Title :

Human papillomavirus - A cause of human prostate cancer.

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Running title:

Human papillomavirus and postate cancer.

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Received: 26.11.2017; Accepted: 26.11.2017; Published: 26.11.2017;

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Abstract

Objective: A series of different studies detected Human papillomavirus (HPV) in malignant and nonmalignant prostate tissues. However, the results of studies on the relationship between HPV infections and prostate cancer (PCa) remain controversial.

Methods: A systematic review and re-analysis of some polymerase-chain reaction (PCR) based case-control studies was performed aimed to answer the following question: Is there a cause effect relationship between human papillomavirus (HPV) and prostatic cancer? The method of *the conditio per quam relationship* was used to proof the hypothesis: *if* presence of human papillomavirus (HPV) in human prostate tissues *then* presence of prostate carcinoma. The mathematical formula of *the causal relationship k* was used to proof the hypothesis, whether there is a cause effect relationship between human papillomavirus (HPV) and prostate cancer. Significance was indicated by a p-value of less than 0.05.

Result: Only one of the studies analyzed failed to provide evidence that there is a cause-effect relationship between human papillomavirus (HPV) and prostate cancer. Two studies were highly significant on this point. The majority of the studies analyzed support the hypothesis that human papillomavirus (HPV) is a sufficient condition of prostate cancer. In other words, *if* presence of human papillomavirus (HPV) in human prostate tissues *then* presence of prostate cancer.

Conclusion: Human papillomavirus (HPV) is a cause of prostate cancer.

Keywords: Human papillomavirus, prostate cancer, cause effect relationship, causality

Introduction

Prostate cancer (PCa), characterized by an abnormal proliferation of epithelial cell of the prostate gland, is a major public health problem worldwide. More than 1 million cases worldwide were diagnosed with PCa while about 300,000 males succumb annually to this disease (Ferlay et al., 2015). Prostate cancer in men age 50 years or younger is diagnosed for approximately 1% (Smith et al., 2000; Thorstenson et al., 2017). Several, different risk factors such as family history, advanced age, testosterone, ethnicity, diet and environmental exposure and Human Papillomavirus (HPV) infection are considered as risk factors of PCa (Brody, 2015; Hoffman, 2011). HPV itself is one of the most commonly diagnosed sexually transmitted infections worldwide (Colón-López et al., 2015). The prevalence of HPV infection for men is approximately 20-70% (Lupi et al., 2014; Orlando et al., 2014). Meanwhile more than 139 HPV genotypes have been recognized and sequenced (Tommasino, 2014). HPV has been established as the main etiological factor in *cervical* cancer (de Villiers et al., 1987). Many studies suggested even a relationship between human papillomavirus (HPV) infection and the risk of prostate cancer (PCa). McNicol et al. detected HPV DNA in prostatic tissue using PCR analysis for the first time in 1990 (McNicol et al., 1990). A growing number of studies (Lin et al., 2011) investigated the relationship between prostate cancer (PCa) and HPV infection. In point of fact, the relationship between HPV infection and prostate cancer (PCa) remains unclear (Bae 2015) and a cause effect relationship between human papillomavirus (HPV) infection and prostate cancer (PCa) has not (Hrbacek et al., 2013) yet been firmly established (Yang et al., 2015). The present study performed a meta/re/analysis of some outstanding studies to re-investigate the relationship between HPV infection and prostate cancer (PCa). Thereby, the purpose of the present study was to investigate whether there is a cause effect relationship between HPV infection and prostate cancer PCa by performing a meta/re-analysis of some outstanding case-control PCR based studies.

Materials and methods

Search strategy

For the questions addressed in this paper, was searched Pubmed for case-control studies conducted in any country and published in English which were tested at least by polymerase chain reaction (PCR).

Statistical analysis

All statistical analyses were performed with Microsoft Excel version 14.0.7166.5000 (32-Bit) software (Microsoft GmbH, Munich, Germany).

Conditio per quam

The formula of the *conditio per quam* (Barukčić, 1998; Barukčić, 1997; Barukčić, 2005; Barukčić, 2006a; Barukčić, 2006b; Barukčić, 2011a; 2011b; Barukčić, 2012; Barukčić, 2016a; Barukčić et al., 2016b; Barukčić, 2016c; Barukčić, 2017a; Barukčić, 2017b; Barukčić, 2017c) relationship

$$\mathrm{p}\left(\text{Human papillomavirus} \rightarrow \text{Human prostate carcinoma}\right)$$

was used to proof the hypothesis: if human papillomavirus infection is present then human prostate cancer is present too.

Scholium.

Historically, the notion *sufficient* condition is known since thousands of years. Many authors testified original contributions of the notion material implication only for *Diodorus Cronus*. Still, Philo the Logician (~ 300 BC), a member of a group of early Hellenistic philosophers (the Dialectical school), is the main forerunner of the notion material implication and has made some groundbreaking contributions (Astorga 2015) to the basics of this relationship. As it turns out, it is very hard to think of the "conditio per quam" relationship without considering the historical background of this concept. Remarkable as it is, Philo's concept of the material implications came very close (Bochenski 1961) to that of modern concept material implication. In propositional logic, a conditional is generally symbolized as "$p \rightarrow q$" or in spoken language "**if** p **then** q". Both q and p are statements, with q the

consequent and p the antecedent. Many times, the logical relation between the consequent and the antecedent is called a material implication. In general, a conditional "if p then q" is false only if p is true and q is false otherwise, in the three other possible combinations, the conditional is always true. In other words, to say that p is a sufficient condition for q is to say that the presence of p guarantees the presence of q. In other words, it is impossible to have p without q. If p is present, then q must also be present. To show that p is not sufficient for q, we come up with cases where p is present but q is not. It is well-known that the notion of a necessary condition can be used in defining what a sufficient condition is (and vice versa). In general, p is a necessary condition for q if it is impossible to have q without p. In fact, the absence of p guarantees the absence of q.

A *necessary condition* is sometimes also called "an essential condition" or a conditio sine qua non. In propositional logic, a necessary condition is generally symbolized as "$p \leftarrow q$" or in spoken language "**without** p **no** q". Both q and p are statements, with p the antecedent and q the consequent. To show that p is not a necessary condition for q, it is necessary to find an event or circumstances where q is present (i. e. an illness) but p (i. e. a risk factor) is not. Especially, necessary and sufficient conditions are converses of each other. Thus far, there is a straightforward way to give a precise and comprehensive account of the meaning of the term necessary (or sufficient) condition itself. On any view, logic has as one of its goals to characterize the most basic, the most simple and the most general laws of objective reality. Especially, in logic, these notions are defined and meanwhile transferred into Biostatistics (Barukčić, 1998; Barukčić, 1997; Barukčić, 2005; Barukčić, 2006a; Barukčić, 2006b; Barukčić, 2011a; 2011b; Barukčić, 2012; Barukčić, 2016a; Barukčić et al., 2016b; Barukčić, 2016c; Barukčić, 2017a; Barukčić, 2017b; Barukčić, 2017c) too.

What, then, is a sufficient or a necessary condition from the standpoint of (Bio) statistics? (Bio) statistics generalizes the notions of a sufficient or a necessary condition from one single Bernoulli trial to N Bernoulli trials (Barukčić, 1998; Barukčić, 1997; Barukčić, 2005; Barukčić, 2006a; Barukčić, 2006b; Barukčić, 2011a; 2011b; Barukčić, 2012; Barukčić, 2016a; Barukčić et al., 2016b; Barukčić, 2016c; Barukčić, 2017a; Barukčić, 2017b; Barukčić, 2017c).

Rule of three

Many times, for some reason or other it is not possible to study exhaustively a whole population. Still, sometimes it is possible to draw a sample from such a population which itself can be studied in detail and used to convince us about the properties of the population. Roughly speaking, statistical inference derived from a randomly selected subset of a population (a sample) can lead to erroneous results. The question raised is how to deal with the uncertainty inherent in such results? The concept of confidence intervals, closely related to statistical significance testing, was formulated to provide an answer to this problem.

Confidence intervals, introduced to statistics by Jerzy Neyman in a paper published in 1937 (Neyman, 1937), specifies a range within a parameter, i. e. the population proportion π, with a certain probability, contain the desired parameter value. Most commonly, the 95% confidence interval is used. Interpreting a confidence interval involves a couple of important but subtle issues. In general, a 95% confidence interval for the value of a random number means that there is a 95% probability that the "true" value of the value of a random number is within the interval. Confidence intervals for proportions or a population mean of random variables which are not normally distributed in the population can be constructed while relying on the central limit theorem as long as the sample sizes and counts are big enough (i. e. a sample size of n=30 and more). A formula, justified by the central limit theorem, is

$$p_{Crit} = p_{Calc} \pm \left(z_{Alpha/2} \times \left(\sqrt[2]{\frac{1}{N} \times p_{Calc} \times (1 - p_{Calc})} \right) \right)$$

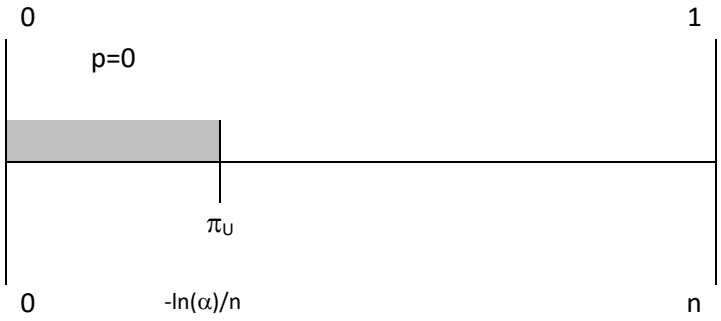
where p_{Calc} is the proportion of successes in a Bernoulli trial process with N trials yielding X successes and N-X failures and z is the 1 – (Alpha/2) quantile of a standard normal distribution corresponding to the significance level alpha. For example, for a 95% confidence level alpha = 0.05 and z is z = 1.96. A very common technique for calculating binomial confidence intervals was published by Clopper-Pearson (Clopper et al., 1934). Agresti-Coull proposed another different method (Agresti et al., 1998)

for calculating binomial *confidence intervals*. A faster and an alternative way to determine the lower and upper "exact" confidence interval is justified by the F distribution (Leemis et al., 1996). Furthermore, an approximate and conservative (one sided) confidence interval was developed by Louis (Louis 1981) and Jovanovic (Jovanovic et al., 1997) known as *the rule of three*. Briefly sketched, the rule of three can be derived from the binomial model. Let π_U denote the upper limit of the exact one-sided $100 \times (1 - \alpha)\%$ confidence interval for the unknown proportion π when in N independent trials *no events occur* (Jovanovic et al., 1997) . Then π_U is the value such that

$$\pi_U = \left(\frac{-\ln(\alpha)}{n} \right) \approx \left(\frac{3}{n} \right)$$

assuming that α=0,05. In other words, an one-sided approximate *upper* 95% confidence bound for the true binomial population proportion π, the rate of occurrences in the population, based on *a sample of size n* where *no successes* are observed is 3/n (Louis 1981) or given approximately by $[0 \leq \pi \leq (3/n)]$. The rule of three is a useful tool especially in the analysis of medical studies.

Table 1. The one-sided approximate upper $100 \times (1 - \alpha)\%$ confidence bound where **no successes** are observed



Under conditions where *a certain event did not occur* (Louis 1981) in a sample with *n subjects* (i. e. p=0) the interval from 0 to $(-\ln(\alpha)/n)$ is called a $100 \times (1 - \alpha)\%$ confidence interval for the binomial parameter for the rate of occurrences in the population.

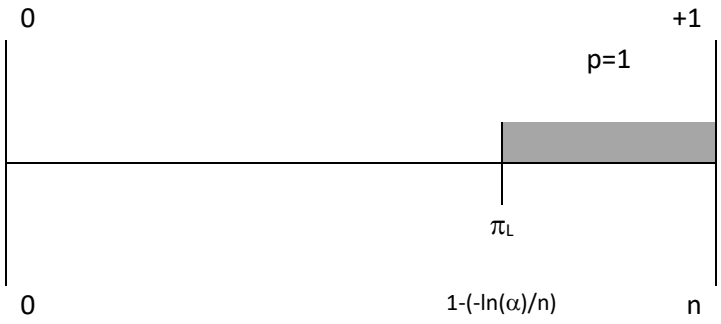
Another special case of the binomial distribution is based on *a sample of size n* where *only successes* are observed. Accordingly, the lower limit of a one-sided $100 \times (1 - \alpha)\%$ confidence interval for a

binomial probability π_L, the rate of occurrences in the population, based on *a sample of size n* where *only successes* are observed is given approximately by $[(1-(-\ln(\alpha)/n)) \leq \pi \leq +1]$ or as

$$\pi_L = 1-\left(\frac{-\ln(\alpha)}{n}\right) \approx 1-\left(\frac{3}{n}\right)$$

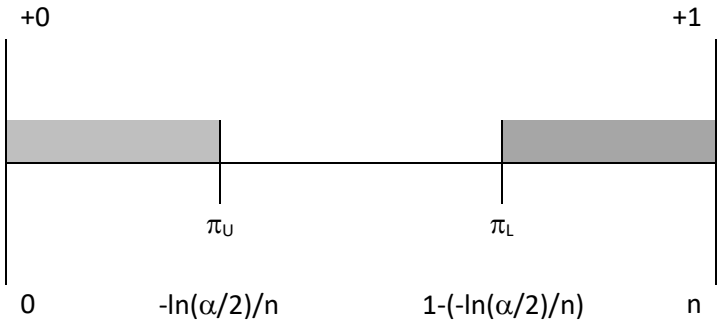
assuming that α=0,05.

Table 2. The one-sided approximate lower 100 × (1 - α)% confidence bound where **only successes** are observed



To construct a two-sided 100 × (1 - α)% interval according to the rule of three, it is necessary to take a one-sided 100 × (1 - α/2)% confidence interval.

Table 3. The two-sided approximate 100 × (1 - α)% confidence bound



The numerator value of 3.51 may be used for the 97% confidence interval, the numerator value of 4.61 may be used for the 99% confidence interval and the numerator value 5.3 may be used for 99.5% confidence interval.

Table 4. The relationship between α and $-\ln(\alpha)$.

α	$-\ln(\alpha)$
0,05	2,995732274
0,03	3,506557897
0,025	3,688879454
0,01	4,605170186
0,005	5,298317367
0,001	6,90775528

In this study, we will use the rule of three (Rumke 1975) to calculate the confidence interval for the value of a random number.

The mathematical formula of the causal relationship k

The mathematical formula of the causal relationship k (Barukčić, 1998; Barukčić, 1997; Barukčić, 2005; Barukčić, 2006a; Barukčić, 2006b; Barukčić, 2011a; 2011b; Barukčić, 2012; Barukčić, 2016a; Barukčić et al., 2016b; Barukčić, 2016c; Barukčić, 2017a; Barukčić, 2017b; Barukčić, 2017c) and the chi-square distribution (Pearson 1900) were applied to determine the significance of causal relationship k. A one-tailed test makes it much easier to reject a null hypothesis (no causal relationship) while a two-tailed test makes it more difficult to reject a null hypothesis and is more conservative on this account. For this reason, in causal relationship testing, a two-tailed test is preferred as much as possible. In general, a p value of < 0.05 is considered as significant.

Scholium.

What is the necessary connection between a cause and effect? What does ties the cause and its own effect together? In point of fact, it is neither justified nor necessary to reduce causation as such to an act of observation or measurement. Sill, case-control studies, experiments, observations et cetera can help us to recognize cause effect relationships. In this context it is necessary to stress out that **every single event (effect) has its own cause**, which is the logical foundation of the *mathematical formula of the causal relationship k.* It is therefore entirely clear that this is the fundamental difference to Pearson's methodological approach. Obviously, although under some certain specified circumstances Pearson's product-moment correlation coefficient (Pearson 1896) or Pearson's Phi (Pearson 1904) coefficient can yield the same numerical result as the *mathematical formula of the causal relationship k*, there is nothing truly exciting about such a coincidence. Nevertheless, when conducting experiments and analyzing data, views in which correlation and causation are brought very close together are incorrect and worthless. The *mathematical formula of the causal relationship k* (Barukčić, 1998; Barukčić, 1997; Barukčić, 2005; Barukčić, 2006a; Barukčić, 2006b; Barukčić, 2011a; 2011b; Barukčić, 2012; Barukčić, 2016a; Barukčić et al., 2016b; Barukčić, 2016c; Barukčić, 2017a; Barukčić, 2017b; Barukčić, 2017c) is neither identical nor can the same mathematical formula be reduced to

Pearson's product-moment correlation coefficient (Pearson 1896) or to Pearson's Phi (Pearson 1904) Coefficient (Mean Square Contingency Coefficient). In contrast to Pearson's product-moment correlation coefficient and to Pearson's Phi Coefficient (Mean Square Contingency Coefficient) the mathematical formula of **the causal relationship k is defined and valid at every single Bernoulli trial t** or at every single event.

Sir Austin Bradford Hill (1897 - 1991), an English epidemiologist, proposed 1965 some criteria (*Bradford Hill criteria*) for establishing a causal relationship between a presumed cause and an observed effect. The Mathematical Formula of the causal relationship k is not just a mathematization of *Bradford Hill criteria* (Hill, 1965).

The chi square distribution

The chi-squared distribution (Pearson, 1900) is a widely known distribution and used in hypothesis testing, in inferential statistics or in construction of confidence intervals. The critical values of the chi square distribution are visualized by a table.

Table 5. The critical values of the chi square distribution (degrees of freedom: 1).

	p-Value	One sided X^2	Two sided X^2
The chi square distribution	0,1000000000	1,642374415	2,705543454
	0,0500000000	**2,705543454**	**3,841458821**
	0,0400000000	3,06490172	4,217884588
	0,0300000000	3,537384596	4,709292247
	0,0200000000	4,217884588	5,411894431
	0,0100000000	5,411894431	6,634896601
	0,0010000000	9,549535706	10,82756617
	0,0001000000	13,83108362	15,13670523
	0,0000100000	18,18929348	19,51142096
	0,0000010000	22,59504266	23,92812698
	0,0000001000	27,03311129	28,37398736
	0,0000000100	31,49455797	32,84125335
	0,0000000010	35,97368894	37,32489311
	0,0000000001	40,46665791	41,82145620

Fisher's exact test

A test statistics of independent and more or less normally distributed data which follow a chi-squared distribution is valid as with many statistical tests due to the central limit theorem. Especially, with large samples, a chi-squared distribution can be used. A sample is considered as large when the sample size n is n = 30 or more. With a small sample (n < 30), the central limit theorem does not apply and erroneous results could potentially be obtained from the few observations if the same is applied. Thus far, when the number of observations obtained from a population is too small, a more appropriate test for of analysis of categorical data i. e. contingency tables is R. A. Fisher's exact test (Fisher, 1922). Fisher's exact test is valid for all sample sizes and calculates the significance of the p-value (i. e. the deviation from a null hypothesis) exactly even if in practice it is employed when sample size is small. Fisher's exact test is called exact because the same uses the exact hypergeometric distribution to compute the p-value rather than the approximate chi-square distribution. Still, computations involved in Fisher's exact test can be time consuming to calculate by hand. The formula for the hypergeometric distribution, a discrete probability distribution, is

$$p(a)=\frac{\binom{U}{a}\times\binom{N-U}{W-a}}{\binom{N}{W}}$$

where p(x) is the probability of x successes in n draws, without replacement, from a finite population of size N that contains exactly U successes. Barnard's exact test (Barnard, 1945; Barnard 1947) is another exact test which is useful for the analysis of contingency tables.

Table 6. The hypergeometric distribution and Human papillomavirus and prostate cancer.

		Prostate carcinoma		
		YES	NO	SUM
HPV DNA	YES	a		U
	NO			N-U
	SUM	W	N-W	N

Study design of Aydin et al. (Turkey)

Aydin et al. (Aydin et al., 2017) investigated the possible role of HPV in the development of prostate cancer (PCa) in 60 PCa tissues and in 36 benign prostatic hyperplasia tissues (control group). The real-time PCR used showed no HPV DNA in any of the 36 BPH tissue samples while HPV-DNA was positive in (1/60)=1.7 % of the 60 PCa samples. The following 2x2 table (Table 7) may illustrate the data as obtained by Aydin et al.

Table 7. Human papillomavirus and prostate cancer due to Aydin et al.

		Prostate carcinoma		
		YES	NO	SUM
HPV DNA	YES	1	0	1
	NO	59	36	95
	SUM	60	36	96

Study design of Atashafrooz *et al. (Iran)*

Atashafrooz et al. (Atashafrooz et al., 2016) designed study, to evaluate the frequency of HPV in 100 cases with prostatic cancer and in 100 cases with benign prostatic hyperplasia (BPH) in Kerman province, Iran. HPV DNA was detected by means of a polymerase chain-reaction assay in (20/100)=20.0% cases and in (8/100) = 8.0% of the control group. The following 2x2 table (Table 8) may illustrate the data as obtained by Atashafrooz et al.

Table 8. Human papillomavirus and prostate cancer due to Atashafrooz et al.

		Prostate cancer		
		YES	NO	SUM
HPV DNA	YES	20	8	28
	NO	40	92	172
	SUM	100	100	200

Study design of Huang et al. (China)

Huang et al. (Huang et al., 2016) conducted a HPV DNA based case-control study to examine the relationship between specific HPV types and prostate cancer. A total of 75 prostate cancer cases and 73 controls were examined. Huang et al. detected the HPV 16 -DNA in (17/75)*100 = 22,6% of the prostate cancer cases and none (0/73)*100 = 0% of the control subjects. The following 2x2 table (Table 9) may illustrate the data as obtained by Huang et al.

Table 9. Human papillomavirus and prostate carcinoma due to Huang et al.

		Prostate carcinoma		
		YES	NO	SUM
HPV 16 DNA	YES	17	**0**	17
	NO	58	73	131
	SUM	75	73	148

Study design of Singh et al. (India)

Singh et al. (Singh et al., 2015) investigated the HPV status in 95 prostate cancer cases and in 55 BPH controls from North Indian population. HPV 16 DNA (polymerase chain reaction) was found in 3/55= 5 % controls and in 30/95=32 % cases. The following 2x2 table (Table 10) may illustrate the data as obtained by Singh et al.

Table 10. Human papillomavirus and prostate carcinoma due to Singh et al.

		Prostate carcinoma		
		YES	NO	SUM
HPV 16 DNA	YES	30	**3**	33
	NO	65	52	117
	SUM	95	55	150

Study design of Michopoulou et al. (Greece)

Michopoulou et al., (Michopoulou et al., 2014) investigated the presence of HPV in 50 paraffin-embedded prostate cancer tissues, as well as in 30 healthy individuals by real-time PCR. HPV DNA was detected in (8/50)=16 % in the prostate cancer samples and in (1/30)=3.33 % of the 30 control samples.The following 2x2 table (Table 11) may illustrate the data as obtained by Michopoulou et al.

Table 11. Human papillomavirus and prostate cancer due to Michopoulou et al.

		Prostate cancer		
		YES	NO	SUM
HPV DNA	YES	8	**1**	9
	NO	42	29	71
	SUM	50	30	80

Study design of Leiros et al. (Argentina)

Leiros et al. (Leiros et al., 2005) performed a polymerase chain reaction based case-control study with 41 prostate carcinoma samples and 30 healthy controls (hyperplasia samples). HPV DNA was detected in 17/41= 41.5 % carcinoma samples, whereas all 30 controls were HPV-negative. The following 2x2 table (Table 12) may illustrate the data as obtained by Leiros et al.

Table 12. Human papillomavirus and prostate cancer due to Leiros et al.

		Prostate cancer		
		YES	NO	SUM
HPV DNA	YES	17	**0**	17
	NO	24	30	54
	SUM	41	30	71

Study design of Carozzi et al. (Italy)

Carozzi et al. (Italy) (Carozzi et al., 2004) conducted a polymerase chain reaction assay based, case-control study to investigate the relation between human papillomavirus (HPV) infection and prostate cancer. High-risk HPV type positivity was observed in 14/26=53.8% cancer and in 5/25=20.0% benign biopsies. The following 2x2 table (Table 13) may illustrate the data as obtained by Carozzi et al.

Table 13. Human papillomavirus and prostate cancer due Carozzi et al.

		Prostate carcinoma		
		YES	NO	SUM
HPV DNA	YES	14	**5**	19
	NO	12	20	32
	SUM	26	25	51

Study design of Serth et al. (Germany)

Serth et al. (Serth et al., 1999) examined a group of 47 prostate cancer and 37 healthy control tissues. HPV 16 DNA was detected in 10/47=21% of cases and in 1 / 37 = 3 % of controls. The following 2x2 table (Table 14) may illustrate the data as obtained by Serth et al.

Table 14. Human papillomavirus and prostate caancer due to Serth et al.

		Prostate carcinoma		
		YES	NO	SUM
HPV 16 DNA	YES	10	**1**	11
	NO	37	37	74
	SUM	47	37	85

Results

The study of Aydin et al.

Human papillomavirus is a sufficient condition (a conditio per quam) of human prostate cancer due to the study of Aydin et al. (2017)

Claims.

Null hypothesis (H_0):

If presence of human papillomavirus (HPV) in human prostate tissues **then** presence of human prostate cancer.

H_0: $p_{Calc} \geq \pi_L$

Alternative hypothesis (H_A)

If presence of human papillomavirus (HPV) in human prostate tissues **then** no presence of human prostate cancer.

H_A: $p_{Calc} < \pi_L$

Significance level (Alpha) below which the null hypothesis will be rejected: 0,05.

Proof.

The data as obtained by Aydin et al. (2017) about the relationship between human papillomavirus and prostate cancer in patients and healthy control subjects are viewed in the 2 × 2 table (Table 7). In general, the proportion of successes of *the conditio per quam relationship*, denoted by the term p_{Calc}(human papillomavirus $\rightarrow$ human prostate cancer) is calculated as (Barukčić, 1998; Barukčić, 1997; Barukčić, 2005; Barukčić, 2006a; Barukčić, 2006b; Barukčić, 2011a; 2011b; Barukčić, 2012; Barukčić, 2016a; Barukčić et al., 2016b; Barukčić, 2016c; Barukčić, 2017a; Barukčić, 2017b; Barukčić, 2017c)

$$p_{Calc}\left(\text{Human papillomavirus [HPV]} \rightarrow \text{prostate cancer [PCa]}\right) = \frac{(1+59+36)}{96} = \frac{96}{96} = 1,0$$

In other words, in about 100,0 % of the sample, HPV is a sufficient condition of PCa. The one sided lower 100*(1-α) % confidence bound (significance level alpha = 0.05) is calculated according to the rule of three approximately as

$$\pi_L = 1 - \frac{3}{96} = 0{,}96875$$

The one sided lower 100*(1-α) % confidence bound is π_L = 0,96875 and is thus far less than the proportion of successes of the sufficient condition, the conditio per quam relationship, calculated as p_{Calc}(human papillomavirus $\rightarrow$ human prostate cancer) = 1,0. The data as published by Aydin et al. (2017) do support our null hypothesis. Consequently, we accept the null hypothesis and reject the alternative hypothesis. In other words, **if** presence of human papillomavirus (HPV) in human prostate tissues **then** presence of human prostate cancer.

Human papillomavirus is a sufficient condition (a conditio per quam) of human prostate cancer.

Q. e. d.

No significant cause-effect relationship between human papillomavirus and human prostate cancer due to study of Aydin et al. (2017)

Claims.

Null hypothesis (H_0): (no causal relationship)

There is not a significant causal relationship between human papillomavirus and prostate cancer.

H_0: k = 0.

Alternative hypothesis (H_A): (causal relationship)

There is a significant causal relationship between human papillomavirus and prostate cancer.

H_A: $k \neq 0$.

Conditions.

Alpha level = 5%.

The two tailed critical Chi square value (degrees of freedom = 1) for alpha level 5% is 3.841458821.

Proof.

The data for this hypothesis test are obtained by Aydin et al. (2017) and illustrated in the 2 × 2 table (Table 7). The causal relationship k(human papillomavirus, human prostate cancer) is calculated as (Barukčić, 1998; Barukčić, 1997; Barukčić, 2005; Barukčić, 2006a; Barukčić, 2006b; Barukčić, 2011a; 2011b; Barukčić, 2012; Barukčić, 2016a; Barukčić et al., 2016b; Barukčić, 2016c; Barukčić, 2017a; Barukčić, 2017b; Barukčić, 2017c)

$$\mathrm{k}\left(\text{Human papillomavirus [HPV]}, \text{prostate cancer [PCa]}\right) = \frac{\left((96\times 1)-(1\times 60)\right)}{\sqrt[2]{(1\times 95)\times(60\times 36)}} = +0{,}079471941$$

The value of the test statistic k = +0,079471941 is equivalent to a calculated chi-square value of

$$\chi^2_{\text{Calculated}} = 96\times\left(\frac{\left((96\times 1)-(1\times 60)\right)}{\sqrt[2]{(1\times 95)\times(60\times 36)}}\right)\times\left(\frac{\left((96\times 1)-(1\times 60)\right)}{\sqrt[2]{(1\times 95)\times(60\times 36)}}\right)$$

$$\chi^2_{\text{Calculated}} = 96\times(0{,}079471941)\times(0{,}079471941)$$

$$\chi^2_{\text{Calculated}} = 0{,}606315789$$

The calculated chi-square statistic, uncorrected for continuity, is 0,606315789 and equivalent to a p value of 0,4361783623. The calculated chi-square statistic does not exceed the critical chi-square value of 3.841458821 (Table 5). Consequently, we accept the null hypothesis and reject the alternative hypothesis. According to the data as obtained by Aydin et al. (2017) there is not a significant causal relationship between human papillomavirus and human prostate cancer (k=+0,079471941, p value=0,4361783623).

Q. e. d.

The study of Atashafrooz et al.

Human papillomavirus is a sufficient condition (a conditio per quam) of human prostate cancer due to the study of Atashafrooz et al. (2016)

Claims.

Null hypothesis (H_0):

If presence of human papillomavirus (HPV) in human prostate tissues **then** presence of human prostate cancer.

H_0: $p_{Calc} \geq \pi_L$

Alternative hypothesis (H_A)

If presence of human papillomavirus (HPV) in human prostate tissues **then** no presence of human prostate cancer.

H_A: $p_{Calc} < \pi_L$

Significance level (Alpha) below which the null hypothesis will be rejected: 0,05.

Proof.

The data as obtained by Atashafrooz et al. (2016) about the relationship between human papillomavirus and prostate cancer in patients and healthy control subjects are viewed in the 2 × 2 table (Table 8). In general, the proportion of successes of *the conditio per quam relationship*, denoted by the term p_{Calc}(human papillomavirus $\rightarrow$ human prostate cancer) is calculated as (Barukčić, 1998; Barukčić, 1997; Barukčić, 2005; Barukčić, 2006a; Barukčić, 2006b; Barukčić, 2011a; 2011b; Barukčić, 2012; Barukčić, 2016a; Barukčić et al., 2016b; Barukčić, 2016c; Barukčić, 2017a; Barukčić, 2017b; Barukčić, 2017c)

$$p_{Calc}\left(\text{Human papillomavirus [HPV]} \rightarrow \text{prostate cancer [PCa]}\right) = \frac{\left(20+40+92\right)}{200} = \frac{192}{200} = 0{,}96$$

In other words, in about 96,0 % of the sample, HPV is a sufficient condition of PCa. The one sided lower 100*(1-α) % confidence bound (significance level alpha = 0.05) is calculated according to the rule of three approximately as

$$\pi_L = 1 - \frac{3}{200} = 0{,}985$$

The one sided lower 100*(1-α) % confidence bound is π_L = 0,985 and is thus far not less than the proportion of successes of the sufficient condition, the conditio per quam relationship, calculated as p_{Calc}(human papillomavirus $\rightarrow$ human prostate cancer) = 0,96. The data as published by Atashafrooz et al. (2016) do not support our null hypothesis. Consequently, we reject the null hypothesis and accept the alternative hypothesis. In other words, **if** presence of human papillomavirus (HPV) in human prostate tissues **then** no presence of human prostate cancer.

Human papillomavirus <u>is not</u> a sufficient condition (a conditio per quam) of human prostate cancer.

Q. e. d.

Significant cause-effect relationship between human papillomavirus and human prostate cancer due to study of Atashafrooz et al.

Claims.

Null hypothesis (H_0): (no causal relationship)

There is not a significant causal relationship between human papillomavirus and prostate cancer.

H_0: k = 0.

Alternative hypothesis (H_A): (causal relationship)

There is a significant causal relationship between human papillomavirus and prostate cancer.

H_A: $k \neq 0$.

Conditions.

Alpha level = 5%.

The two tailed critical Chi square value (degrees of freedom = 1) for alpha level 5% is 3.841458821.

Proof.

The data for this hypothesis test are obtained by Atashafrooz et al. (2016) and illustrated in the 2 × 2 table (Table 8). The causal relationship k(human papillomavirus, human prostate cancer) is calculated as (Barukčić, 1998; Barukčić, 1997; Barukčić, 2005; Barukčić, 2006a; Barukčić, 2006b; Barukčić, 2011a; 2011b; Barukčić, 2012; Barukčić, 2016a; Barukčić et al., 2016b; Barukčić, 2016c; Barukčić, 2017a; Barukčić, 2017b; Barukčić, 2017c)

$$\mathrm{k}\left(\text{Human papillomavirus [HPV]}, \text{prostate cancer [PCa]}\right) = \frac{\left((200\times 20)-(28\times 100)\right)}{\sqrt[2]{(28\times 172)\times(100\times 100)}} = +0{,}172917125$$

The value of the test statistic k = + 0,172917125 is equivalent to a calculated chi-square value of

$$\chi^2_{\text{Calculated}} = 200\times\left(\frac{\left((200\times 20)-(28\times 100)\right)}{\sqrt[2]{(28\times 172)\times(100\times 100)}}\right)\times\left(\frac{\left((200\times 20)-(28\times 100)\right)}{\sqrt[2]{(28\times 172)\times(100\times 100)}}\right)$$

$$\chi^2_{\text{Calculated}} = 200\times(0{,}172917125)\times(0{,}172917125)$$

$$\chi^2_{\text{Calculated}} = 5{,}980066445$$

The calculated chi-square statistic, uncorrected for continuity, is 5,980066445 and equivalent to a p value of 0,0144684571. The calculated chi-square statistic exceeds the critical chi-square value of 3.841458821 (Table 5). Consequently, we reject the null hypothesis and accept the alternative hypothesis. According to the data as obtained by Atashafrooz et al. (2016) there is a significant **causal relationship between human papillomavirus and human prostate cancer** (k=+0,172917125, p value= 0,0144684571).

Q. e. d.

The study of Huang et al.

Human papillomavirus type 16 is a sufficient condition (a conditio per quam) of human prostate cancer due to the study of Huang et al. (2016)

Claims.

Null hypothesis (H_0):

If presence of human papillomavirus (HPV type 16) in human prostate tissues **then** presence of human prostate cancer.

H_0: $p_{Calc} \geq \pi_L$

Alternative hypothesis (H_A)

If presence of human papillomavirus (HPV type 16) in human prostate tissues **then** no presence of human prostate cancer.

H_A: $p_{Calc} < \pi_L$

Significance level (Alpha) below which the null hypothesis will be rejected: 0,05.

Proof.

The data as obtained by Huang et al. (2016) about the relationship between human papillomavirus and prostate cancer in patients and healthy control subjects are viewed in the 2 × 2 table (Table 9). In general, the proportion of successes of *the conditio per quam relationship*, denoted by the term p_{Calc}(human papillomavirus $\rightarrow$ human prostate cancer) is calculated as (Barukčić, 1998; Barukčić, 1997; Barukčić, 2005; Barukčić, 2006a; Barukčić, 2006b; Barukčić, 2011a; 2011b; Barukčić, 2012; Barukčić, 2016a; Barukčić et al., 2016b; Barukčić, 2016c; Barukčić, 2017a; Barukčić, 2017b; Barukčić, 2017c)

$$p_{Calc}\left(\text{Human papillomavirus [HPV 16]} \rightarrow \text{prostate cancer [PCa]}\right) = \frac{(17+58+73)}{148} = \frac{148}{148} = +1,0$$

In other words, in about 100,0 % of the sample, HPV 16 is a sufficient condition of PCa. The one sided lower 100*(1-α) % confidence bound (significance level alpha = 0.05) is calculated according to the rule of three approximately as

$$\pi_L = 1 - \frac{3}{148} = +0{,}97972973$$

The one sided lower 100*(1-α) % confidence bound is π_L = 0,97972973 and is thus far less than the proportion of successes of the sufficient condition, the conditio per quam relationship, calculated as p_{Calc}(human papillomavirus $\rightarrow$ human prostate cancer) = 1,0. The data as published by Huang et al. (2016) do support our null hypothesis. Consequently, we accept the null hypothesis and reject the alternative hypothesis. In other words, **if** presence of human papillomavirus (HPV type 16) in human prostate tissues **then** presence of human prostate cancer.

Human papillomavirus type 16 is a sufficient condition (a conditio per quam) of human prostate cancer.

Q. e. d.

Highly significant cause-effect relationship between human papillomavirus type 16 and human prostate cancer due to study of Huang et al.

Claims.

Null hypothesis (H_0): (no causal relationship)

There is not a significant causal relationship between human papillomavirus type 16 and prostate cancer.

H_0: k = 0.

Alternative hypothesis (H_A): (causal relationship)

There is a significant causal relationship between human papillomavirus type 16 and prostate cancer.

H_A: $k \neq 0$.

Conditions.

Alpha level = 5%.

The two tailed critical Chi square value (degrees of freedom = 1) for alpha level 5% is 3.841458821.

Proof.

The data for this hypothesis test are obtained by Huang et al. (2016) and illustrated in the 2 × 2 table (Table 9). The causal relationship k(human papillomavirus 16, human prostate cancer) is calculated as (Barukčić, 1998; Barukčić, 1997; Barukčić, 2005; Barukčić, 2006a; Barukčić, 2006b; Barukčić, 2011a; 2011b; Barukčić, 2012; Barukčić, 2016a; Barukčić et al., 2016b; Barukčić, 2016c; Barukčić, 2017a; Barukčić, 2017b; Barukčić, 2017c)

$$\mathrm{k}\left(\text{Human papillomavirus [HPV 16]}, \text{prostate cancer [PCa]}\right) = \frac{\left((148\times 17)-(17\times 75)\right)}{\sqrt[2]{(17\times 131)\times(75\times 73)}} = +0{,}35540179$$

The value of the test statistic k = +0,35540179 is equivalent to a calculated chi-square value of

$$\chi^2_{\text{Calculated}} = 148\times\left(\frac{\left((148\times 17)-(17\times 75)\right)}{\sqrt[2]{(17\times 131)\times(75\times 73)}}\right)\times\left(\frac{\left((148\times 17)-(17\times 75)\right)}{\sqrt[2]{(17\times 131)\times(75\times 73)}}\right)$$

$$\chi^2_{\text{Calculated}} = 148\times(0{,}35540179)\times(0{,}35540179)$$

$$\chi^2_{\text{Calculated}} = 18{,}69394402$$

The calculated chi-square statistic, uncorrected for continuity, is 18,69394402 and equivalent to a p value of 0,0000153469. The calculated chi-square statistic exceeds the critical chi-square value of 3.841458821 (Table 5). Consequently, we reject the null hypothesis and accept the alternative hypothesis. According to the data as obtained by Huang et al. (2016) there is a **highly significant causal relationship between human papillomavirus type 16 and human prostate cancer** (k=+ 0,35540179, p value= 0,0000153469).

Q. e. d.

The study of Singh et al.

Human papillomavirus type 16 is a sufficient condition (a conditio per quam) of human prostate cancer due to the study of Singh et al. (2015)

Claims.

Null hypothesis (H_0):

If presence of human papillomavirus (HPV type 16) in human prostate tissues **then** presence of human prostate cancer.

H_0: $p_{Calc} \geq \pi_L$

Alternative hypothesis (H_A)

If presence of human papillomavirus (HPV type 16) in human prostate tissues **then** no presence of human prostate cancer.

H_A: $p_{Calc} < \pi_L$

Significance level (Alpha) below which the null hypothesis will be rejected: 0,05.

Proof.

The data as obtained by Singh et al. (2015) about the relationship between human papillomavirus and prostate cancer in patients and healthy control subjects are viewed in the 2 × 2 table (Table 10). In general, the proportion of successes of *the conditio per quam relationship*, denoted by the term p_{Calc}(human papillomavirus $\rightarrow$ human prostate cancer) is calculated as (Barukčić, 1998; Barukčić, 1997; Barukčić, 2005; Barukčić, 2006a; Barukčić, 2006b; Barukčić, 2011a; 2011b; Barukčić, 2012; Barukčić, 2016a; Barukčić et al., 2016b; Barukčić, 2016c; Barukčić, 2017a; Barukčić, 2017b; Barukčić, 2017c)

$$p_{Calc}\left(\text{Human papillomavirus [HPV 16]} \rightarrow \text{prostate cancer [PCa]}\right) = \frac{(30+65+52)}{150} = \frac{147}{150} = 0{,}98$$

In other words, in about 98,0 % of the sample, HPV type 16 is a sufficient condition of PCa. The one sided lower 100*(1-α) % confidence bound (significance level alpha = 0.05) is calculated according to the rule of three approximately as

$$\pi_L = 1 - \frac{3}{150} = +0{,}98$$

The one sided lower 100*(1-α) % confidence bound is π_L = 0,98 and is thus far less or equal than the proportion of successes of the sufficient condition, the conditio per quam relationship, calculated as p_{Calc}(human papillomavirus $\rightarrow$ human prostate cancer) = 0,98. The data as published by Singh et al. (2015) do support our null hypothesis. Consequently, we accept the null hypothesis and reject the alternative hypothesis. In other words, **if** presence of human papillomavirus (HPV type 16) in human prostate tissues **then** presence of human prostate cancer.

Human papillomavirus 16 is a sufficient condition (a conditio per quam) of human prostate cancer.

Q. e. d.

Highly significant cause-effect relationship between human papillomavirus type 16 and human prostate cancer due to study of Singh et al. (2015)

Claims.

Null hypothesis (H_0): (no causal relationship)

There is not a significant causal relationship between human papillomavirus type 16 and prostate cancer.

H_0: k = 0.

Alternative hypothesis (H_A): (causal relationship)

There is a significant causal relationship between human papillomavirus type 16 and prostate cancer.

H_A: $k \neq 0$.

Conditions.

Alpha level = 5%.

The two tailed critical Chi square value (degrees of freedom = 1) for alpha level 5% is 3.841458821.

Proof.

The data for this hypothesis test are obtained by Singh et al. (2015) and illustrated in the 2 × 2 table (Table 10). The causal relationship k(human papillomavirus, human prostate cancer) is calculated as (Barukčić, 1998; Barukčić, 1997; Barukčić, 2005; Barukčić, 2006a; Barukčić, 2006b; Barukčić, 2011a; 2011b; Barukčić, 2012; Barukčić, 2016a; Barukčić et al., 2016b; Barukčić, 2016c; Barukčić, 2017a; Barukčić, 2017b; Barukčić, 2017c)

$$\mathrm{k}\left(\text{Human papillomavirus [HPV 16]}, \text{prostate cancer [PCa]}\right) = \frac{\left((150\times 30)-(33\times 95)\right)}{\sqrt[2]{(33\times 117)\times(95\times 55)}} = +0{,}30390623$$

The value of the test statistic k = +0,30390623 is equivalent to a calculated chi-square value of

$$\chi^2_{\text{Calculated}} = 150\times\left(\frac{\left((150\times 30)-(33\times 95)\right)}{\sqrt[2]{(33\times 117)\times(95\times 55)}}\right)\times\left(\frac{\left((150\times 30)-(33\times 95)\right)}{\sqrt[2]{(33\times 117)\times(95\times 55)}}\right)$$

$$\chi^2_{\text{Calculated}} = 150\times(0{,}30390623)\times(0{,}30390623)$$

$$\chi^2_{\text{Calculated}} = 13{,}8538495$$

The calculated chi-square statistic, uncorrected for continuity, is 13,8538495 and equivalent to a p value of 0,0001975916. The calculated chi-square statistic exceeds the critical chi-square value of 3.841458821 (Table 5). Consequently, we reject the null hypothesis and accept the alternative hypothesis. According to the data as obtained by Singh et al. (2015) there is **a highly significant causal relationship between human papillomavirus type 16 and human prostate cancer** (k=+0,30390623, p value= 0,0001975916).

Q. e. d.

The study of Michopoulou et al. (2014)

Human papillomavirus is a sufficient condition (a conditio per quam) of human prostate cancer due to the study of Michopoulou et al. (2014)

Claims.

Null hypothesis (H_0):

If presence of human papillomavirus (HPV) in human prostate tissues **then** presence of human prostate cancer.

H_0: $p_{Calc} \geq \pi_L$

Alternative hypothesis (H_A)

If presence of human papillomavirus (HPV) in human prostate tissues **then** no presence of human prostate cancer.

H_A: $p_{Calc} < \pi_L$

Significance level (Alpha) below which the null hypothesis will be rejected: 0,05.

Proof.

The data as obtained by Michopoulou et al. (2014) about the relationship between human papillomavirus and prostate cancer in patients and healthy control subjects are viewed in the 2 × 2 table (Table 11). In general, the proportion of successes of *the conditio per quam relationship*, denoted by the term p_{Calc}(human papillomavirus $\rightarrow$ human prostate cancer) is calculated as (Barukčić, 1998; Barukčić, 1997; Barukčić, 2005; Barukčić, 2006a; Barukčić, 2006b; Barukčić, 2011a; 2011b; Barukčić, 2012; Barukčić, 2016a; Barukčić et al., 2016b; Barukčić, 2016c; Barukčić, 2017a; Barukčić, 2017b; Barukčić, 2017c)

$$p_{Calc}\left(\text{Human papillomavirus [HPV]} \rightarrow \text{prostate cancer [PCa]}\right) = \frac{\left(8+42+29\right)}{80} = \frac{79}{80} = +0{,}9875$$

In other words, in about 98,75 % of the sample, HPV is a sufficient condition of PCa. The one sided lower 100*(1-α) % confidence bound (significance level alpha = 0.05) is calculated according to the rule of three approximately as

$$\pi_L = 1 - \frac{3}{80} = +0{,}9625$$

The one sided lower 100*(1-α) % confidence bound is π_L = 0,9625 and is thus far less than the proportion of successes of the sufficient condition, the conditio per quam relationship, calculated as p_{Calc}(human papillomavirus $\rightarrow$ human prostate cancer) = 0,9875. The data as published by Michopoulou et al. (2014) do support our null hypothesis. Consequently, we accept the null hypothesis and reject the alternative hypothesis. In other words, **if** presence of human papillomavirus (HPV) in human prostate tissues **then** presence of human prostate cancer.

Human papillomavirus is a sufficient condition (a conditio per quam) of human prostate cancer.

Q. e. d.

No two sided significant cause-effect relationship between human papillomavirus and human prostate cancer due to study of Michopoulou et al. (2014)

Claims.

Null hypothesis (H_0): (no causal relationship)

There is not a significant causal relationship between human papillomavirus and prostate cancer.

H_0: k = 0.

Alternative hypothesis (H_A): (causal relationship)

There is a significant causal relationship between human papillomavirus and prostate cancer.

H_A: $k \neq 0$.

Conditions.

Alpha level = 5%.

The two tailed critical Chi square value (degrees of freedom = 1) for alpha level 5% is 3.841458821.

Proof.

The data for this hypothesis test are obtained by Michopoulou et al. (2014) and illustrated in the 2×2 table (Table 11). The causal relationship k(human papillomavirus, human prostate cancer) is calculated as (Barukčić, 1998; Barukčić, 1997; Barukčić, 2005; Barukčić, 2006a; Barukčić, 2006b; Barukčić, 2011a; 2011b; Barukčić, 2012; Barukčić, 2016a; Barukčić et al., 2016b; Barukčić, 2016c; Barukčić, 2017a; Barukčić, 2017b; Barukčić, 2017c)

$$\mathrm{k}\left(\text{Human papillomavirus [HPV], prostate cancer [PCa]}\right)=\frac{\left(\left(80\times 8\right)-\left(9\times 50\right)\right)}{\sqrt[2]{\left(9\times 71\right)\times\left(50\times 30\right)}}=+0{,}194069614$$

The value of the test statistic k = +0,194069614 is equivalent to a calculated chi-square value of

$$\chi^2_{\text{Calculated}}=80\times\left(\frac{\left(\left(80\times 8\right)-\left(9\times 50\right)\right)}{\sqrt[2]{\left(9\times 71\right)\times\left(50\times 30\right)}}\right)\times\left(\frac{\left(\left(80\times 8\right)-\left(9\times 50\right)\right)}{\sqrt[2]{\left(9\times 71\right)\times\left(50\times 30\right)}}\right)$$

$$\chi^2_{\text{Calculated}}=80\times\left(0{,}194069614\right)\times\left(0{,}194069614\right)$$

$$\chi^2_{\text{Calculated}}=3{,}01304121$$

The calculated chi-square statistic, uncorrected for continuity, is 3,01304121 and equivalent to a two-sided p value of 0,0825971880. The calculated chi-square statistic does not exceed the **two sided** critical chi-square value of 3.841458821 (Table 5). The **one sided** critical chi-square value is 2,705543454 (Table 5). Still, we reject the (**two sided**) null hypothesis and accept the alternative hypothesis. According to the data as obtained by Michopoulou et al. (2014) there is **no two sided significant causal relationship between human papillomavirus and human** (k=+ 0,194069614, p value = 0,0825971880).

Q. e. d.

The study of Leiros et al.

Human papillomavirus is a sufficient condition (a conditio per quam) of human prostate cancer due to the study of Leiros et al. (2005)

Claims.

Null hypothesis (H_0):

If presence of human papillomavirus (HPV) in human prostate tissues **then** presence of human prostate cancer.

H_0: $p_{Calc} \geq \pi_L$

Alternative hypothesis (H_A)

If presence of human papillomavirus (HPV) in human prostate tissues **then** no presence of human prostate cancer.

H_A: $p_{Calc} < \pi_L$

Significance level (Alpha) below which the null hypothesis will be rejected: 0,05.

Proof.

The data as obtained by Leiros et al. (2005) about the relationship between human papillomavirus and prostate cancer in patients and healthy control subjects are viewed in the 2 × 2 table (Table 12). In general, the proportion of successes of *the conditio per quam relationship*, denoted by the term p_{Calc}(human papillomavirus $\rightarrow$ human prostate cancer) is calculated as (Barukčić, 1998; Barukčić, 1997; Barukčić, 2005; Barukčić, 2006a; Barukčić, 2006b; Barukčić, 2011a; 2011b; Barukčić, 2012; Barukčić, 2016a; Barukčić et al., 2016b; Barukčić, 2016c; Barukčić, 2017a; Barukčić, 2017b; Barukčić, 2017c)

$$p_{Calc}\left(\text{Human papillomavirus [HPV]} \rightarrow \text{prostate cancer [PCa]}\right) = \frac{(17+24+30)}{71} = \frac{71}{71} = +1,0$$

In other words, in about 100,0 % of the sample, HPV is a sufficient condition of PCa. The one sided lower 100*(1-α) % confidence bound (significance level alpha = 0.05) is calculated according to the rule of three approximately as

$$\pi_L = 1 - \frac{3}{71} = +0,957746479$$

The one sided lower 100*(1-α) % confidence bound is π_L = 0,957746479and is thus far less than the proportion of successes of the sufficient condition, the conditio per quam relationship, calculated as p_{Calc}(human papillomavirus $\rightarrow$ human prostate cancer) = 1,0. The data as published by Leiros et al. (2005) do support our null hypothesis. Consequently, we accept the null hypothesis and reject the alternative hypothesis. In other words, **if** presence of human papillomavirus (HPV) in human prostate tissues **then** presence of human prostate cancer.

Human papillomavirus is a sufficient condition (a conditio per quam) of human prostate cancer.

Q. e. d.

Highly significant cause-effect relationship between human papillomavirus and human prostate cancer due to study of Leiros et al. (2005)

Claims.

Null hypothesis (H_0): (no causal relationship)

There is not a significant causal relationship between human papillomavirus and prostate cancer.

H_0: k = 0.

Alternative hypothesis (H_A): (causal relationship)

There is a significant causal relationship between human papillomavirus and prostate cancer.

H_A: $k \neq 0$.

Conditions.

Alpha level = 5%.

The two tailed critical Chi square value (degrees of freedom = 1) for alpha level 5% is 3.841458821.

Proof.

The data for this hypothesis test are obtained by Leiros et al. (2005) and illustrated in the 2 × 2 table (Table 12). The causal relationship k(human papillomavirus, human prostate cancer) is calculated as (Barukčić, 1998; Barukčić, 1997; Barukčić, 2005; Barukčić, 2006a; Barukčić, 2006b; Barukčić, 2011a; 2011b; Barukčić, 2012; Barukčić, 2016a; Barukčić et al., 2016b; Barukčić, 2016c; Barukčić, 2017a; Barukčić, 2017b; Barukčić, 2017c)

$$k\left(\text{Human papillomavirus [HPV], prostate cancer [PCa]}\right)=\frac{\left((71\times17)-(17\times41)\right)}{\sqrt[2]{(17\times54)\times(41\times30)}}=+0{,}479950314$$

The value of the test statistic k =+0,479950314 is equivalent to a calculated chi-square value of

$$\chi^2_{\text{Calculated}}=71\times\left(\frac{\left((71\times17)-(17\times41)\right)}{\sqrt[2]{(17\times54)\times(41\times30)}}\right)\times\left(\frac{\left((71\times17)-(17\times41)\right)}{\sqrt[2]{(17\times54)\times(41\times30)}}\right)$$

$$\chi^2_{\text{Calculated}}=71\times(0{,}479950314)\times(0{,}479950314)$$

$$\chi^2_{\text{Calculated}}=16{,}35501355$$

The calculated chi-square statistic, uncorrected for continuity, is 16,35501355 and equivalent to a p value of 0,000052517051367. The calculated chi-square statistic exceeds the critical chi-square value of 3.841458821 (Table 5). Consequently, we reject the null hypothesis and accept the alternative hypothesis. According to the data as obtained by Leiros et al. (2005) there is **a highly significant causal relationship between human papillomavirus and human prostate cancer** (k=+ 0,479950314, p value= 0,000052517051367).

Q. e. d.

The study of Carozzi et al.

Human papillomavirus is not a sufficient condition (a conditio per quam) of human prostate cancer due to the study of Carozzi et al. (2004)

Claims.

Null hypothesis (H_0):

If presence of human papillomavirus (HPV) in human prostate tissues **then** presence of human prostate cancer.

H_0: $p_{Calc} \geq \pi_L$

Alternative hypothesis (H_A)

If presence of human papillomavirus (HPV) in human prostate tissues **then** no presence of human prostate cancer.

H_A: $p_{Calc} < \pi_L$

Significance level (Alpha) below which the null hypothesis will be rejected: 0,05.

Proof.

The data as obtained by Carozzi et al. (2004) about the relationship between human papillomavirus and prostate cancer in patients and healthy control subjects are viewed in the 2 × 2 table (Table 13). In general, the proportion of successes of *the conditio per quam relationship*, denoted by the term p_{Calc}(human papillomavirus $\rightarrow$ human prostate cancer) is calculated as (Barukčić, 1998; Barukčić, 1997; Barukčić, 2005; Barukčić, 2006a; Barukčić, 2006b; Barukčić, 2011a; 2011b; Barukčić, 2012; Barukčić, 2016a; Barukčić et al., 2016b; Barukčić, 2016c; Barukčić, 2017a; Barukčić, 2017b; Barukčić, 2017c)

$$p_{Calc}\left(\text{Human papillomavirus [HPV]} \rightarrow \text{prostate cancer [PCa]}\right) = \frac{(14+12+20)}{51} = \frac{46}{51} = +0{,}901960784$$

In other words, in about 90,1960784 % of the sample, HPV is a sufficient condition of PCa. The one sided lower 100*(1-α) % confidence bound (significance level alpha = 0.05) is calculated according to the rule of three approximately as

$$\pi_L = 1 - \frac{3}{51} = +0{,}941176471$$

The one sided lower 100*(1-α) % confidence bound is π_L = 0,941176471 and is thus far not less than the proportion of successes of the sufficient condition, the conditio per quam relationship, calculated as p_{Calc}(human papillomavirus $\rightarrow$ human prostate cancer) = 0,901960784. The data as published by Carozzi et al. (2004) do not support our null hypothesis. Consequently, we reject the null hypothesis and accept the alternative hypothesis. In other words, **if** presence of human papillomavirus (HPV) in human prostate tissues **then** no presence of human prostate cancer.

Human papillomavirus is not a sufficient condition (a conditio per quam) of human prostate cancer.

Q. e. d.

Significant cause-effect relationship between human papillomavirus and human prostate cancer due to study of Carozzi et al. (2004)

Claims.

Null hypothesis (H_0): (no causal relationship)

There is not a significant causal relationship between human papillomavirus and prostate cancer.

H_0: k = 0.

Alternative hypothesis (H_A): (causal relationship)

There is a significant causal relationship between human papillomavirus and prostate cancer.

H_A: $k \neq 0$.

Conditions.

Alpha level = 5%.

The two tailed critical Chi square value (degrees of freedom = 1) for alpha level 5% is 3.841458821.

Proof.

The data for this hypothesis test are obtained by Carozzi et al. (2004) and illustrated in the 2 × 2 table (Table 13). The causal relationship k(human papillomavirus, human prostate cancer) is calculated as (Barukčić, 1998; Barukčić, 1997; Barukčić, 2005; Barukčić, 2006a; Barukčić, 2006b; Barukčić, 2011a; 2011b; Barukčić, 2012; Barukčić, 2016a; Barukčić et al., 2016b; Barukčić, 2016c; Barukčić, 2017a; Barukčić, 2017b; Barukčić, 2017c)

$$k\left(\text{Human papillomavirus [HPV]}, \text{prostate cancer [PCa]}\right) = \frac{\left((51\times 14)-(19\times 26)\right)}{\sqrt[2]{(19\times 32)\times(26\times 25)}} = +0{,}34995662$$

The value of the test statistic k = +0,34995662 is equivalent to a calculated chi-square value of

$$\chi^2_{\text{Calculated}} = 51\times\left(\frac{\left((51\times 14)-(19\times 26)\right)}{\sqrt[2]{(19\times 32)\times(26\times 25)}}\right)\times\left(\frac{\left((51\times 14)-(19\times 26)\right)}{\sqrt[2]{(19\times 32)\times(26\times 25)}}\right)$$

$$\chi^2_{\text{Calculated}} = 51\times(0{,}34995662)\times(0{,}34995662)$$

$$\chi^2_{\text{Calculated}} = 6{,}245951417$$

The calculated chi-square statistic, uncorrected for continuity, is 6,245951417 and equivalent to a p value of 0,012447749917968. The calculated chi-square statistic exceeds the critical chi-square value of 3.841458821 (Table 5). Consequently, we reject the null hypothesis and accept the alternative hypothesis. According to the data as obtained by Carozzi et al. (2004) there is a significant causal relationship between human papillomavirus and human prostate cancer (k=+0,34995662, p value= 0,012447749917968).

Q. e. d.

The study of Serth et al. (1999)

Human papillomavirus type 16 is a sufficient condition (a conditio per quam) of human prostate cancer due to the study of Serth et al. (1999)

Claims.

Null hypothesis (H_0):

If presence of human papillomavirus (HPV type 16) in human prostate tissues **then** presence of human prostate cancer.

H_0: $p_{Calc} \geq \pi_L$

Alternative hypothesis (H_A)

If presence of human papillomavirus (HPV type 16) in human prostate tissues **then** no presence of human prostate cancer.

H_A: $p_{Calc} < \pi_L$

Significance level (Alpha) below which the null hypothesis will be rejected: 0,05.

Proof.

The data as obtained by Serth et al. (1999) about the relationship between human papillomavirus and prostate cancer in patients and healthy control subjects are viewed in the 2 × 2 table (Table 14). In general, the proportion of successes of *the conditio per quam relationship*, denoted by the term p_{Calc}(human papillomavirus $\rightarrow$ human prostate cancer) is calculated as (Barukčić, 1998; Barukčić, 1997; Barukčić, 2005; Barukčić, 2006a; Barukčić, 2006b; Barukčić, 2011a; 2011b; Barukčić, 2012; Barukčić, 2016a; Barukčić et al., 2016b; Barukčić, 2016c; Barukčić, 2017a; Barukčić, 2017b; Barukčić, 2017c)

$$p_{Calc}\left(\text{Human papillomavirus [HPV 16]} \rightarrow \text{prostate cancer [PCa]}\right) = \frac{(10+37+37)}{85} = \frac{84}{85} = +0{,}988095238$$

In other words, in about 98,8095238% of the sample, HPV type 16 is a sufficient condition of PCa. The one sided lower 100*(1-α) % confidence bound (significance level alpha = 0.05) is calculated according to the rule of three approximately as

$$\pi_L = 1 - \frac{3}{85} = +0{,}964285714$$

The one sided lower 100*(1-α) % confidence bound is π_L = 0,964285714 and is thus far less than the proportion of successes of the sufficient condition, the conditio per quam relationship, calculated as p_{Calc}(human papillomavirus $\rightarrow$ human prostate cancer) = 0,988095238. The data as published by Serth et al. (1999) do support our null hypothesis. Consequently, we accept the null hypothesis and reject the alternative hypothesis. In other words, **if** presence of human papillomavirus (HPV type 16) in human prostate tissues **then** presence of human prostate cancer.

Human papillomavirus type 16 is a sufficient condition (a conditio per quam) of human prostate cancer.

Q. e. d.

Significant cause-effect relationship between human papillomavirus type 16 and human prostate cancer due to study of Serth et al. (1999)

Claims.

Null hypothesis (H_0): (no causal relationship)

There is not a significant causal relationship between human papillomavirus type 16 and prostate cancer.

H_0: k = 0.

Alternative hypothesis (H_A): (causal relationship)

There is a significant causal relationship between human papillomavirus type 16 and prostate cancer.

H_A: $k \neq 0$.

Conditions.

Alpha level = 5%.

The two tailed critical Chi square value (degrees of freedom = 1) for alpha level 5% is 3.841458821.

Proof.

The data for this hypothesis test are obtained by Serth et al. (1999) and illustrated in the 2 × 2 table (Table 14). The causal relationship k(human papillomavirus, human prostate cancer) is calculated as (Barukčić, 1998; Barukčić, 1997; Barukčić, 2005; Barukčić, 2006a; Barukčić, 2006b; Barukčić, 2011a; 2011b; Barukčić, 2012; Barukčić, 2016a; Barukčić et al., 2016b; Barukčić, 2016c; Barukčić, 2017a; Barukčić, 2017b; Barukčić, 2017c)

$$\mathrm{k}\left(\text{Human papillomavirus [HPV 16]}, \text{prostate cancer [PCa]}\right) = \frac{\left((85\times 10)-(11\times 47)\right)}{\sqrt[2]{(11\times 74)\times(47\times 37)}} = +0{,}273334819$$

The value of the test statistic k = +0,273334819 is equivalent to a calculated chi-square value of

$$\chi^2_{\text{Calculated}} = 85\times\left(\frac{\left((85\times 10)-(11\times 47)\right)}{\sqrt[2]{(11\times 74)\times(47\times 37)}}\right)\times\left(\frac{\left((85\times 10)-(11\times 47)\right)}{\sqrt[2]{(11\times 74)\times(47\times 37)}}\right)$$

$$\chi^2_{\text{Calculated}} = 85\times(0{,}273334819)\times(0{,}273334819)$$

$$\chi^2_{\text{Calculated}} = 6{,}275801569$$

The calculated chi-square statistic, uncorrected for continuity, is 6,275801569 and equivalent to a p value of 0,012239774206126. The calculated chi-square statistic exceeds the critical chi-square value of 3.841458821 (Table 5). Consequently, we reject the null hypothesis and accept the alternative hypothesis. According to the data as obtained by Serth et al. (1999) there is **a significant causal relationship between human papillomavirus type 16 and human prostate cancer** (k=+ 0,273334819, p value= 0,012239774206126).

Q. e. d.

Discussion

Many observational studies reported that HPV infection is significantly higher in prostatic cancer compare to controls which supports the hypothesis that sexual activity/behavior (Boccalini et al., 2012; Chelimo et al., 2013) which plays an important role in increasing or reducing sexually transmitted infections is related with human papillomavirus (HPV) infection and thus far with the risk of prostate cancer (PCa). This hypothesis is consistent with the fact that prostate cancer has not been described in very, very young and thus far due natural laws sexually non-active male children.

Several meta-analyses which have been published on the relationship between HPV infections and prostate cancer provided results which were not consistent. One study which combined studies in tissues and sera together provide evidence of a significantly increased risk of prostate cancer in relation to HPV infection (Taylor et al., 2005) while other meta-analyses studies which focused on the infection of HPV type 16 and/or HPV type 18 in relation to prostate cancer, found the overall risk of prostate cancer significantly (Lin et al., 2011; Bae et al., 2015) increased only when HPV DNA detected in prostate tissues. The meta-analysis of Yan et al. (2015) and of Yin et al. (2017) found that HPV infections contributes to the risk of prostate cancer. Despite the increasing number of studies conducted to re-evaluate the relationship between HPV infections and prostate cancer, this question still need to be answered. Whether human papilloma viruses (HPVs) are involved in the pathogenesis of prostate cancers is an ongoing subject of great controversy.

The study purpose was to re-investigate the relationship between human papillomavirus (HPV) infection and prostate cancer. The most of the studies presented (Table 15) provided evidence that there is a significant **cause-effect relationship between HPV and prostate cancer**. In particular, especially the studies of Huang et al. (Huang et al., 2016), Singh et al. (Singh et al., 2015), Leiros et al. (Leiros et al., 2005) and Serth et al. (Serth et al., 1999) provided significant evidence that **the presence of human papillomavirus (HPV) in the prostate tissues guarantees the presence of human prostate cancer**. The same result was achieved by Aydin et al. (Aydin et al., 2017) and Michopoulou et al. (Michopoulou et al., 2014). In contrast to the studies of Aydin et al. (Aydin et al., 2017) and

Michopoulou et al. (Michopoulou et al., 2014) the studies Huang et al. (Huang et al., 2016), Singh et al. (Singh et al., 2015), Leiros et al. (Leiros et al., 2005), Serth et al. (Serth et al., 1999) and the studies of Carozzi et al. (Carozzi et al., 2004), Atashafrooz et al. (Atashafrooz et al., 2016) support the hypothesis that there is **a significant cause effect relationship between human papillomavirus (HPV) and human prostate cancer.** The studies of Huang et al. (Huang et al., 2016), Singh et al. (Singh et al., 2015), Leiros et al. (Leiros et al., 2005) are highly significant in this context.

Table 15. Overview of the results achieved.

Study	Country	Year	N	**p_{IMP}**	$p_{Critical}$	Signif.	**Causal relationship**	p-value	significant
Aydin et al.	Turkey	2017	96	1	0,96875	YES	0,079471941	0,4361783623	NO
Atashafrooz et al.	Iran	2016	200	0,96	0,985	NO	0,172917125	0,0144684571	YES
Huang et al.	**China**	**2016**	**148**	**1**	**0,97972973**	**YES**	**0,35540179**	**0,0000153469**	**YES**
Singh et al.	**India**	**2015**	**150**	**0,98**	**0,98**	**YES**	**0,30390623**	**0,0001975916**	**YES**
Michopoulou et al.	Greece	2014	80	0,9625	0,9875	YES	0,194069614	0,0825971880	*(YES, 1 sided)*
Leiros et al.	**Argentina**	**2005**	**71**	**1**	**0,957746479**	**YES**	**0,479950314**	**0,0000525171**	**YES**
Carozzi et al.	Itally	2004	51	0,90196078	0,941176471	NO	0,34995662	0,0124477499	YES
Serth et al.	**Germany**	**1999**	**85**	**0,98823529**	**0,964705882**	**YES**	**0,276179414**	**0,0108887679**	**YES**

The studies of HPV in the prostate tissues presented are reporting conflicting findings to some extent. Therefore, to clarify the contradictory results of investigations and to address these and similar issues, it is necessary to point out that human papilloma viral nucleic acids in prostate cancers can be detected while using PCR technology. But PCR technology as such is a highly sensitive technology and this is in *fact* a difficult and delicate *matter* too. Contaminated specimens which may have been included in a study can induce false positive results. As a matter of fact, it is possible to ignore further factors like varying inclusion criteria, the dependence of detection rates of HPV on different HPV type-specific PCR primers, cut off values et cetera. With respect to HPV detection methods in prostate cancer tissues, broad spectrum PCR primers, type-specific PCR primers and both combined were used. Ex-post investigations of some *cervical* cancer specimens that appeared to be HPV-PCR DNA negative provided evidence that these were largely false negatives (Bosch et al., 1995; Walboomers et al., 1999). Thus far, methodological factors have contributed and may contribute to the numerous contradictions as discussed with regard to the different studies presented above. With the development of technology and science as such, the methods for detecting HPV DNA should improve and become increasingly

more sensitive. In this context it is important to note that the **in situ hybridization** (ISH) technology is able to differentiate between an infection in other cells and viral infections in tumor cells and is regarded as superior to PCR. Future studies should take the aforementioned and other factors into account while avoiding contamination as much as possible. Adequate procedures, standardized studies and more reliable techniques (quality and quantity of extracted DNA, cut-off values et cetera) should bring more evidence on the presence or absence of involvement of HPV in prostate cancer.

Relating facts and hypothesis of a particular kind is of key importance and equally a major task of every single scientific investigation. In point of fact, every scientific investigation harbors a large variety of (theoretical and practical) errors. Central to this relation between data and hypothesis is the question which concerns the justification or non- justification of inferences which extrapolate from data of a sample to predictions and general facts. In the light of empirical facts and recordings of observations and events in the scientific studies analyzed, it is insightful to consider the answer to the question: how can so many studies provide impressive and view times highly significant evidence of a cause-effect relationship between human papillomavirus and prostate cancer while other studies fail on this topic? Must we ignore the studies especially of Huang et al. (2016), Singh et al. (2015) and Leiros et al. (2005) completely? Despite disagreements in published studies, the studies analyzed suggest a highly significant cause-effect relationship between HPV infection and prostate cancer and encourage the necessity of further and more detailed research into this issue. Larger case-control or population-based studies are needed to clarify the relation between prostate carcinoma and HPV infection definitely. At this point we must acknowledge that the studies presented provide some generous support for the hypothesis that HPV is a cause of prostate cancer. In general, HPV vaccination is expected to reduce the incidence of *cervical* cancer. Thus far, our results indicate that HPV is a cause of prostate cancer and provide support for a wider use of HPV vaccine in addition to its use in *cervical* cancer prevention, in principle.

Conclusion

Human papilloma virus is a cause of human prostate cancer.

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