REVIEW ARTICLE

Human papillomavirus – The cause of prostate cancer

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ABSTRACT

BACKGROUND: Several observational studies investigated the relationship between human papillomavirus (HPV) infection and the risk of prostate cancer (PC) and have suggested conflicting results about this relationship. However, the relationship between HPV infection and PC remains unclear. The aim of the present meta-analysis study is to investigate whether HPV serves as a cause of PC.
METHODS: The PubMed database was searched for suitable articles. Previously published expert review and systematic review were used as an additional source to identify appropriate articles. Articles selected for this meta-analysis should fulfil the following inclusion criteria: (a) no data access barrier (b) PCR DNA based identification of HPV.
RESULTS: The studies analysed were able provide evidence that without being married no (HPV infection of a men/prostate cancer).The X^2 value of the total 20 articles indicated a significant causal relationship between HPV and PC. In other words, if HPV infection of human prostate, then prostate cancer.
CONCLUSION: In conclusion, HPV is the cause of prostate cancer.

KEYWORDS: Human papillomavirus, prostate cancer, causal relationship, causality

INTRODUCTION

Despite great research efforts, the aetiology of prostate cancer is still not known in detail. To date, some risk factors (1) for prostate cancer (PC) are established and limited to certain 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 while evidence is conflicting (2). Prostate cancer is one of the major causes of disease and mortality among men and a growing concern in global public health. Each year more than 1.6 million cases are diagnosed annually, and the mortality burden has risen to over 360,000 deaths per year (3). Human papillomavirus (HPV) infection is estimated to be one of the most common sexually transmitted infections. In heterosexually active couples, up to a total of 72.9% of their male partners are HPV positive (4). A discovery of an infectious agent as the cause or a cause of prostate cancer would be of great medical importance. Dillner et al. (5) found that (154/164) of al prostate cancer cases or 93,9 % have ever been married at enrolment of the study. Badar et al. (6) reported no evidence of human prostate cancer in very young and sexually inactive male children. These data provide some biological support for HPV transmission between sex partners as the route to prostate cancer. Still, most HPV infections are asymptomatic or subclinical and become undetectable over time while more than 100 types of human papillomaviruses (HPVs) have been identified. About ~40 types infect the anogenital region and have been further classified into low-risk types (e.g., 6 and 11) and high-risk types (e.g., 16, 18, 31, and 45). Several expert review published investigated whether HPV infection is a risk factor for PC but opposing reports were stated. Lin et al. (7) published a systematic review paper in 2011 concluded that statistical significance was observed when analysis was limited to HPV DNA 16 infection with respect to PC. However, Hrbacek et al. (8) concluded, however, that there was no evidence to support a relationship between HPV and PC.

Bae (9) investigated whether HPV type 16 infection is a risk factor for PC and published that the data provide evidence of a causal role of HPV-16 infection in prostate carcinogenesis. Yang et al. (10) concluded that HPV infections may contribute to the risk of prostate cancer (11). However, the relationship between human papillomavirus (HPV) infection and prostate cancer (PC) carcinogenesis remains conflicting and has not yet been firmly established. The causal role of HPV infections in prostate cancer is a subject of great controversy.

METHODS AND MATERIALS

Search strategy:
A systematic review of the literature that was published in PUBMED database have carried out. The search terms included "human papillomavirus" and "prostate cancer" and "PCR" and "case control study" et cetera. Additionally, (review) articles were considered as a potential source. Studies witch provided inappropriate data information or studies with data access barriers were excluded from the review. At the end 20 PCR based studies with a sample size of N= 2128 were review. The data are view by a table (Table 1).

Data analysis: The raw data collected from different studies were re-analysed using the software program Microsoft Excel. Significance testing between some factors and PC was conducted using the conditio sine qua non relationship, the conditio per quam relationship and the mathematical formula of the causal relationship k. The results are viewed by the **Table 1** and Table 2.

RESULTS

Without being married no HPV infection: Dillner et al. (5) investigated the relationship between several risk factor and concluded that neither *smoking* (X^2 (SINE) = 6,76978022, k = -0,04812363, p value (k) = 0,30465026) see (**Table 2**) nor *Chlamydia pneumoniae* (X^2 (SINE) = 0,5280219, k = 0,0241275, p value (k) = 0,6067913) infection (**Table 2**), nor *Chlamydia psittaci* (X^2 (IMP) = 0,0929, k = 0,0003, X^2(k) =0, p-val (k) = 0,9944) infection (**Table 2**), nor *Chlamydia trachomatis* (X^2 (IMP) = 2,0445, k=0,0034, X^2(k) = 0,0053, p-val (k) = 0,9421) infection (**Table 2**) nor being ever *married* at enrolment (**Table 2**) is associated with increased risk for prostate cancer. In particular, Dillner et al. (5) investigated the relationship between being ever *married* at enrolment (**Table 2**) and the risk for *prostate cancer*. In contrast to the lines before, in about 442/452 of the sample (97,8 %) Dillner et al. (5) evaluated that *without* ever being married at enrolment *no* prostate cancer (X^2 (Sine) = 0,199668142, p val (k) =0,148169487, **Table 2**). More or less, being married is a necessary condition of prostate cancer. The task of addressing the relationship between sexual behaviour and prostate cancer is heavily influenced by the study of Ghasemian et al. (17). Ghasemian et al. (17) agree with Dillner et al. (5) and found that in 195/196 of the sample (99,5 %), *without* being married *no* HPV positivity of a male (X^2 (SINE) = 0,00127551, k = 0,467818832, p value (k) = 5,77441E-11), a highly significant result. In other words, according to Ghasemian et al. (17), in Iran as a male it is necessary to be married to become HPV positive. In short, according to Ghasemian et al. (17), *without* being married *no* HPV infection of a men.

If HPV DNA then prostate cancer: The studies of Aydin et al. (12), Michopoulou et al. (16), Aghakhani et al. (19), Chen et al. (20), Silvestre et al. (22), Terris et al. (27), Wideroff et al. (28), Moyret-Lalle et al. (29) *failed* to provide evidence of the absence of independence (**Table 2**) between human papilloma virus PCR DNA and prostate cancer. Still, combining the results of independent PCR DNA based studies is possible while using *the additive property of the chi square distribution*. Altogether, the 20 studies reviewed provide highly significant evidence (N = 2128, $X^2_{critical}$ (IMP) = 31.4104, $X^2_{calculated}$ (IMP) = 2.98858, X^2(k) = 112.006, p val (k) = 8,4E-15) of a cause effect relationship between HPV and PC. In the same context, it is $X^2_{critical}$ (IMP) = 31.4104 and greater then $X^2_{calculated}$ (IMP) = 2.98858 with the consequence that we do accept the Null-hypothesis too, *If* HPV DNA *then* PC (32)-(44).

DISCUSSION

Human prostate cancer in sexually inactive male children has not (6) been reported. In contrast to young male children, HPV infection is reported to be highly prevalent in sexually active men. HPV prevalence in men in which multiple anatomic sites or specimens were evaluated varied on the basis of study populations or sampling, geographic location, processing methods, and the anatomic site(s) or specimen(s) sampled, age and racial/ethnic groups and were evaluated up to 72.9% (4). In line with Dillner et al. (5) the study group of Ghasemian et al. (17) provided evidence that *without* being married *no* HPV positivity of a men.

The studies considered for a review which investigated the presence of human papillomavirus (HPV) in prostatic tissue have yielded very different detection rates. This discrepancy can be explained by different factors: (a) inappropriate laboratory conditions, (b) contamination by viral DNA, (c) less than optimal oligonucleotide primers utilized for amplification, (d) the search for different and inappropriate segments of the viral HPV genome, (e) paraffin-embedded archival samples often lead to variable and unsatisfactory results, (f) HPV DNA/tumor cells isolation and detection techniques with unique limitations, (g) and many other factors too. The unique limitations and pitfalls of the techniques and tissue-based methods (polymerase chain reaction, immunohistochemistry, and in situ hybridization) used to isolate and characterize HPV or tumor cells is a subtle, but not negligibles source of bias.

Besides of the limitations as associated with the HPV detection methods, the studies analysed were able to provide striking evidence of a highly significant causal relationship between HPV and PC (X^2 (Critical k)= 31.4104, X^2 (Calculated k)= 112.006, p value (k)= 8.4E-15 (Table 1)). In the same context, according to the data of the study group of Ghasemian et al. (17), HPV is a necessary condition (Table 3),

Table 3: The Study of Ghasemian et al. (17)

		Prostate cancer <B>		
		Yes	No	Total
HPV (D N A) <A>	Yes	5	8	13
	No	24	159	183
Total		29	167	196

WITHOUT <A> NO <B>.

p (SINE) = 0.87755102

X^2(SINE) = 2.81760204

k = 0.17764904

p val (k) = 0.01287941

a sufficient condition (**Table 4**)

Table 4: The study of Ghasemian et al. (17)

		Prostate cancer <B>		
		Yes	No	Total
HPV (D N A) <A>	Yes	5	8	13
	No	24	159	183
Total		29	167	196

IF <A> THEN <B>.

p (IMP) = 0.9592

X^2(IMP) = 0.287

k = 0.1776

p val (k) = 0.0129

and necessary and sufficient condition (**Table 5**) of human PC.

Table 5: The study of Ghasemian et al. (17)

		Prostate cancer <B>		
		Yes	No	Total
HPV (DNA) <A>	Yes	5	8	13
	No	24	159	183
	Total	29	167	196

<A> is necces. and suff. for <B>.

p (SINE ^ IMP) = 0.83673469

X^2(SINE ^ IMP) = 3.10459184

k = 0.17764904

p val (k) = 0.01287941

Notably, the evidence is growing and the pathogenetic link between HPV and PC is convincing, the conclusion is inescapable. Human prostate cancer is a sexually transmitted disease and an infection with an oncogenic HPV is the cause (**Table 5**) of prostate cancer. Counseling men to increase sexual abstinence or to practice or use safer sex methods among heterosexually active adolescents is to date of strategic importance in reducing risk of prostate cancer. On the long run, the development of an *n-valent HPV vaccine* is necessary and any barriers to HPV vaccination to men are scientifically not justified. In particular, human papillomavirus oncogenes represent an excellent target for cancer immunotherapy. There is an urgent need to develop something like a therapeutic (HPV DNA) vaccine against prostate cancer.

CONCLUSION

Human papillomavirus is the cause of human prostate cancer.

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Table 1: The data of the studies analysed.

No.	Study Id	Year	Country	N	a_t	b_t	c_t	d_t	p(IMP)	X^2(IMP)	k	X^2(k)	p-val (k)
1	Aydin et al. (12)	2017	Turkey	96	1	0	59	36	1,0000	0,0026	0,0795	0,6063	0,4362
2	Atashafrooz et al. (13)	2016	Iran	200	20	8	80	92	0,9600	0,2813	0,1729	5,9801	0,0145
3	Huan et al. (14)	2016	China	148	17	0	58	73	1,0000	0,0017	0,3554	18,693	0,0000
4	Singh et al. (15)	2015	India	150	30	3	65	52	0,9800	0,0417	0,3039	13,853	0,0002
5	Michopoulou et al. (16)	2014	Greece	80	8	1	42	29	0,9875	0,0031	0,1941	3,0130	0,0826
6	Ghasemian et al. (17)	2013	Iran	196	5	8	24	159	0,9592	0,2870	0,1776	6,1856	0,0129
7	Mokhtari et al. (18)	2013	Iran	120	3	1	27	89	0,9917	0,0021	0,2144	5,5172	0,0188
8	Aghakhani et al. (19)	2011	Iran	208	13	8	91	96	0,9615	0,2704	0,0798	1,3242	0,2498
9	Chen et al. (20)	2011	Australia	62	7	3	44	8	0,9516	0,1008	-0,1407	1,2276	0,2679
10	Martinez-Fierro et al. (21)	2010	Mexico	130	11	4	44	71	0,9692	0,0942	0,2268	6,6871	0,0097
11	Silvestre et al. (22)	2009	Brazil	71	2	0	63	6	1,0000	0,0035	0,0517	0,1900	0,6629
12	Leiros et al. (23)	2005	Argentina	71	17	0	24	30	1,0000	0,0035	0,4800	16,35	0,0001
13	Carozzi et al. (24)	2004	Italy	51	14	5	12	20	0,9020	0,3971	0,3500	6,2460	0,0124
14	Kuczyk et al. (25)	2000	Germany	84	10	1	37	36	0,9881	0,0030	0,2733	6,2758	0,0122
15	Serth et al. (26)	1999	Germany	84	10	1	37	36	0,9881	0,0030	0,2733	6,2758	0,0122
16	Terris et al. (27)	1997	USA	90	10	5	43	32	0,9444	0,2250	0,0707	0,4498	0,5024
17	Wideroff et al. (28)	1996	USA	98	7	4	49	38	0,9592	0,1250	0,0467	0,2133	0,6442
18	Moyret-Lalle et al. (29)	1995	France	51	14	8	13	16	0,8431	1,1029	0,1866	1,7764	0,1826
19	Ibrahim et al. (30)	1992	USA	60	6	2	18	34	0,9667	0,0375	0,2802	4,7115	0,0300
20	Anwar et al. (31)	1992	Japan	78	28	0	40	10	1,0000	0,0032	0,2870	6,4235	0,0113
			Total	2128	233	62	870	963	0,9709	2,9886		112,006	

Alpha =	0,05000	Alpha =	0,05
Degrees of freedom (D. f.) =	20	D. f. =	20
X^2 (Critical IMP) =	31,4104	X^2 (Critical k)=	31,4104
X^2 (Calculatedl IMP)=	2,98858	X^2 (Calculated k)=	112,006
		p value (k)=	8,4E-15

Table 2: Risk factors and prostate cancer.

Study Id	Year	Risk factor / Condition	Country	N	a_t	b_t	c_t	d_t	p value	X^2	k	$X^2(k)$	p val (k)
Dillner et al. (5)	1998	Smoking	USA	455	109	205	56	85	0,87692	6,769780	0,04812363	1,053727	0,3046502
Dillner et al. (5)	1998	Chlamydia pneumoniae	USA	455	149	266	16	24	0,96483	0,528021	0,02412758	0,264873	0,6067913
Dillner et al. (5)	1998	Chlamydia trachomatis	USA	455	18	31	147	259	0,9319	2,0445	0,0034	0,0053	0,9421
Dillner et al. (5)	1998	Chlamydia psittaci	USA	455	4	7	161	283	0,9846	0,0929	0,0003	0	0,9944
Dillner et al. (5)	1998	Ever married at enrolment	USA	452	154	259	10	29	0,97787	0,199668	0,06801541	2,090995	0,1481694
Ghasemian et al. (17)	2013	Married	Iran	196	12	29	1	154	0,99489	0,001275	0,46781883	42,89547	5,77E-11