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Research Article

Human papillomavirus is the cause of human prostate cancer

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ABSTRACT

Objective: The aim of the present meta-analysis study is to investigate whether human papillomavirus (HPV) serves as a cause or as the cause of human prostate cancer (PC).

Methods: The PubMed database was searched for suitable articles. Previously published expert reviews and systematic meta-analysis were used as an additional source to identify appropriate articles. Articles selected for this meta-analysis should fulfill the following inclusion criteria: (a) no data access barrier, (b) polymerase chain reaction (PCR) DNA based identification of HPV. The method of the *conditio sine qua non* relationship was used to prove the hypotheses whether being married is a necessary condition (a *conditio sine qua non*) of PC. In other words, without being married no PC. The method of the *conditio per quam* relationship (sufficient condition) was used to prove the hypotheses if HPV is present in human prostate tissues then PC is present too. The mathematical formula of the causal relationship *k* was used to prove the hypothesis, whether there is a cause effect relationship between HPV and PC. Significance was indicated by a *p*-value (two sided) of less than 0.05.

Results: In more than 33 studies were considered for a meta-analysis. Several studies support the hypotheses without being married no PC. All the studies considered for a re-analysis support the null-hypotheses if HPV then PC, while the cause effect relationship between HPV and PC was highly significant.

Conclusions: HPV is the cause of PC.

Keywords: Human papillomavirus, prostate cancer, causality

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INTRODUCTION

Human¹ papilloma² virus³ (HPV) is a small DNA⁴ virus and responsible for several benign and malignant diseases. More than 200 types⁵ of HPV have been identified to date. Meanwhile, HPV is identified as the cause⁶ of human cervical cancer⁷ while equally one of the most prevalent sexually transmitted infections (STI) in the United States⁸ and worldwide⁹ too. In about 72.9% of the male partners in heterosexually active couples are HPV positive¹⁰. McNicol and Dodd¹¹ detected HPV even in prostate cancer (PC) tissues of adults. Oddly enough, PC has not been documented in very young and sexually inactive male¹² children. The mortality burden of PC has risen to over 360,000 deaths per year¹³. Some risk factors¹⁴ for PC like genetic polymorphisms, family history of prostate cancer, race, age, height, physical activity, BMI, total energy consumption, intakes of calcium, tomato sauce and alpha-linolenic acid and cigarette smoking history are discussed in literature while evidence is conflicting¹⁵. Especially, several different systematic reviews and meta-analysis^{16, 17, 18, 19, 20} investigated HPV in relation to PC but opposing reports were

stated. To clarify the contradictory results of these and other investigations, this meta-analysis with updated data has been carried out to obtain a more precise picture of the relationship between HPV and PC.

MATERIAL AND METHODS

Search strategy

The electronic database PubMed was searched for appropriate studies conducted in any country which investigated the relationship between HPV and PC. In assessing the shortcomings of PubMed, additionally, appropriate review articles and references published within the same were checked.

Study selection

To be eligible for inclusion, no data access barriers were accepted. The titles and abstracts of all the retrieved articles using the inclusion criteria were screened. Data extraction was performed on included articles.

Table 1. Flow Diagram of the article selection process. Adopted from PRISMA^{21, 22} 2009.

	Size	Total
1. Identification of records		
Records identified by searching in the databases		
PubMed	45	
Additional records identified from other sources:	58	
Review of Yin (n=24)		
Review of Bae (n=30)		
Dillner et al., 1998		
Pourmand et al., 2007		
Schiffmann et al., 2015		
Loeb et al., 2017		103
2. Clean-up of search		
Inappropriate articles excluded	64	
3. Eligibility		
Articles evaluated for eligibility	39	
Articles excluded for various reasons		
Self-contradictory data	13	
4. Included		
Articles included in the meta-analysis		26

Data analysis

The following data were recorded for analysis.

The data of the studies analyzed

The studies reviewed²³⁻⁴⁴ in this publication investigated the condition per quam relationship between HPV and PC while using the highly sensitive PCR technique are presented in more detail by a table (Table 2).

Table 2. The HPV PCR Studies²³⁻⁴⁴ considered for a re-analysis of condition per quam.

Study Id	Year	Country	Risk Factor	Case_ P	Case_ T	Con_ P	Con_ T	k	p-val	IOU	X ² (IMP)
Ibrahim et al.	1992	USA	High-risk HPV16/18 PCR	6	24	2	36	0.280224	0.03314108	-0.47	0.28
Anwar et al.	1992	Japan	High-risk HPV16/18/33 PCR	28	68	0	10	0.286972	0.00816351	0.23	0.01
Tu et al.	1994	USA	High-risk HPV16/18 PCR	1	43	0	1	0.023255	0.97727272	0.00	0.25
Moyret-Lalle et al.	1995	France	High-risk HPV16/18 PCR	14	27	8	24	0.186630	0.09451920	-0.04	2.56
Suzuki et al.	1996	Japan	High-risk HPV16 PCR	8	51	0	51	0.291729	0.00290368	-0.42	0.03
Wideroff et al.	1996	USA	HPV PCR	7	56	4	42	0.046657	0.23167954	-0.32	1.11
Terris & Peehl et al.	1997	USA	High-risk HPV16/18 PCR	10	53	5	37	0.070692	0.18559829	-0.24	1.35
Serth et al.	1999	Germany	HPV16 PCR	10	47	1	37	0.273334	0.01031477	-0.31	0.02
Carozzi et al.	2004	Italy	High-risk HPV type	14	26	5	25	0.349956	0.01058851	-0.12	1.07
Leiros et al.	2005	Argentina	HPV PCR	17	41	0	30	0.479950	1.46345E-05	-0.18	0.01
Silvestre et al.	2009	Brasil	HPV PCR	2	65	0	6	0.051726	0.837022133	-0.06	0.13
Martinez-Fierro et al.	2010	Mexico	HPV PCR	11	55	4	75	0.226803	0.008602189	-0.46	0.82
Aghakhani et al.	2011	Iran	HPV PCR	13	104	8	104	0.079788	0.095738433	-0.40	2.68
Salehi and Hadavi	2012	Iran	HPV PCR	3	68	0	85	0.158113	0.085627977	-0.54	0.08
Mokhtari et al.	2013	Iran	HPV PCR	3	30	1	90	0.214422	0.044481939	-0.72	0.06
Whitaker et al.	2013	Australia	HPV PCR	7	10	2	10	0.502518	0.032150512	-0.05	0.25
Michopoulou et al.	2014	Greece	HPV PCR	8	50	1	30	0.194069	0.069453811	-0.26	0.03
Singh et al.	2015	India	HPV PCR	39	95	11	55	0.215211	0.004234054	-0.03	2.21
Huang et al.	2016	China	High-risk HPV16/18 PCR	30	75	0	73	0.497451	3.80058E-11	-0.29	0.01
Atashafrooz et al.	2016	Iran	HPV PCR	20	100	8	100	0.172917	0.008230537	-0.36	2.01
Aydin et al.	2017	Turkey	HPV PCR	1	60	0	36	0.079471	0.625	-0.36	0.25
Zhao et al.	2017	China	High-risk HPV16 PCR	48	75	14	80	0.474341	2.10403E-09	-0.12	2.94
Total				300	1223	74	1037	0.233234	1.27175E-30		14.444

N = 2260

Alpha = 0.05

=

Degrees of freedom (d. f.) = 22

X² Critical (IMP) = 33.92

44

X² Calculated (IMP) = 14.44

45

Index of unfairness = -0.29

33

Case_P: cases, positive; Case_T: cases, total; Con_P: controls, positive; Con_T: controls, total.

The studies reviewed²³⁻⁴⁴ in this publication which investigated the causal relationship between HPV and PC while using the highly sensitive PCR technique are presented in more detail by a table (**Table 3**).

Table 3. The causal relationship between human papilloma virus and prostate cancer

Study Id	Year	Country	Risk Factor	Case_P	Case_T	Con_P	Con_T	k	p-val (HGD)	IOU	X ² (k)
Huang et al.	2016	China	High-risk HPV16/18 PCR	30	75	0	73	0.497451	3.80058E-11	-0.29	36.62
Zhao et al.	2017	China	High-risk HPV16 PCR	48	75	14	80	0.474341	2.10403E-09	-0.12	34.88
Leiros et al.	2005	Argentina	HPV PCR	17	41	0	30	0.479950	1.46345E-05	-0.18	16.36
Suzuki et al.	1996	Japan	High-risk HPV16 PCR	8	51	0	51	0.291729	0.002903682	-0.42	8.68
Singh et al.	2015	India	HPV PCR	39	95	11	55	0.215211	0.004234054	-0.03	6.95
Anwar et al.	1992	Japan	High-risk HPV16/18/33 PCR	28	68	0	10	0.286972	0.008163513	0.23	6.42
Atashafrooz et al.	2016	Iran	HPV PCR	20	100	8	100	0.172917	0.008230537	-0.36	5.98
Martinez-Fierro et al.	2010	Mexico	HPV PCR	11	55	4	75	0.2268030	0.008602189	-0.46	6.69
Serth et al.	1999	Germany	HPV16 PCR	10	47	1	37	0.273334	0.010314777	-0.31	6.28
Carozzi et al.	2004	Italy	High-risk HPV type	14	26	5	25	0.349956	0.01058851	-0.12	6.25
Whitaker et al.	2013	Australia	HPV PCR	7	10	2	10	0.502518	0.032150512	-0.05	5.05
Ibrahim et al.	1992	USA	High-risk HPV16/18 PCR	6	24	2	36	0.280224	0.033141089	-0.47	4.71
Mokhtari et al.	2013	Iran	HPV PCR	3	30	1	90	0.214422	0.044481939	-0.72	5.52
Total				241	697	48	672	0.698497	2.95206E-73	-0.49	150
										N =	1369
										Alpha =	0.05
										Degrees of freedom (d. f.) =	13
										X² Critical (k) =	22.36
										X ² Calculated (k) =	150.37
										p value (k) <	0.00001

Case_P: cases, positive; Case_T: cases, total; Con_P: controls, positive; Con_T: controls, total.

The Data of the studies not analyzed

Studies^{11,45-56} which published data self-contradictory are viewed by **Table 4** and have not been considered for a review of the causal relationship. The reason for the contradiction is highlighted

by bold letters. However, the majority of these studies (i. e. 12/20) excluded from the review support the hypotheses that HPV is a sufficient condition of PC since X² (IMP) is less than 3.841458821.

Table 4. The studies^{11,45-56} not considered for a re-analysis

Study Id	Year	Country	Risk Factor	Case_P	Case_T	Con_P	Con_T	k	p-val	IOU	X ² (SINE)	X ² (IMP)	X ² (IMP^SINE)	X ² (EXCL)
McNicol and Dodd	1991	Canada	HPV PCR	14	27	34	56	-0.08407643	0.139723165	-0.10	5.79	23.38	29.17	10.55
Masood et al.	1991	USA	HPV PCR	0	20	0	20	#DIV/0!	1	-0.50	19.01	#DIV/0!	#DIV/0!	#DIV/0!
Rotola et al.	1992	Italy	HPV PCR	6	8	14	17	-0.08574929	0.358366271	0.12	0.28	9.11	9.39	5.29
Dodd et al.	1993	Canada	HPV PCR	3	7	5	10	-0.07042952	0.362813657	-0.12	1.75	2.53	4.28	1.67
Effert et al.	1992	USA	High-risk HPV16/18 PCR	0	30	0	0	#DIV/0!	1	0.00	29.01	#DIV/0!	#DIV/0!	#DIV/0!
Anderson et al.	1997	UK	HPV PCR	0	0	0	0	#DIV/0!	1	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!
Noda et al.	1998	Japan	HPV PCR	0	38	3	71	-0.12307513	0.272252232	-0.62	37.01	2.08	39.09	0.09
Strickler et al.	1998	USA	HPV PCR	0	63	0	61	#DIV/0!	1	-0.49	62.00	#DIV/0!	#DIV/0!	#DIV/0!
Gazzaz and Mosli	2009	Saudi Arabia	HPV PCR	0	6	0	50	#DIV/0!	1	-0.89	5.04	#DIV/0!	#DIV/0!	#DIV/0!
Chen et al.	2011	Australia	HPV PCR	7	51	3	11	-0.14071179	0.177670024	-0.02	37.10	0.63	37.73	5.05
Tachezy et al.	2012	Czech Republic	HPV PCR	1	51	2	95	-0.00485537	0.448187293	-0.63	48.04	0.75	48.79	0.09
Ghahass	2013	Iran	HPV	5	29	8	167	0.17764904	0.02231058	-0.79	19.04	4.33	23.37	2.26
Yow	2014	Australia	HPV	0	115	0	51	#DIV/0!	1	-0.31	114.00	#DIV/0!	#DIV/0!	#DIV/0!
			Total	36	445	69	609							
					N = 1054									

Marital status and HPV positivity

The Iranian study and Ghasemian⁵⁵ et al. provided detailed information about the marital status and HPV positivity. The data

on the relationship between marital status and HPV positivity are viewed by the **Table 5**. The data of study of Pourmand⁵⁷ et al. are self-contradictory and were not considered for a review on this topic.

Table 5. Marital status⁵⁵ and HPV positivity

The study of	HPV			
	positive			
	Yes = +1	No = +0	Total	
Ghasemian et al.	Yes =+1	12	167	179
	No = +0	1	16	17
	Total	13	183	196

Marital status and prostate cancer

Data on the relationship between marital status and prostate cancer were published by Ghasemian⁵⁵ et al. are viewed by the **Table 6**. The Iranian data on the relationship between marital

status and prostate cancer were compared with the data as published by the study of Dillner⁵⁸ et al. The data as published by Dillner et al. are viewed by the **Table 6** too. The data as provided by Schiffmann⁵⁹ et al. and Huang⁶⁰ et al. and Loeb⁶¹ et al. are not appropriate enough and were not considered for a re-analysis.

Table 6. Marital status and prostate cancer

Study	Year	N	Case_P	Case_T	Con_P	Con_T	k	p(k)	X ² (SINE B _t)	X ² (SINE A _t)	p(IOU)	p(IOI)
Dillner et al.	1998	452	154	164	259	288	+0,07	0,05	0,61	2,56	0,27655	0,55088
Ghasemian et al.	2013	196	27	29	152	167	+0,03	0,278	0,14	0,24	0,06122	0,76531

Statistical Analysis

All the statistical analyses for the meta-analysis were conducted by Microsoft @ Excel @ for Mac @ version 16.2 (181208) software (© 2018, Microsoft GmbH, Munich, Germany), with statistical significance at P < 0.05. P value, provided with capital letter P, is stated as exact number with three decimal places (i.e. P = 0.027).

The data extracted from the papers were checked for self-contradictions and publication bias by the index of unfairness⁶² and by the index of independence. The *conditio sine qua non* relationship, the *conditio per quam* relationship⁶ and the mathematical formula of the *causal*⁶³ relationship were used to prove the relationship between HPV and PC for causality. The hypergeometric distribution was used to calculate P values.

Whether a *sample* distribution observed is identical with a *theoretical* distribution expected was proofed by Pearson's Chi-square goodness of fit test⁶³ too. The applicability of using the Pearson chi-squared statistic in cases where the cell frequencies of a 2x 2 contingency table are not greater than five is widely discussed in literature. *The rule of three*⁶³ has been applied by the analysis of the study of Whitaker et al.³⁸. The use of Yate's continuity correction in this context is to some extent controversial and not essential.

Additionally, the odds ratio⁶³ (OR), even if severely and justifiably criticized and disproved especially by Karl Pearson⁶³ (1857–1925) and Heron, with a confidence interval of 95% was determined.

Definitions

Definition 1. (The 2x2 Table)

A two by two table (also called a contingency table, a notion first used by Karl Pearson in 1904) is a useful tool for examining relationships between Bernoulli (i. e. Binomial) distributed random variables. Consider the case of a Bernoulli distributed random variable A_t occurring/existing et cetera with the probability p(A_t) at the Bernoulli trial (period of time) t. Furthermore, consider the case of another Bernoulli distributed random variable B_t occurring/existing et cetera with the probability p(B_t) at the same Bernoulli trial (period of time) t. Let p(a_t)= p(A_t ∩ B_t) denote the joint probability distribution of A_t and B_t at the same Bernoulli trial (period of time) t. The following table (**Table 7**) may show the relationships in more details.

Table 7. The probabilities of a contingency table

	Conditioned			
	B			
	Yes = +1	No = +0	Total	
Condition A	Yes =+1	p(a _t)	p(b _t)	p(A _t)
	No = +0	p(c _t)	p(d _t)	p(Δ _t)
	Total	p(B _t)	p(B̄ _t)	1

In this context, it is *per definitionem*

$$\begin{aligned}
 p(A_t) &\equiv p(a_t) + p(b_t) &= 1 - p(\underline{A}_t) \\
 p(B_t) &\equiv p(a_t) + p(c_t) &= 1 - p(\underline{B}_t) \\
 p(a_t) &\equiv p(A_t \cap B_t) &= 1 - p(b_t) - p(c_t) - p(d_t) \\
 +1 &\equiv p(a_t) + p(b_t) &+ p(c_t) + p(d_t) \\
 +1 &\equiv p(A_t) + p(\underline{A}_t) &= p(B_t) + p(\underline{B}_t) \\
 p(B_t) + p(\Lambda_t) &\equiv p(A_t) &= 1 - p(\underline{B}_t) + p(\Lambda_t) \\
 p(\underline{A}_t) &= 1 - (1 - p(\underline{B}_t) + p(\Lambda_t)) &= p(\underline{B}_t) - p(\Lambda_t) \\
 p(\Lambda_t) &= p(A_t) - p(B_t) &= p(b_t) - p(c_t) \\
 p(b_t) + p(c_t) &= (2 \times p(c_t)) + p(\Lambda_t) &= 1 - p(a_t) - p(d_t)
 \end{aligned} \tag{1}$$

while +1 denotes the *normalized sample space* of A_t and B_t . Under conditions of Einstein’s general theory of relativity, Λ indicates the cosmological “constant”. Einstein’s field equation expressed completely under conditions of classical logic and equally of probability theory simplifies to $\mathbf{p(B_t)} + \mathbf{p(\Lambda_t)} = \mathbf{1} - \mathbf{p(\underline{B_t})} + \mathbf{p(\Lambda_t)} = \mathbf{p(A_t)}$ at each point in space-time t while $p(a_t)$, $p(b_t)$, $p(c_t)$ and $p(d_t)$ may denote equally the probability as associated with the four basic fields of nature. Under circumstances where the probability of an event is constant from trial to trial (i. e. Binomial distribution), the relationships before simplify. We obtain some of the relationships *per definitionem*

$$\begin{aligned}
 A &\equiv n \times p(a_t) + n \times p(b_t) &= n \times p(A_t) \\
 B &\equiv n \times p(a_t) + n \times p(c_t) &= n \times p(B_t) \\
 a &\equiv n \times p(a_t) &= n \times p(A_t \cap B_t) \\
 b & n \times p(b_t) \\
 c & n \times p(c_t) \\
 d & n \times p(d_t) \\
 n &\equiv n \times p(a_t) + n \times p(b_t) + n \times p(c_t) + n \times p(d_t) \\
 n &\equiv n \times p(A_t) + n \times p(\underline{A}_t) &= n \times p(B_t) + n \times p(\underline{B}_t)
 \end{aligned} \tag{2}$$

The meaning of the abbreviations a, b, c, d, n et cetera are explained by following 2 by 2-table (Table 8).

Table 8. The sample space of a contingency table

		Conditioned B (Outcome)		
		Yes = +1	No = +0	Total
Condition A (risk factor)	Yes =+1	a	b	A
	No = +0	c	d	<u>A</u>
Total		B	<u>B</u>	n

Definition 2. Index of unfairness

The probability of an index of unfairness (IOU) is defined as

$$p(IOU) \equiv \text{Absolute} \left(\left(\frac{A + B}{n} \right) - 1 \right) \tag{3}$$

Definition 3. The Chi Square of an Index of unfairness

The index of unfairness is grounded on the relationship that $N = A + B$. Under very appropriate conditions, there should be no deviation of $A + B$ from N and the IOU should be equal to 0. The Chi square of an index of unfairness (IOU) is defined as

$$\text{Chi square (IOU)} \equiv \left(\frac{\left(\left((A + B) - n \right) \times \left((A + B) - n \right) \right)}{n} \right) + 0 \quad (4)$$

Definition 4. Index of independence (IOI)

The probability of an index of independence (IOI) is defined as

$$p(\text{IOI}) \equiv \text{Absolute} \left(\left(\frac{A + B}{n} \right) - 1 \right) \quad (5)$$

Definition 5. The Chi square of an Index of independence

The index of independence is grounded on the relationship that $N = A + B$. Under very appropriate conditions, there should be no deviation of $A + B$ from N and the IOI should be equal to 0. The Chi square of an index of independence (IOI) is defined as

$$\text{Chi square (IOI)} \equiv \left(\frac{\left(\left((A + B) - n \right) \times \left((A + B) - n \right) \right)}{n} \right) + 0 \quad (6)$$

Definition 6. Independence

In the case of independence⁶³ of A_t and B_t it is generally valid that

$$p(A_t \cap B_t) \equiv p(A_t) \times p(B_t) \quad (7)$$

Definition 7. The Mathematical Formula of the Causal Relationship k

The mathematical formula of the causal relationship k ⁶³ is defined at every single event, at every single Bernoulli trial t , as

$$k(A_t, B_t) \equiv \frac{p(A_t \cap B_t) - (p(A_t) \times p(B_t))}{\sqrt{p(A_t) \times (1 - p(A_t)) \times p(B_t) \times (1 - p(B_t))}} \quad (8)$$

where A_t denotes the cause and B_t denotes the effect. Under some certain circumstances, the chi-square distribution can be applied to determine the significance of causal relationship k . Again, it necessary to point out that *neither* Pearson's concept of correlation *nor* Pearson's concept of ϕ is identical with causation. The mathematical formula of the causal relationship k has nothing to do with Pearson's methods and is not identical with correlation. This has been proved many times and is widely discussed in many publications.

Definition 8. The 95% Confidence Interval of the Causal Relationship k

The 95% interval for the causal relationship k was calculated by the formula

$$\left\{ k(A_t, B_t) - \sqrt{\frac{5}{n}} ; k(A_t, B_t) + \sqrt{\frac{5}{n}} \right\} \quad (9)$$

Definition 9. The Chi Square Distribution

The following critical values of the chi square distribution⁶³ as visualized by **Table 9** are used in this publication.

Table 9. The critical values of the chi square distribution (degrees of freedom: 1)

	p-Value	One sided X ²	Two sided X ²
	0.1000000000	1.642374415	2.705543454
The chi square distribution	0.0500000000	2.705543454	3.841458821

RESULTS

Theorem 1. Without being married no HPV positivity.

Claims.

Null hypothesis:

Marriage is a necessary condition (a *conditio sine qua non*) of HPV positivity of an Iranian man. In other words, the *sample distribution* of the study analyzed agrees with the hypothetical (*theoretical*) distribution of a necessary condition.

Alternative Hypothesis:

Marriage is not a necessary condition (a *conditio sine qua non*) of HPV positivity of an Iranian man. In other words, the sample distribution of the study analyzed does not agree with the hypothetical (*theoretical*) distribution of a necessary condition.

The significance level (Alpha) below which the null hypothesis will be rejected is $\alpha = 0.05$.

Proof.

The results of the data reviewed and re-analyzed by this article which investigated the relationship between marital status and HPV positivity of an Iranian man are viewed by the table (Table 5). The study design of the study of Ghasemian et al. is very impressive ($p(\text{IOU}) = 0,06$). The data can be used for causal analysis and for the analysis of conditions too. The study analyzed was able to provide evidence of a positive cause effect relationship. Furthermore, the null-hypothesis: *without* being married no HPV positivity of an Iranian man (Table 10) could not be rejected. Marriage is a necessary condition (a *conditio sine qua non*) of HPV positivity of an Iranian man ($p_{\text{Sine}}(\text{Married} \leftarrow \text{HPV positive}) = 0,995$; Chi sq. 1 (SINE) = 0,08; Chi sq. 2 (SINE) = 0,06; $p(\text{IOU}) = 0,02$, $k > 0$).

Quod erat demonstrandum.

Table 10. Statistical analysis of the marital status and HPV positivity

Statistical Analysis.	$p(\text{IOU}) = 0,020$	$p(\text{IOI}) = 0,847$
Causal relationship $k = +0,009$	95 % CI (k): (-0,150 - 0,169)	
P value ($k \text{HGD}$) = 0,391	Chi sq. (k) = 0,017	
Odds ratio (OR) = 1,150	95 % CI (OR): (0,140 - 9,422)	
p (SINE) = 0,995	Chi sq. 1 (SINE) = 0,077	Chi sq. 2 (SINE) = 0,059
p (IMP) = 0,148	Chi sq. 1 (IMP) = 152,399	Chi sq. 2 (IMP) = 155,804
p (SINE ^ IMP) = 0,143	Chi sq. 1 (SINE ^ IMP) = 152,476	Chi sq. 2 (SINE ^ IMP) = 155,863
p (EXCL) = 0,939	Chi sq. 1 (EXCL) = 11,077	Chi sq. 2 (EXCL) = 0,804

Theorem 2. Without being married no prostate cancer

Claims.

Null hypothesis:

Marriage is a necessary condition (a *conditio sine qua non*) of prostate cancer. In other words, the *sample distribution* of the study analyzed agrees with the hypothetical (*theoretical*) distribution of a necessary condition.

Alternative Hypothesis:

Marriage is not a necessary condition (a *conditio sine qua non*) of prostate cancer. In other words, the sample distribution of the study analyzed does not agree with the hypothetical (*theoretical*) distribution of a necessary condition.

The significance level (Alpha) below which the null hypothesis will be rejected is $\alpha = 0.05$.

Proof.

The results of the re-analyses of the data reviewed by this article which investigated the relationship between marital status and prostate cancer are viewed by the table (Table 6). Altogether, both studies (Finland and Iran) which were meta-analyzed provided significant evidence of a *conditio sine qua non* relationship between marital status and prostate cancer. In the

same respect, the causal relationship k was $k > 0$. The null-hypothesis cannot be rejected. Thus far, the conclusion with respect to the studied sample is inescapable, *without* being married no prostate cancer.

Quod erat demonstrandum.

Theorem 3. Human papilloma virus is a sufficient condition of prostate cancer

Claims.

Null hypothesis:

HPV is a sufficient condition (a *conditio per quam*) of prostate cancer. In other words, the *sample distribution* of the studies analyzed agrees with the hypothetical (*theoretical*) distribution of a sufficient condition.

Alternative Hypothesis:

HPV is not a sufficient condition (a *conditio per quam*) of prostate cancer. In other words, the *sample distribution* of the studies analyzed does not agree with the hypothetical (*theoretical*) distribution of a sufficient condition.

The significance level (Alpha) below which the null hypothesis will be rejected is $\alpha = 0.05$.

Proof.

The results of the re-analyses of the data which investigated the conditio per quam relationship between HPV and prostate cancer are viewed by the table (Table 2). Altogether, if was not possible to reject the null-hypothesis: *if* HPV infection (HPV PCR DNA positive) *then* prostate cancer (X^2 Calculated (IMP) = 14,4445 < X^2 Critical (IMP) = 33,9244; degrees of freedom: 22; sample size n = 2260). HPV is a sufficient condition of PC.

Quod erat demonstrandum.

Theorem 4. Human papilloma virus is a cause of prostate cancer

Claims.

Null hypothesis:

HPV is not a cause of prostate cancer. In other words, $k = 0$.

Alternative Hypothesis:

HPV is a cause of prostate cancer. In other words, $k > 0$.

The significance level (Alpha) below which the null hypothesis will be rejected is $\alpha = 0.05$.

Proof.

The data which investigated the causal relationship between HPV and prostate cancer are viewed by the table (Table 3). Altogether, if was necessary to reject the null-hypothesis and to accept the alternative hypothesis: HPV is a cause of prostate cancer (X^2 Calculated (k) = 150.37 > X^2 Critical (k) = 22.36; degrees of freedom: 13; sample size n = 1369).

Quod erat demonstrandum.

Theorem 5. Human papilloma virus is the cause of prostate cancer

Claims.

Null hypothesis:

HPV is not the cause of prostate cancer. In other words, $k = 0$.

Alternative Hypothesis:

HPV is the cause of prostate cancer. In other words, $k > 0$.

The significance level (Alpha) below which the null hypothesis will be rejected is $\alpha = 0.05$.

Proof.

The study group of Whitaker et al.³⁸ investigated the relationship between HPV and prostate cancer and provided data view by Table 11. The statistical analysis is illustrated by Table 12. The Fisher exact test statistic value is 0.0198 for conditio sine qua non relationship and for the conditio per quam relationship. The critical value of the conditio sine qua non relationship calculated according to the rule of three⁶³ is $p_{critical}(SINE) = 1 - (3/20) = 0,85$. Based on the data of Whitaker et al.³⁸ *without* HPV *no* PC and equally *if* HPV *then* PC. The conclusion is inescapable: HPV is the cause of PC.

Quod erat demonstrandum.

Table 11. HPV is the cause of PC

The study of Whitaker et al. ³⁸		PC		Total
		Yes = +1	No = +0	
HPV	Yes =+1	7	1	8
	No = +0	3	9	12
	Total	10	10	20

Table 12. The study of Whitaker et al.³⁸

Statistical Analysis.	p(IOU) = 0,100	p(IOI) = 0,100
Causal relationship k = +0,612	95 % CI (k): (0,112 -1,112)	
P value (k HGD) = 0,010	Chi sq. (k) = 7,500	
Odds ratio (OR) = 21,000	95 % CI (k): (1,777 -248,11)	
p (SINE) = 0,850	Chi sq. 1 (SINE) = 0,900	Chi sq. 2 (SINE) = 0,750
p (IMP) = 0,950	Chi sq. 1 (IMP) = 0,100	Chi sq. 2 (IMP) = 0,125
p (SINE ^ IMP) = 0,800	Chi sq. 1 (SINE ^ IMP) = 1,000	Chi sq. 2 (SINE ^ IMP) = 0,875
p (EXCL) = 0,650	Chi sq. 1 (EXCL) = 4,900	Chi sq. 2 (EXCL) = 6,125

4. DISCUSSION

Besides of the multiple advantages of the highly valuable and very sensitive polymerase chain reaction⁶⁴ (PCR) technique, PCR does have severe limitations⁶⁵ too. A key factor is the skill of the personnel involved in performing and interpreting the investigations.

Studies analyzed the impact of *marital status* (single, married, divorced/separated, and widowed) on PC with contradictory results. The Iranian study of Ghasemian et al. provided data which support the hypothesis that being married is a necessary condition to become HPV positive. In other words, **without being married no HPV positivity** ($p_{\text{Sine}}(\text{Married} \leftarrow \text{HPV positive}) = 0,995$; Chi sq. 1 (SINE) = 0,08; Chi sq. 2 (SINE) = 0,06; $p(\text{IOU}) = 0,02$, $k > 0$). The study design is extremely fair ($p(\text{IOU}) = 0,02$) while the causal relationship is positive but not significant. The study of Dillner et al. and of Ghasemian et al. provided data on the relationship between the marital status and prostate cancer. Both studies support the hypothesis, **without being married no PC**. The study design of Dillner et al. with $p(\text{IOU}) = 0,28$ was a very unfair ($p_{\text{Sine}}(\text{Married} \leftarrow \text{PC}) = 0,978$; Chi sq.1 (SINE) = 0,61; Chi sq. 2 (SINE) = 2,56; $k > 0$). The study design of Ghasemian et al. with $p(\text{IOU}) = 0,06$ was a little bit unfair ($p_{\text{Sine}}(\text{Married} \leftarrow \text{PC}) = 0,989$; Chi sq. 1 (SINE) = 0,14; Chi sq. 2 (SINE) = 0,24).

The studies analyzed provided a very convincing evidence of a cause effect relationship between HPV and PC (X^2 Calculated (k) = 150.37 > X^2 Critical (k) = 22.36; degrees of freedom: 13; sample size $n = 1369$). Whitaker et al.³⁸ provided data which support the hypothesis that HPV is the cause of PC (P value 0.0198).

5. CONCLUSION

HPV is the cause of PC.

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Conflict of interest statement

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