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Review Article

Identification of correlation between human papillomavirus and prostate cancer: Bradford Hill Criteria Based Evaluation.

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Abstract

Background: Human papillomavirus (HPV) association has effectively been decoded in prostate cancer (PC) worldwide with controverting conclusions. Though the different groups of researchers explored the potential association of HPV with PC using meta-analysis but it still remains controversial due to the major limitations. Therefore, the present study was designed to investigate the potential link of HPV with PC using Bradford Hill criteria.

Methodology: Initially using PubMed, we extracted studies that associated HPV to PC. Then, to assess the potential association of HPV with PC, an examination of the available data on HPV in PC, normal/benign samples was conducted using all the major Bradford Hill criteria postulates. Furthermore, to improve the authenticity of the present study, we have also critically evaluated the methodologies of the identified studies to check the possibility of false-negative and false-positive results.

Results: After a careful assessment of the previous studies against Bradford Hill criteria postulates, we observed that all the major postulates were not fulfilled, including strength, temporality, consistency, plausibility, biological gradient, experiment, specificity, and analogy.

Conclusion: The findings of this systematic review suggest no casual association of HPV with PC.

Keywords

Prostate Cancer, Bradford Hill Criteria, Statistical Meta-Analysis, Human Papillomavirus.

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Introduction

Prostate Cancer (PC) ranked second most common type of cancer and fifth leading cause of cancer-related mortality in male's worldwide[1]. The potential role of infectious agents has been well recognized in cancer development and pathogenesis[1]. Molecular evidence has shown that infections may cause chronic inflammation, which results in an inflammatory microenvironment that promotes cell proliferation[2].

Worldwide, the infection of HPV has been recognized as the most commonly transmitted infections (sexually)[3]. According to the previous epidemiological reports, 12 different HPV subtypes have been recognized as human carcinogens[4], which are involved in the development of different human cancers[5].

Considering the involvement of HPV in PC, different worldwide studies documented the role of HPV in PC so far, and their results were contradictory[6-8]. Various researchers used statistical meta-analysis to resolve this disagreement and obtain a more accurate association between HPV and PC. However, due to significant limitations of the statistical meta-analysis, including the inability to critically evaluate the methodologies, providing no information regarding the heterogeneity of the studied populations, and publication biasness, the evaluation of correlation among HPV and PC is due with an additional strategy.

In our study, we evaluated the correlation between HPV and PC using Bradford Hill criteria postulates. These postulates are worldwide effective for linking a presumed cause with an effect[9-11]. In the evaluation, we analyzed the data of previous studies to document whether or not the previous studies met the Bradford Hill criteria postulates to declare a causal association between HPV and PC. Additionally, to make our outcomes more authentic, we also critically reviewed the methodologies of identified studies to address the propensity of false results.

Methodology

In our study, we implemented a two-phase methodology (Figure 1). Related studies associating HPV with PC were searched via PubMed using the keywords: "Prostate cancer" AND "Human papillomavirus." Additionally, "Retroviridae" AND "Prostate intraepithelial" were also used as medical subject heading (MeSH) terms. All the original articles were searched till December 2020, and we managed to retrieve 244 original articles. Out of 244 studies, 36 relevant studies were shortlisted, which studied the association between HPV and PC initially by reading their titles, abstract, and then the complete text. Besides, a detailed table was built after acquiring the required data from shortlisted studies.

Based on the acquired data, we critically evaluated the selected studies using eight major Bradford Hill criteria postulates: (1) Strength, (2) Temporality, (3) Consistency, (4) Plausibility, (5) Biological gradient, (6) Experiment, (7) Specificity, and (8) Analogy[12].

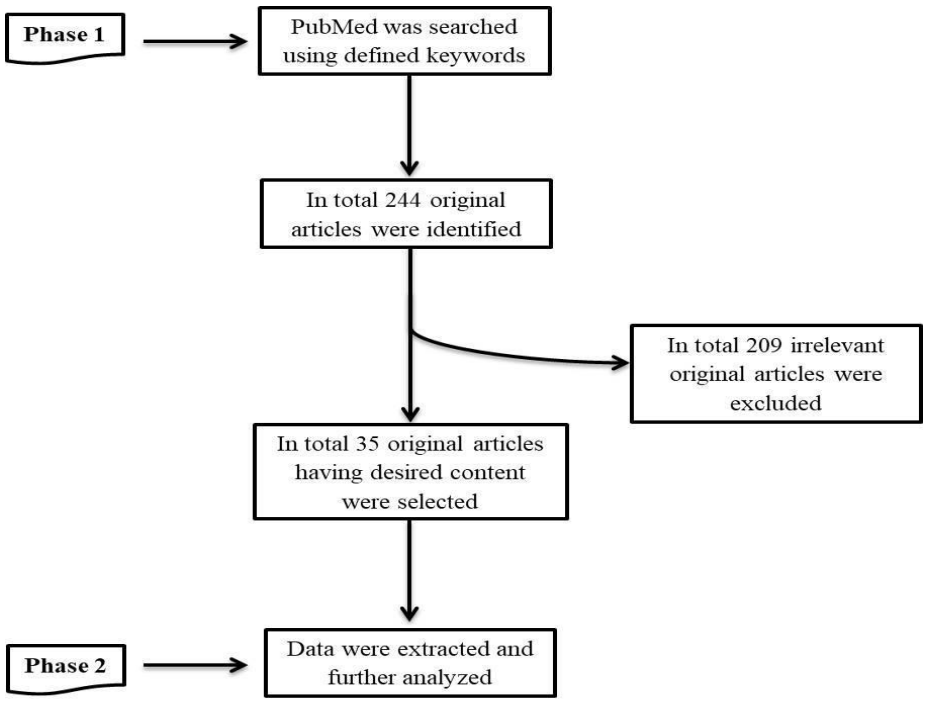

Figure 1: Overview of the methodology used in the present study

Results

In total, 35 original studies were identified that have examined the potential link of HPV with PC[6-8,13-44]. Table 1 summarizes the selected studies and includes the important acquired data from these studies essential for the assessment of Bradford Hill criteria postulates, including information of the studied population, names of the technique(s) utilized for the HPV identification, targeted gene, HPV detected strain, CI and P values, name of the prevalent identified HPV strain, totally analyzed samples count (normal, benign and PC) with respective population-wide detection positivity ratios.

The positivity ratio of HPV detection in the PC samples was varied population-wide from 0%[7, 14, 19, 23, 29, 30, 44] to100%[8]. While, in normal and adjacent or benign samples, it was varied from 0% 15 to 20%[8] and 0%[14, 15, 19, 21-23, 29, 33, 38, 44] to 93.3%[8], respectively.

The existence of a weak association does not rule out the possibility of a causal association; however, weak associations are more likely to be clarified by undetected biases. The argument that stronger associations tend to be casual is reasonable. In total, 33 case-control studies[6]were found in the literature reporting association between HPV and PC[6,8,13-29,31-44]. However, only of them have reported the CI, P-values and higher HPV detection ratio in PC samples as compared to the controls except one study[6, 24, 26, 32-34, 39, 43]. All these studies found a significant association between HPV and PC in Italy, Germany, Mexico, Germany, Czech Republic and USA populations except two studies, conducted in Iranian populations[24, 43]. These data overall support a negligible strength of association between HPV and PC.

Table 1: Information of the HPV positivity ratios in controls and prostate cancer samples relative to the selected articles

Studied Population	Technique used	Targeted gene / protein	Prevalent strains	Number of the normal sample screened	Percentage positivity of HPV in normal samples (%)	Number of the adjacent or benign samples screened	Percentage positivity of HPV in adjacent or benign samples (%)	Number of the total prostate cancer samples screened	Percentage positivity of HPV in prostate cancer samples (%)	References	P-value	CI
USA	In situ hybridization	--	--	0	0	20	0	20	0	23	--	--
	PCR	L1	16	20	10	16	0	24	25	21	--	--
	PCR (dot blot hybridization)	L1	16	0	0	42	9.5	56	12.5	43	--	95
	PCR	L1	16	1	0	0	0	43	2.3	41	--	--
	PCR	L1, E6	16	0	0	78	5.1	53	3.7	40	--	--
Canada	PCR	E6	16	0	0	56	60.7	27	51.9	25	--	--
	PCR	E6, E7	16	0	0	10	50	7	42.9	18	--	--
	PCR	E6	16	5	20	15	93.33	4	100	8	--	--
Italy	PCR	E6	16	0	0	17	82.3	8	75	31	--	--
	PCR	L1	--	0	0	25	48	26	65.4	6	0.33	--
Japan	PCR	--	16	10	0	10	0	68	41.2	15	--	--
	PCR	L1	16	0	0	51	0	51	15.7	38	--	--
	PCR	E6, E7	16	0	0	71	4.2	38	0	29	--	--
France	PCR	E6	16	0	0	22	31.8	17	52.9	28	--	--
United Kingdom	PCR	E1, E2, E6	16	0	0	10	0	14	0	14	--	--
Germany	PCR	E6	16	0	0	37	2.7	47	21.3	34	0.02	--
	PCR	--	--	0	0	163	17.7	50	20	24	--	95
Argentina	PCR	L1	11, 16	0	0	30	0	41	41.5	22	--	--
Saudi Arabia	Hybrid capture	--	--	0	0	50	0	6	0	19	--	--
Australia	PCR	L1	18	0	0	11	27	51	14	17	--	--
	PCR	L1	18	0	0	10	20	10	70	42	--	--
	PCR	L1	--	0	0	51	0	115	0	44	--	--

Iran	PCR	L1	16	0	0	104	7.7	104	12.5	13	--	--
	PCR	L1	--	0	0	85	0	68	4.4	33	0.71	--
	PCR	L1	--	0	0	167	4.8	29	17.2	20	--	--
	PCR	E7, E2	16	0	0	32	15.6	58	32.7	32	0.07	95
Czech Republic	PCR	L1	16	0	0	95	2.1	51	2	39	1	--
Greece	PCR	L1	16, 18, 31	0	0	30	3.3	50	16	27	--	--
India	PCR	L1	16, 18	0	0	55	20	95	41.1	36	--	--
Brazil	Linear Array HPV Genotyping Test	L1	16	0	0	6	0	65	3	35	--	--
	PCR	L1, E6, E7	--	0	0	0	0	104	0	7	--	--
Mexico	PCR	L1	52, 58	0	0	167	9.6	189	19.6	26	0.01	95
Netherland	PCR	L1	16, 33	0	0	14	0	61	3.27	37	--	--
Turkey	PCR	L1	57	0	0	36	0	60	1.7	16	--	--
Chile	PCR	L1	--	0	0	0	0	69	0	30	--	--

Temporality refers to the necessity for HPV to cause PC. The HPV detection ratios scenario in the current study has shown differential outcomes. In a total of 7 cross-sectional studies, the authors have reported no HPV detection in PC samples[7, 14, 19, 23, 29, 30, 44]. In comparison, in 5 cross-sectional studies, the higher HPV detection ratio was reported in normal controls relative to PC sample[17, 25, 29, 31, 39]. Moreover, in a few other case-control studies, HPV was detected in both normal and PC samples which supported the idea of PC development without HPV infection[6, 8, 13, 17, 18, 20, 21, 24-28, 31, 32, 34, 36, 39, 40, 42, 43]. Such conflicting results thus failed to fulfill the temporality postulate.

Plausibility refers to a proper mechanism between cause and effect. HPV is well recognized as a potent inhibitor of TP53 in cervical cancer by making aE6/E6AP/p53 complex, resulting in the degradation of TP53 protein[45]. In the literature, only one study[32] found analyzing the association between HPV presence and expression variations in TP53 level: they have validated their results as TP53 was down regulated in the PC patients. Thus, the HPV role in the etiology of PC is biologically not plausible.

This postulate refers to the evidence from either animal or clinical studies. However, evidence-based on animal models and clinical studies were absent in all the studies found in the literature. Therefore, this postulate was not fulfilled. Causation is possible if a certain population develops PC in a certain region where the suspected cause is not clarified otherwise. Higher the specificity of the association between a factor and its effect, the more precise the relationship between a factor and its effect. PC is a multi-factorial disease[46]. Together with HPV, the role of other non-infectious factors and oncogenic viruses (EBV and John Cunningham virus) in PC development is also well studied worldwide[42, 47]. Thus, the complexity of the involved factors in PC development suggested no specificity.

Similar diseases to PC that can be considered PC analogous are breast cancer and cervical cancer caused by other viral agents like Epstein–Barr virus (EBV) and Mouse mammary tumour virus (MMTV)[48, 49]. However, the role of MMTV and EBV in breast cancer and cervical cancer development is yet not fully established. Thus, in the present study, the scenario of analogy also suggested no association between HPV and PC.

Discussion

PC is the second most prevalent cancer subtype that affects people all over the world. So far, many studies were conducted worldwide documenting the relationship between HPV and PC to identify the possible oncogenic pathways regulating HPV in PC development; however, the findings were inconsistent. Besides, a statistical meta-analysis has also been performed by different groups of scientists worldwide to generate a more meaningful relationship between HPV and PC; due to statistical meta-analysis shortcomings, scientists failed to find a reliable relationship between HPV and PC. Therefore, we aim to find an association between HPV and PC using Bradford Hill criteria postulates in the present study. 35 original articles were included in the present study[6-8, 13-44]. The HPV detection ratio reported in these studies was varied between 0%[7, 14, 19, 23, 29, 30, 44], to 100%[8] in PC samples. In most case-control studies, the detection ratio of HPV was more significant in the PC samples than the controls[6, 8, 13-29, 31-44]. In contrast, in five studies, HPV detection ratios were greater in the controls than in the PC samples[17, 25, 29, 31, 39].

Best to our knowledge, no study has applied the Bradford Hill postulates so far to identify the association between HPV and PC. However, one study utilized these postulates to analyze the causal association between Zika infection and microcephaly, and they suggested no link between the studied parameters[50]. Since the initial identification of HPV in PC, more evidence has become available. We systematically applied Bradford Hill's postulates on the available evidence to find an association between HPV and PC. The results were not in favour of a causal association. Therefore, we speculated that HPV, along with other different viruses like human immunodeficiency virus (HIV) and hepatitis and C virus (HCV and B), as well as other genetic abnormalities, smoking, alcohol consumption increases the risk of developing PC by affecting the body's immune system[51].

Moreover, deficiencies and some of the major drawbacks linked with the methodologies of the included studies have been discussed below.

Possible causes of false-negative

Few studies did not detect HPV in any of the PC or control samples they were utilizing. How do we be sure that the negative results were not because of the low-quality DNA? Several studies used positive control to address the question. However, studies did not utilize the positive control in their

experiment; thus, there is no mean to validate the negative findings[6-8, 11, 13-16, 18, 21, 22, 25-30, 32-38, 40-44]. Primer selection targeting L1 and E1 genes of HPV might be inefficient for detecting HPV presence in the advanced carcinoma and thus results in a false negative since L1 and E1 regions might be lost during viral genome integration with the genome of the host. In contrast, the E6/E7 regions remained consistently present in any circumstances so, this is the plausible explanation for the completely negative results of studies[7, 14, 19, 23, 30, 44].

Possible causes of the false-positive

Most of the summarized studies utilized PCR for the HPV detection, but none have used any second technique to validate their PCR results, except 2 studies, which utilized dot blot hybridization, In-situ hybridization and the results have deviated from the PCR[6-8, 13-18, 20-34, 36-44]. In HPV-positive PC patients, expression profiling of various genes such as p14, p16, p53, RB, and others may be used as a surrogate biomarker. In addition to the HPV detection, expression profiling of these biomarkers were also done by few studies to further validate their findings, out of which, only one study has validated their findings by analyzing p53 and RB genes as surrogate biomarkers; however, the other three studies unable to validate their findings concerning surrogate biomarkers[26, 27, 32, 33]. These inconsistencies in the previous studies' results pose a significant question mark regarding the choice of suitable methods and their sensitivities.

Comparison between normal, benign and malignant samples

Case-control studies are essential when looking for a causal association between cause and the disease. Few of the selected studies used the PC samples only, which did not compare with normal, adjacent or benign and PC samples[7, 30]. However, on the other side, few of the selected studies analyzed both normal or adjacent/benign and PC samples, and this comparison revealed higher HPV detection ratios in PC samples in studies while lower in other studies as compared to the control[6, 8, 13-29, 31-44]. However, no study has found a correlation between HPV and a certain PC subtype or histologic grade.

Conclusion

The findings of this study have reported no causal association between HPV and PC. However, considering the constraints in the used methodologies, additional experiments are proposed to prove a proper HPV etiology in PC.

Conflicts of Interest

The authors have declared that no competing interests exist.

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