrary.com]

Previous meta-analysis studies have been shown that a high HPV prevalence in Africa whereas a low prevalence in Europe and North America in cervical cancer.[34] In this study, the most studies were conducted in America [13/24 (86%)] but the risk of HPV in PC was shown to be higher in Asia and Oceana. High-risk HPVs have been identified in PCs in North/South America, Europe, Asia and Pacific region. More importantly, studies demonstrated up to 22.3% of men with a preliminary negative prostate biopsy, develop PC within 11 years.[35,36] Hence, follow-up the presence of the pathogenic agent in benign tissues before the development of the disease is a missing step of many published researches to comprise further HPV role in PC development. Yang *et al*. demonstrated that the prevalence of HPV was higher (OR = 1.29; 95% CI, 1.03–1.63) in studies published during 2000–2015 (19.43%; 95% CI, 18.25–20.65%) than those in 1990–1999 (15.74%; 95% CI, 13.06–18.73%), whereas we showed the prevalence of HPV was (OR = 1.38; 95% CI, 1.13–1.69) in studies published before 2004 ($P < 0.001$). This issue could be due to the development of hygienic habits and methods of transmission of genital infections. Also, according to Lowess smoothing analysis, the OR for the association between HPV infection and risk of PC decreased over time until 2003, but after that, it increased again (Figure 3). Another aspect about the prevalence of HPV increasing is due to detection protocols improvement.[15]

Professional European/American guidelines and recommendations for PC screening initiate with measuring prostate-specific antigen (PSA) elevations, prostate cancer antigen 3 gene (PCA3) evaluation and digital rectal examination (DRE) for nodules, induration or asymmetry.[37,38] Should the results come back abnormal, patients would be referred to a urologist for a prostate biopsy.[39] Biopsy specimens are subjected to up-to-date molecular tests to determine the aggressiveness of prostate cancer better. There are tests based on cell proliferation consist of immunohistochemistry (IHC) evaluation of Ki-67, and the cell-cycle progression (CCP) score measured by quantitative reverse transcription polymerase chain reaction (RT-PCR). The results provide valuable information that could affect the extent of therapy.[40,41] Also, there are tests on the basis of molecular characteristics including PTEN tumor suppressor loss on chromosome 10q assessment, prostate cancer classifier (Decipher), Cancer gene panel (Oncotype DX prostate), and Proteomic biomarkers. This category of detection methods will determine markers specific to prostate cancer prognosis.[41–44] Furthermore, there are molecular basis methods that detect pathogens such as HPV that contributes to the PC. Here, the dominant detection method of subjected studies was PCR which is parallel with the results of the previously mentioned meta-analysis. Advancements in molecular biology resulted in three major categories to detect HPVs in PC patients. HPV DNA testing is the first approach developed for routine clinical testing. One of the important factors in the sensitivity of PCR is using L1 primer, because when use L1 primer for HPV detecting often L1 gene is lost during HPV integration into the host genome, and that it causes many of positive samples was reported as negative sample.[45]

The second approach, HPV RNA testing, looks for expression of E6 and E7 RNA, would provide equivalent sensitivity and better specificity than HPV DNA testing. The third approach is cellular marker detection, which diagnoses HPV-associated disease.[46] It is notable that in the PCR-based methods, type-specific primers could be more sensitive to distinguish 200 bp smaller HPV DNA sequences.[47]

The link was prominent in studies with HPV detected in tissues. Furthermore, we revealed the geographic variations in the association strengths and emphasized other methodological parameters (e.g., detection method) in further analyses that have never been shown in the previous studies. Previous studies have been shown that HPV infection is associated with prostate cancer, but a comprehensive study should be conducted that has the following characteristics: study of the type-specific prevalence of HPV infections based on region, age of patients, diagnostic methods, type of sample and year of study. This informative information could be provided a comprehensive map data for possible vaccine. For this purpose, we done this meta-analysis and analyzed the relationship between HPV infections and the risk of prostate cancer.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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