Human papillomavirus - The cause of human cervical cancer.

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Abstract

Objective: Cervical cancer is the second most prevalent cancer in females worldwide. Infection with human papillomavirus (HPV) is regarded as the main risk factor of cervical cancer. Our objective was to conduct a qualitative systematic review of some case-control studies to examine the role of human papillomavirus (HPV) in the development of human cervical cancer beyond any reasonable doubt.

Methods: We conducted a systematic review and re-analysis of some impressive key studies aimed to answer the following question. Is there a cause effect relationship between human papillomavirus (HPV) and cervical cancer? The method of *the conditio sine qua non relationship* was used to proof the hypothesis whether the presence of human papillomavirus (HPV) guarantees the presence of cervical carcinoma. In other words, if human papillomavirus (HPV) is present, then cervical carcinoma is present too. 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 cervical carcinoma. Significance was indicated by a p-value of less than 0.05.

Result: One study was able to provide strict evidence that human papillomavirus (HPV) is a *conditio sine qua non* (a necessary condition) of cervical carcinoma while the other studies analyzed failed on this point. The studies analyzed provide impressive evidence of a cause-effect relationship between human papillomavirus (HPV) and cervical carcinoma.

Conclusion: Human papillomavirus (HPV) is the cause of cervical carcinoma.

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

Introduction

Malignant (cancer) cells can be formed in the tissues of the cervix, the lower, narrow end of the uterus to result in cervical cancer. Cervical cancer, predominantly attributable to infection, usually develops slowly over time and is the second (Pisani et al., 1999; Pisani et al., 2002) most common cancer in women worldwid and a leading cause of morbidity and mortality in women. Each year about 265,700 women die from cervical cancer worldwide while approximately 527,600 new cases are diagnosed (Torre et al., 2012).

Human papillomavirus is considered to be one of the most important risk factors in the development of cervical cancer, HPV has been suggested as the main etiological risc factor in cervical cancer (de Villiers et al., 1987) while sexual transmission (Colón-López et al., 2015) is the predominant route of HPV infection. Meanwhile more than 140 different HPV genotypes have been recognized and fully sequenced (Tommasino, 2014).

Treatment options for patients with cervical cancer depend on several factors and include surgery or a concurrent chemo-radiotherapy regimen consisting of cisplatin-based chemotherapy with external beam radiotherapy and brachytherapy. A large and consistent body of studies (case series, case-control studies, cohort studies, and intervention studies) documented a relationship between a human papillomavirus (HPV) infection, particularly the oncogenic subtypes such as HPV 16 and 18, and the development of human cervical cancer. In the absence human papillomavirus (HPV) viral DNA, human cervical cancer appears not to develop. Thus far, most studies conducted identified human papillomavirus as key risk factors of human cervical cancer.

Even if the research in relation to the etiology of human cervical cancer has made substantial progress, a cause or the cause of human cervical cancer is still not identified.

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 sine qua non

The formula of the *condition sine qua non* (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

$$\mathrm{p}\left(\text{Human pappillomavirus} \leftarrow \text{Human cerical carcinoma}\right)$$

was used to proof the hypothesis: without a Human papillomavirus infection no development of human cervical cancer.

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. To show that p is not a necessary condition for q, it is necessary to find an event or circumstances where q is present but p 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)

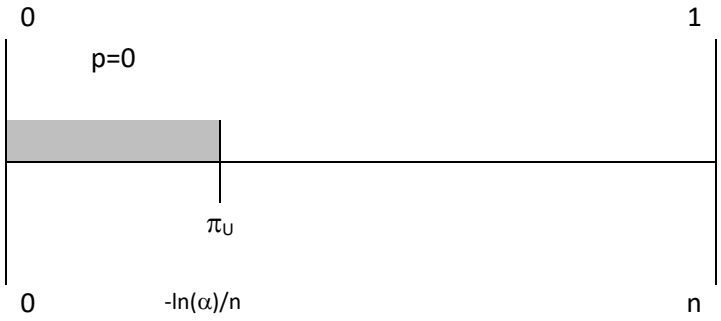
for calculating binomial *confidence intervals*. A faster and an alternative way to determine the lower and upper "exact" confidence interval is justified by the F distribution (Leemis et al., 1996). Furthermore, an approximate and conservative (one sided) confidence interval was developed by Louis (Louis 1981) and Jovanovic (Jovanovic et al., 1997) known as *the rule of three*. Briefly sketched, the rule of three can be derived [16] from the binomial model. Let π_U denote the upper limit of the exact one-sided 100 × (1 - α)% 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 × (1 - α)%

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(α)/n) is called a 100 × (1 - α)% confidence interval for the binomial parameter for the rate of occurrences in the population.

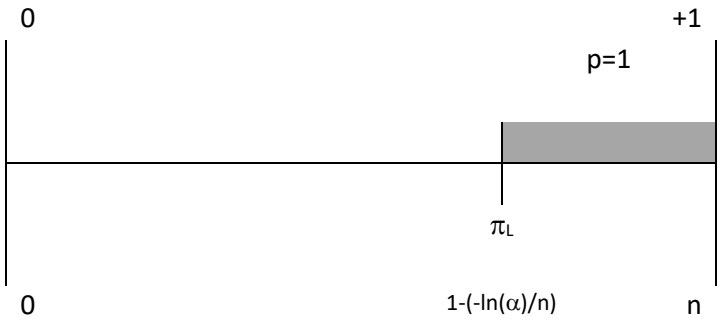
Another special case of the binomial distribution is based on *a sample of size n* where *only successes* are observed. Accordingly, the lower limit of a one-sided 100 × (1 - α)% confidence interval for a

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

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

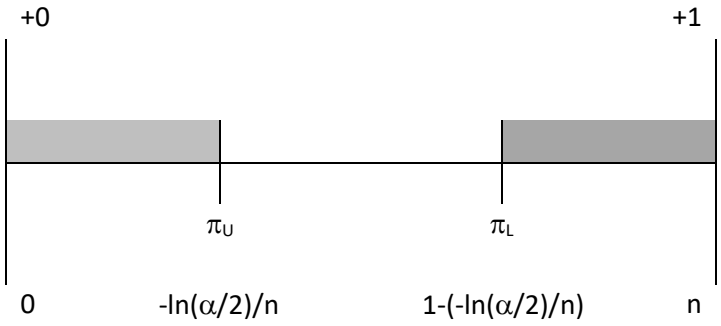
assuming that α=0,05.

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 more 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.

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 dervical carcinoma.

		Cervical carcinoma		
		YES	NO	SUM
HPV DNA	YES	a		U
	NO			N-U
	SUMM	W	N-W	N

Study design of Franceschi et al.

Franceschi et al. (Franceschi et al., 2003) designed a case-control study to investigate the presence of human papillomavirus (HPV) DNA in 205 cases and in 213 controls. HPV DNA was detected by means of a polymerase chain-reaction assay in all but one CC cases and in (59/213) = 27.7% of the control group. The following 2x2 table (Table 7) may illustrate the data as obtained by Franceschi et al.

Table 7. Human papillomavirus and cervical carcinoma due to Franceschi et al.

		Cervical carcinoma		
		YES	NO	SUM
HPV DNA	YES	204	59	263
	NO	1	154	155
	SUMM	205	213	418

Study design of Asato et al.

Asato et al. (Asato et al., 2004) conducted a nucleotide sequencing-based genotyping case-control study to examine the relationship between cervical cancer and human papillomavirus (HPV). Asato et al. detected HPV DNA in by polymerase chain reaction (PCR) in 311 of 356 patients with cervical cancer and within 333 of 3249 controls. The following 2x2 table (Table 8) may illustrate the data as obtained by Asato et al.

Table 8. Human papillomavirus and cervical carcinoma due to Asato et al.

		Cervical carcinoma		
		YES	NO	SUM
HPV DNA	YES	311	333	644
	NO	45	2916	2961
	SUMM	356	3249	3605

Study design of Bernal et al.

Bernal et al. (Bernal et al., 2008) performed a polymerase chain reaction (PCR) and oligonucleotide microarray-based case-control study to investigate the presence of human papillomavirus (HPV) in Papanicolau smears from women with and without cancer of the uterine cervix from 600 cases (540 women with cervical intraepithelial neoplasms (CIN) and 60 with invasive cancer) and 1200 controls (women without those lesions). Bernal et al. detected HPV in (56/60) = 93.3% of all samples with invasive cervical cancer versus (210/1200) = 17.5% of controls. The following 2x2 table (Table 9) may illustrate the data as obtained by Bernal et al.

Table 9. Human papillomavirus and cervical carcinoma due to Bernal et al.

		Cervical carcinoma		
		YES	NO	SUM
HPV DNA	YES	56	210	266
	NO	4	990	994
	SUMM	60	1200	1260

Study design of Ngelangel et al.

Ngelangel et al. (Ngelangel et al., 1998) performed a polymerase chain reaction assay and hospital-based, case-control study with 356 cases who had histologically confirmed cervical cancer and 381 controls. HPV DNA was detected in (303/323)*100=93.8% of cases with squamous cell carcinoma and in (30/33)*100=90.9% of cases with adenocarcinoma/adenosquamous carcinoma compared with (35/381)*100=9.2% of control subjects. The following 2x2 table (Table 10) may illustrate the data as obtained by Ngelangel et al.

Table 10. Human papillomavirus and cervical carcinoma due to Ngelangel et al..

		Cervical carcinoma		
		YES	NO	SUM
HPV DNA	YES	333	35	368
	NO	23	346	369
	SUMM	356	381	737

Study design of Chichareon et al.

Chichareon et al. (Chichareon et al., 1998) conducted a polymerase chain reaction assay and hospital-based, case-control study to investigate the relation bewteen HPV and invasive cervical cancer in a total of 338 patients with squamous cell carcinoma, 39 patients with adenocarcinoma/adenosquamous carcinoma and 261 controls. Chichareon et al. HPV DNA detected was in (321/338)*100= 95% of patients with squamous cell carcinoma, (35/39)*100 = 90% of those with adenocarcinoma/adenosquamous carcinoma, and (42/261)*100 = 16 % of control subjects. The following 2x2 table (Table 11) may illustrate the data as obtained by Chichareon et al.

Table 11. Human papillomavirus and cervical carcinoma due to Chichareon et al.

		Cervical carcinoma		
		YES	NO	SUM
HPV	YES	356	42	398
DNA	NO	21	219	240
	SUMM	377	261	638

Study design of Eluf-Neto et al.

Eluf-Neto et al. (Eluf-Neto et al., 1994) performed a polymerase chain reaction technique and hospital-based case-control study to investigate the role of human papillomavirus (HPV) in the development of invasive cervical cancer. Eluf-Neto et al. included 199 histologically confirmed cases and 225 controls. Eluf-Neto et al. found HPV DNA in cervical specimens in (167/199)*100=84% of cases compared with (38/225)*100=17% of controls. The following 2x2 table (Table 12) may illustrate the data as obtained by Eluf-Neto et al.

Table 12. Human papillomavirus and cervical carcinoma due to Eluf-Neto et al..

		Cervical carcinoma		
		YES	NO	SUM
HPV	YES	167	38	205
DNA	NO	32	187	219
	SUMM	199	225	424

Study design of Chaouki et al.

Chaouki et al. (Chaouki et al., 1998) completed a polymerase chain reaction and hospital-based case-control study which included 214 cases of invasive cervical cancer (squamous cell carcinomas, adenocarcinoma and adenosquamous cell carcinomas and cervical cancer without other specification) and 203 controls. A total of 186 cases and 185 controls was tested for HPV DNA. Chaouki et al. found HPV DNA in (176/186)*100= 94,6 of cases compared to (38/185)*100 = 20,5 % of controls. The following 2x2 table (Table 13) may illustrate the data as obtained by Chaouki et al.

Table 13. Human papillomavirus and cervical carcinoma due to Chaouki et al..

		Cervical carcinoma		
		YES	NO	SUM
HPV DNA	YES	176	38	214
	NO	10	147	157
	SUMM	186	185	371

Study design of et al. Rolón et al.

Rolón et al. (Rolón et al., 2000) conducted a HPV DNA based case-control study to examine the relationship between specific HPV types and invasive cervical cancer. A total of 113 histologically confirmed invasive cervical cancer cases and 91 controls were examined. Rolón et al. detected the HPV-DNA in (109/113)*100 = 97% of the cervical cancer cases and within (18/91)*100 = 20% of the control subjects. The following 2x2 table (Table 14) may illustrate the data as obtained by Rolón et al.

Table 14. Human papillomavirus and cervical carcinoma due to Rolón et al..

		Cervical carcinoma		
		YES	NO	SUM
HPV DNA	YES	109	18	127
	NO	4	73	77
	SUMM	113	91	204

Results

The study of Franceschi et al.

Human papillomavirus is necessary condition (a conditio sine qua non) of human cervical carcinoma due to Franceschi et al. (Franceschi et al., 2003)

Claims.

Null hypothesis (H_0):

Without the presence of human papillomavirus (HPV) there is **no** presence of human cervical carcinoma.

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

Alternative hypothesis (H_A)

Without the presence of human papillomavirus (HPV) there is presence of human cervical carcinoma.

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 Franceschi et al. (Franceschi et al., 2003) about the relationship between human papillomavirus and cervical 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 sine qua non relationship, denoted by the term p_{Calc}(human papillomavirus ← cervical carcinoma) is calculated (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) as

$$p_{Calc}\left(\text{Human papillomavirus [HPV]} \leftarrow \text{Cercival cancer [CC]}\right) = \frac{\left(204+59+154\right)}{418} = \frac{417}{418} = 0{,}997607656$$

In other word, in about 99,7 % of the sample, HPV is a necessary condition of CC. The one sided lower 100*(1-α) % confidence bound (significance level alpha = 0.05) is calculated according to the rule of three approximately as

$$\pi_L = 1 - \frac{3}{418} = 0{,}992822967$$

The one sided lower 100*(1-α) % confidence bound is π_L = 0,992822967 and is thus far less than the proportion of successes of the necessary condition, the conditio sine qua non relationship, calculated as p_{Calc}(human papillomavirus $\leftarrow$ cervical carcinoma) = 0,997607656. Consequently, we cannot reject the null hypothesis in favor of the alternative hypotheses. The data as published by Franceschi et al. (Franceschi et al., 2003) do support our null hypothesis. We reject the alternative hypothesis and accept the null hypothesis.

In other words, **without** the presence of human papillomavirus (HPV) in human cervical tissues there is **no** presence of human cervical carcinoma. **Human papillomavirus is a conditio sine qua non (a necessary condition) of human cervical carcinoma**.

Q. e. d.

Highly significant cause-effect relationship between human papillomavirus and human cervical carcinoma due to Franceschi et al. (Franceschi et al., 2003)

Claims.

Null hypothesis (H_0): (no causal relationship)

There is not a highly significant causal relationship between human papillomavirus and cervical carcinoma.

H_0: k = 0.

Alternative hypothesis (H_A): (causal relationship)

There is a highly significant causal relationship between human papillomavirus and cervical carcinoma.

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 Franceschi et al. *(Franceschi et al., 2003)* and illustrated in the 2 × 2 table (Table 7). The causal relationship k(human papillomavirus, cervical carcinoma) is calculated (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) as

$$k\left(\text{Human papillomavirus [HPV]}, \text{Cercival cancer [CC]}\right) = \frac{\left((418\times 204)-(263\times 205)\right)}{\sqrt[2]{(263\times 155)\times(205\times 213)}} = +0{,}743231402$$

The value of the test statistic k = +0,743231402is equivalent to a calculated chi-square value of

$$\chi^2_{\text{Calculated}} = 418\times \frac{\left((418\times 204)-(263\times 205)\right)}{\sqrt[2]{(263\times 155)\times(205\times 213)}} \times \frac{\left((418\times 204)-(263\times 205)\right)}{\sqrt[2]{(263\times 155)\times(205\times 213)}}$$

$$\chi^2_{\text{Calculated}} = 418\times(0{,}743231402)\times(0{,}743231402)$$

$$\chi^2_{\text{Calculated}} = 230{,}9002391$$

The calculated chi-square statistic, uncorrected for continuity, is 230,9002391 and equivalent to a p value of less than 0,000001. 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 hypotheses. According to the data as obtained by Franceschi et al. (Franceschi et al., 2003) there is a highly significant causal relationship between human papillomavirus and human cervical carcinoma (k=+0,743231402394, p value < 0,000001).

Q. e. d.

The study of Asato et al.

Human papillomavirus is not a necessary condition (a conditio sine qua non) of human cervical carcinoma due to Asato et al. (Asato et al., 2004)

Claims.

Null hypothesis (H_0):

Without the presence of human papillomavirus (HPV) there is **no** presence of human cervical carcinoma.

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

Alternative hypothesis (H_A)

Without the presence of human papillomavirus (HPV) there is presence of human cervical carcinoma.

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 Asato et al. (Asato et al., 2004) about the relationship between human papillomavirus and cervical 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 sine qua non relationship, denoted by the term p_{Calc}(human papillomavirus ← cervical carcinoma) is calculated (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) as

$$p_{Calc}\left(\text{Human papillomavirus [HPV]} \leftarrow \text{Cercival cancer [CC]}\right) = \frac{(311+333+2916)}{3605} = \frac{3560}{3605} = 0{,}997607656$$

In other word, in about 99,7607656 % of the sample, HPV is a necessary condition of CC. The one sided lower 100*(1-α) % confidence bound (significance level alpha = 0.05) is calculated according to the rule of three approximately as

$$\pi_L = 1 - \frac{3}{3605} = 0{,}999167822$$

The one sided lower 100*(1-α) % confidence bound is π_L = 0,999167822 and is thus far not less than the proportion of successes of the necessary condition, the conditio sine qua non relationship, calculated as p_{Calc}(human papillomavirus $\leftarrow$ cervical carcinoma) = 0,997607656 Consequently, we reject the null hypothesis in favor of the alternative hypotheses. The data as published by Asato et al. (Asato et al., 2004) do not support our null hypothesis. We accept the alternative hypothesis and reject the null hypothesis.

In other words, without the presence of human papillomavirus (HPV) in human cervical tissues there is presence of human cervical carcinoma. Human papillomavirus is not a conditio sine qua non (a necessary condition) of human cervical carcinoma.

Q. e. d.

Highly significant cause-effect relationship between human papillomavirus and human cervical carcinoma due to Asato et al. (Asato et al., 2004)

Claims.

Null hypothesis (H_0): (no causal relationship)

There is not a highly significant causal relationship between human papillomavirus and cervical carcinoma.

H_0: k = 0.

Alternative hypothesis (H_A): (causal relationship)

There is a highly significant causal relationship between human papillomavirus and cervical carcinoma.

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 Asato et al. (Asato et al., 2004) and illustrated in the 2 × 2 table (Table 8). The causal relationship k(human papillomavirus, cervical carcinoma) is calculated (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) as

$$\mathrm{k}\left(\text{Human papillomavirus [HPV]}, \text{Cercival cancer [CC]}\right) = \frac{\left(\left(3605\times 311\right)-\left(644\times 356\right)\right)}{\sqrt[2]{\left(644\times 2961\right)\times\left(356\times 3249\right)}} = +0{,}600550855$$

The value of the test statistic k = +0,600550855 equivalent to a calculated chi-square value of

$$\chi^2_{\text{Calculated}} = 3605\times\frac{\left(\left(3605\times 311\right)-\left(644\times 356\right)\right)}{\sqrt[2]{\left(644\times 2961\right)\times\left(356\times 3249\right)}}\times\frac{\left(\left(3605\times 311\right)-\left(644\times 356\right)\right)}{\sqrt[2]{\left(644\times 2961\right)\times\left(356\times 3249\right)}}$$

$$\chi^2_{\text{Calculated}} = 3605\times\left(0{,}600550855\right)\times\left(0{,}600550855\right)$$

$$\chi^2_{\text{Calculated}} = 1300{,}184092$$

The calculated chi-square statistic, uncorrected for continuity, is 1300,184092 and equivalent to a p value of less than 0,000001. 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 hypotheses. According to the data as obtained by Asato et al. (Asato et al., 2004) there is a highly significant causal relationship between human papillomavirus and human cervical carcinoma (k=+0,600550855, p value < 0,000001).

Q. e. d.

The study of Bernal et al.

Human papillomavirus is not a necessary condition (a conditio sine qua non) of human cervical carcinoma due to Bernal et al. (Bernal et al., 2008)

Claims.

Null hypothesis (H_0):

Without the presence of human papillomavirus (HPV) there is **no** presence of human cervical carcinoma.

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

Alternative hypothesis (H_A)

Without the presence of human papillomavirus (HPV) there is presence of human cervical carcinoma.

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 Bernal et al. about the relationship between human papillomavirus and cervical cancer in patients and healthy control subjects (Bernal et al., 2008) are viewed in the 2 × 2 table (Table 9). In general, the proportion of successes of the conditio sine qua non relationship, denoted by the term p_{Calc}(human papillomavirus ← cervical carcinoma) is calculated (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) as

$$p_{Calc}\left(\text{Human papillomavirus [HPV]} \leftarrow \text{Cercival cancer [CC]}\right) = \frac{(56+210+990)}{1260} = \frac{1256}{1260} = +0{,}996825397$$

In other word, in about 99,6825397 % of the sample, HPV is a necessary condition of CC. The one sided lower 100*(1-α) % confidence bound (significance level alpha = 0.05) is calculated according to the rule of three approximately as

$$\pi_L = 1 - \frac{3}{1260} = +0{,}997619048$$

The one sided lower 100*(1-α) % confidence bound is π_L = 0,997619048 and is thus far not less than the proportion of successes of the necessary condition, the conditio sine qua non relationship, calculated as p_{Calc}(human papillomavirus ← cervical carcinoma) = 0,996825397. Consequently, we must reject the null hypothesis in favor of the alternative hypotheses. The data as published by Bernal et al. do not (Bernal et al., 2008) support our null hypothesis. We accept the alternative hypothesis and reject the null hypothesis.

In other words, without the presence of human papillomavirus (HPV) in human cervical tissues there is presence of human cervical carcinoma. Human papillomavirus is not a conditio sine qua non (a necessary condition) of human cervical carcinoma.

Q. e. d.

Highly significant cause-effect relationship between human papillomavirus and human cervical carcinoma due to Bernal et al. (Bernal et al., 2008)

Claims.

Null hypothesis (H_0): (no causal relationship)

There is not a highly significant causal relationship between human papillomavirus and cervical carcinoma.

H_0: k = 0.

Alternative hypothesis (H_A): (causal relationship)

There is a highly significant causal relationship between human papillomavirus and cervical carcinoma.

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 Bernal et al. (Bernal et al., 2008) and illustrated in the 2 × 2 table (Table 9). The causal relationship k(human papillomavirus, cervical carcinoma) is calculated (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) as

$$k\left(\text{Human papillomavirus [HPV]}, \text{Cercival cancer [CC]}\right) = \frac{\left(\left(1260\times 56\right)-\left(266\times 60\right)\right)}{\sqrt[2]{\left(266\times 994\right)\times\left(60\times 1200\right)}} = +0{,}395723994$$

The value of the test statistic k = + 0,395723994 equivalent to a calculated chi-square value of

$$\chi^2_{\text{Calculated}} = 1260\times\frac{\left(\left(1260\times 56\right)-\left(266\times 60\right)\right)}{\sqrt[2]{\left(266\times 994\right)\times\left(60\times 1200\right)}}\times\frac{\left(\left(1260\times 56\right)-\left(266\times 60\right)\right)}{\sqrt[2]{\left(266\times 994\right)\times\left(60\times 1200\right)}}$$

$$\chi^2_{\text{Calculated}} = 1260\times\left(0{,}395723994\right)\times\left(0{,}395723994\right)$$

$$\chi^2_{\text{Calculated}} = 197{,}3128243$$

The calculated chi-square statistic, uncorrected for continuity, is 197,3128243 and equivalent to a p value of less than 0,000001. 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 hypotheses. According to the data as obtained by Bernal et al. (Bernal et al., 2008) there is a highly significant causal relationship between human papillomavirus and human cervical carcinoma (k=+ 0,395723994, p value < 0,000001).

Q. e. d.

The study of Ngelangel et al.

Human papillomavirus is not a necessary condition (a conditio sine qua non) of human cervical carcinoma due to Ngelangel et al. (Ngelangel et al., 1998)

Claims.

Null hypothesis (H_0):

Without the presence of human papillomavirus (HPV) there is **no** presence of human cervical carcinoma.

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

Alternative hypothesis (H_A)

Without the presence of human papillomavirus (HPV) there is presence of human cervical carcinoma.

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 Ngelangel et al. about the relationship between human papillomavirus and cervical cancer in patients and healthy control subjects (Ngelangel et al., 1998) are viewed in the 2 × 2 table (Table 10). In general, the proportion of successes of the conditio sine qua non relationship, denoted by the term p_{Calc}(human papillomavirus ← cervical carcinoma) is calculated (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) as

$$p_{Calc}\left(\text{Human papillomavirus [HPV]} \leftarrow \text{Cercival cancer [CC]}\right) = \frac{(333+35+346)}{737} = \frac{714}{737} = +0{,}968792402$$

In other word, in about 96,8792402 % of the sampel, HPV is a necessary condition of CC. The one sided lower 100*(1-α) % confidence bound (significance level alpha = 0.05) is calculated according to the rule of three approximately as

$$\pi_L = 1 - \frac{3}{737} = +0{,}995929444$$

The one sided lower 100*(1-α) % confidence bound is π_L = 0,995929444 and is thus far not less than the proportion of successes of the necessary condition, the conditio sine qua non relationship, calculated as p_{Calc}(human papillomavirus ← cervical carcinoma) = 0,968792402. Consequently, we reject the null hypothesis in favor of the alternative hypotheses. The data as published by Ngelangel et al. (Ngelangel et al., 1998) do not support our null hypothesis. We accept the alternative hypothesis and reject the null hypothesis.

In other words, without the presence of human papillomavirus (HPV) in human cervical tissues there is presence of human cervical carcinoma. Human papillomavirus is not a conditio sine qua non (a necessary condition) of human cervical carcinoma.

Q. e. d.

Highly significant cause-effect relationship between human papillomavirus and human cervical carcinoma due to Ngelangel et al. (Ngelangel et al., 1998)

Claims.

Null hypothesis (H_0): (no causal relationship)

There is not a highly significant causal relationship between human papillomavirus and cervical carcinoma.

H_0: k = 0.

Alternative hypothesis (H_A): (causal relationship)

There is a highly significant causal relationship between human papillomavirus and cervical carcinoma.

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 Ngelangel et al. (Ngelangel et al., 1998) and illustrated in the 2 × 2 table (Table 10). The causal relationship k(human papillomavirus, cervical carcinoma) is calculated (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) as

$$k\left(\text{Human papillomavirus [HPV]}, \text{Cercival cancer [CC]}\right) = \frac{\left(\left(737\times 333\right)-\left(368\times 356\right)\right)}{\sqrt[2]{\left(368\times 369\right)\times\left(356\times 381\right)}} = +0{,}843045072$$

The value of the test statistic k = + 0,843045072 equivalent to a calculated chi-square value of

$$\chi^2_{\text{Calculated}} = 737\times\frac{\left(\left(737\times 333\right)-\left(368\times 356\right)\right)}{\sqrt[2]{\left(368\times 369\right)\times\left(356\times 381\right)}}\times\frac{\left(\left(737\times 333\right)-\left(368\times 356\right)\right)}{\sqrt[2]{\left(368\times 369\right)\times\left(356\times 381\right)}}$$

$$\chi^2_{\text{Calculated}} = 737\times\left(+0{,}843045072\right)\times\left(+0{,}843045072\right)$$

$$\chi^2_{\text{Calculated}} = 523{,}8043201$$

The calculated chi-square statistic, uncorrected for continuity, is 523,8043201 and equivalent to a p value of less than 0,000001. 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 hypotheses. According to the data as obtained by Ngelangel et al. (Ngelangel et al., 1998) there is a highly significant causal relationship between human papillomavirus and human cervical carcinoma (k=+0,843045072, p value < 0,000001).

Q. e. d.

The study of Chichareon et al.

Human papillomavirus is not a necessary condition (a conditio sine qua non) of human cervical carcinoma due to Chichareon et al. (Chichareon et al., 1998)

Claims.

Null hypothesis (H_0):

Without the presence of human papillomavirus (HPV) there is **no** presence of human cervical carcinoma.

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

Alternative hypothesis (H_A)

Without the presence of human papillomavirus (HPV) there is presence of human cervical carcinoma.

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 Chichareon et al. about the relationship between human papillomavirus and cervical cancer in patients and healthy control subjects (Chichareon et al., 1998) are viewed in the 2 × 2 table (Table 11). In general, the proportion of successes of the conditio sine qua non relationship, denoted by the term p_{Calc}(human papillomavirus ← cervical carcinoma) is calculated (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) as

$$p_{Calc}\left(\text{Human papillomavirus [HPV]} \leftarrow \text{Cercival cancer [CC]}\right) = \frac{(356+42+219)}{638} = \frac{617}{638} = 0{,}967084639$$

In other word, in about 96,7084639 % of the sample, HPV is a necessary condition of CC. The one sided lower 100*(1-α) % confidence bound (significance level alpha = 0.05) is calculated according to the rule of three approximately as

$$\pi_L = 1 - \frac{3}{638} = +0{,}995297806$$

The one sided lower 100*(1-α) % confidence bound is π_L = +0,995297806 and is thus far not less than the proportion of successes of the necessary condition, the conditio sine qua non relationship, calculated as p_{Calc}(human papillomavirus ← cervical carcinoma) = +0,967084639. Consequently, we must reject the null hypothesis in favor of the alternative hypotheses. The data as published by Chichareon et al. (Chichareon et al., 1998) do not support our null hypothesis. We accept the alternative hypothesis and reject the null hypothesis.

In other words, without the presence of human papillomavirus (HPV) in human cervical tissues there is presence of human cervical carcinoma. Human papillomavirus is not a conditio sine qua non (a necessary condition) of human cervical carcinoma.

Q. e. d.

Highly significant cause-effect relationship between human papillomavirus and human cervical carcinoma due to Chichareon et al. (Chichareon et al., 1998)

Claims.

Null hypothesis (H_0): (no causal relationship)

There is not a highly significant causal relationship between human papillomavirus and cervical carcinoma.

H_0: k = 0.

Alternative hypothesis (H_A): (causal relationship)

There is a highly significant causal relationship between human papillomavirus and cervical carcinoma.

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 Chichareon et al. (Chichareon et al., 1998) and illustrated in the 2 × 2 table (Table 11). The causal relationship k(human papillomavirus, cervical carcinoma) is calculated (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) as

$$k\left(\text{Human papillomavirus [HPV]}, \text{Cercival cancer [CC]}\right) = \frac{\left((638\times 356)-(398\times 377)\right)}{\sqrt[2]{(398\times 240)\times(377\times 261)}} = +0{,}795087432$$

The value of the test statistic k = + 0,795087432 equivalent to a calculated [9] chi-square value of

$$\chi^2_{\text{Calculated}} = 638\times\frac{\left((638\times 356)-(398\times 377)\right)}{\sqrt[2]{(398\times 240)\times(377\times 261)}}\times\frac{\left((638\times 356)-(398\times 377)\right)}{\sqrt[2]{(398\times 240)\times(377\times 261)}}$$

$$\chi^2_{\text{Calculated}} = 638\times(+0{,}795087432)\times(+0{,}795087432)$$

$$\chi^2_{\text{Calculated}} = 403{,}3206481$$

The calculated chi-square statistic, uncorrected for continuity, is 403,3206481 and equivalent to a p value of less than 0,000001. 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 hypotheses. According to the data as obtained by Chichareon et al. (Chichareon et al., 1998) there is a highly significant causal relationship between human papillomavirus and human cervical carcinoma (k=+0,795087432, p value < 0,000001).

Q. e. d.

The study of Eluf-Neto et al.

Human papillomavirus is not a necessary condition (a conditio sine qua non) of human cervical carcinoma due to Eluf-Neto et al. (Eluf-Neto et al., 1994)

Claims.

Null hypothesis (H_0):

Without the presence of human papillomavirus (HPV) there is **no** presence of human cervical carcinoma.

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

Alternative hypothesis (H_A)

Without the presence of human papillomavirus (HPV) there is presence of human cervical carcinoma.

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 Eluf-Neto et al. about the relationship between human papillomavirus and cervical cancer in patients and healthy control subjects (Eluf-Neto et al., 1994) are viewed in the 2 × 2 table (Table 12). In general, the proportion of successes of the conditio sine qua non relationship, denoted by the term p_{Calc}(human papillomavirus ← cervical carcinoma) is calculated (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) as

$$p_{Calc}\left(\text{Human papillomavirus [HPV]} \leftarrow \text{Cercival cancer [CC]}\right) = \frac{(167+38+187)}{424} = \frac{392}{424} = +0{,}924528302$$

In other word, in about 92,4528302 % of the sample, HPV is a necessary condition of CC. The one sided lower 100*(1-α) % confidence bound (significance level alpha = 0.05) is calculated according to the rule of three approximately as

$$\pi_L = 1 - \frac{3}{424} = +0{,}992924528$$

The one sided lower 100*(1-α) % confidence bound is π_L = +0,992924528 and is thus far not less than the proportion of successes of the necessary condition, the conditio sine qua non relationship, calculated as p_{Calc}(human papillomavirus ← cervical carcinoma) = +0,924528302. Consequently, we must reject the null hypothesis in favor of the alternative hypotheses. The data as published by Eluf-Neto et al. do not (Eluf-Neto et al., 1994) support our null hypothesis. We accept the alternative hypothesis and reject the null hypothesis.

In other words, without the presence of human papillomavirus (HPV) in human cervical tissues there is presence of human cervical carcinoma. Human papillomavirus is not a conditio sine qua non (a necessary condition) of human cervical carcinoma.

Q. e. d.

Highly significant cause-effect relationship between human papillomavirus and human cervical carcinoma due to Eluf-Neto et al. (Eluf-Neto et al., 1994)

Claims.

Null hypothesis (H_0): (no causal relationship)

There is not a highly significant causal relationship between human papillomavirus and cervical carcinoma.

H_0: k = 0.

Alternative hypothesis (H_A): (causal relationship)

There is a highly significant causal relationship between human papillomavirus and cervical carcinoma.

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 Eluf-Neto et al. (Eluf-Neto et al., 1994) and illustrated in the 2 × 2 table (Table 12). The causal relationship k(human papillomavirus, cervical carcinoma) is calculated (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) as

$$\mathrm{k}\left(\text{Human papillomavirus [HPV], Cercival cancer [CC]}\right)=\frac{\left(\left(424\times167\right)-\left(205\times199\right)\right)}{\sqrt[2]{\left(205\times219\right)\times\left(199\times225\right)}}=+0{,}669410659$$

The value of the test statistic k = +0,669410659 equivalent to a calculated chi-square value of

$$\chi^2_{\text{Calculated}}=424\times\frac{\left(\left(424\times167\right)-\left(205\times199\right)\right)}{\sqrt[2]{\left(205\times219\right)\times\left(199\times225\right)}}\times\frac{\left(\left(424\times167\right)-\left(205\times199\right)\right)}{\sqrt[2]{\left(205\times219\right)\times\left(199\times225\right)}}$$

$$\chi^2_{\text{Calculated}}=424\times\left(+0{,}669410659\right)\times\left(+0{,}669410659\right)$$

$$\chi^2_{\text{Calculated}}=189{,}998907$$

The calculated chi-square statistic, uncorrected for continuity, is 189,998907 and equivalent to a p value of less than 0,000001. 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 hypotheses. According to the data as obtained by Eluf-Neto et al. (Eluf-Neto et al., 1994) there is a highly significant causal relationship between human papillomavirus and human cervical carcinoma (k=+0,669410659, p value < 0,000001).

Q. e. d.

The study of Chaouki et al.

Human papillomavirus is not a necessary condition (a conditio sine qua non) of human cervical carcinoma due to Chaouki et al. (Chaouki et al., 1998)

Claims.

Null hypothesis (H_0):

Without the presence of human papillomavirus (HPV) there is **no** presence of human cervical carcinoma.

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

Alternative hypothesis (H_A)

Without the presence of human papillomavirus (HPV) there is presence of human cervical carcinoma.

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 Chaouki et al. about the relationship between human papillomavirus and cervical cancer in patients and healthy control subjects (Chaouki et al., 1998) are viewed in the 2 × 2 table (Table 13). In general, the proportion of successes of the conditio sine qua non relationship, denoted by the term p_{Calc}(human papillomavirus ← cervical carcinoma) is calculated (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) as

$$p_{Calc}\left(\text{Human papillomavirus [HPV]} \leftarrow \text{Cercival cancer [CC]}\right) = \frac{(176+38+147)}{371} = \frac{361}{371} = +0{,}973045822$$

In other word, in about 97,3045822 % of the sample, HPV is a necessary condition of CC. The one sided lower 100*(1-α) % confidence bound (significance level alpha = 0.05) is calculated according to the rule of three approximately as

$$\pi_L = 1 - \frac{3}{371} = +0{,}991913747$$

The one sided lower 100*(1-α) % confidence bound is π_L = +0,991913747 and is thus far not less than the proportion of successes of the necessary condition, the conditio sine qua non relationship, calculated as p_{Calc}(human papillomavirus ← cervical carcinoma) = +0,973045822. Consequently, we must reject the null hypothesis in favor of the alternative hypotheses. The data as published by Chaouki et al. do not (Chaouki et al., 1998) support our null hypothesis. We accept the alternative hypothesis and reject the null hypothesis.

In other words, without the presence of human papillomavirus (HPV) in human cervical tissues there is presence of human cervical carcinoma. Human papillomavirus is not a conditio sine qua non (a necessary condition) of human cervical carcinoma.

Q. e. d.

Highly significant cause-effect relationship between human papillomavirus and human cervical carcinoma due to Chaouki et al. (Chaouki et al., 1998)

Claims.

Null hypothesis (H_0): (no causal relationship)

There is not a highly significant causal relationship between human papillomavirus and cervical carcinoma.

H_0: k = 0.

Alternative hypothesis (H_A): (causal relationship)

There is a highly significant causal relationship between human papillomavirus and cervical carcinoma.

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 Chaouki et al. (Chaouki et al., 1998) and illustrated in the 2 × 2 table (Table 13). The causal relationship k(human papillomavirus, cervical carcinoma) is calculated (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) as

$$k\left(\text{Human papillomavirus [HPV]}, \text{Cercival cancer [CC]}\right) = \frac{\left(\left(371\times176\right)-\left(214\times186\right)\right)}{\sqrt[2]{\left(214\times157\right)\times\left(186\times185\right)}} = +0{,}749729951$$

The value of the test statistic k = +0,749729951 is equivalent to a calculated chi-square value of

$$\chi^2_{\text{Calculated}} = 371\times\frac{\left(\left(371\times176\right)-\left(214\times186\right)\right)}{\sqrt[2]{\left(214\times157\right)\times\left(186\times185\right)}}\times\frac{\left(\left(371\times176\right)-\left(214\times186\right)\right)}{\sqrt[2]{\left(214\times157\right)\times\left(186\times185\right)}}$$

$$\chi^2_{\text{Calculated}} = 371\times\left(+0{,}749729951\right)\times\left(+0{,}749729951\right)$$

$$\chi^2_{\text{Calculated}} = 208{,}5372446$$

The calculated chi-square statistic, uncorrected for continuity, is 208,5372446 and equivalent to a p value of less than 0,000001. 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 hypotheses. According to the data as obtained by Chaouki et al. there is a highly significant causal relationship (Chaouki et al., 1998) between human papillomavirus and human cervical carcinoma (k=+0,749729951, p value < 0,000001).

Q. e. d.

The study of et al. Rolón et al.

Human papillomavirus is not a necessary condition (a conditio sine qua non) of human cervical carcinoma due to Rolón et al.. (Rolón et al., 2000)

Claims.

Null hypothesis (H_0):

Without the presence of human papillomavirus (HPV) there is **no** presence of human cervical carcinoma.

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

Alternative hypothesis (H_A)

Without the presence of human papillomavirus (HPV) there is presence of human cervical carcinoma.

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 Rolón et al. about the relationship between human papillomavirus and cervical cancer in patients and healthy control subjects (Rolón et al., 2000) are viewed in the 2 × 2 table (Table 14. In general, the proportion of successes of the conditio sine qua non relationship, denoted by the term p_{Calc}(human papillomavirus ← cervical carcinoma) is calculated (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) as

$$p_{Calc}\left(\text{Human papillomavirus [HPV]} \leftarrow \text{Cercival cancer [CC]}\right) = \frac{(109+18+73)}{204} = \frac{200}{204} = +0{,}980392157$$

In other word, in about 98,0392157 % of the sample, HPV is a necessary condition of CC. The one sided lower 100*(1-α) % confidence bound (significance level alpha = 0.05) is calculated according to the rule of three approximately as

$$\pi_L = 1 - \frac{3}{204} = +0{,}985294118$$

The one sided lower 100*(1-α) % confidence bound is π_L = +0,985294118 and is thus far not less than the proportion of successes of the necessary condition, the conditio sine qua non relationship, calculated as p_{Calc}(human papillomavirus ← cervical carcinoma) = +0,980392157. Consequently, we must reject the null hypothesis in favor of the alternative hypotheses. The data as published by Rolón et al. do not (Rolón et al., 2000) support our null hypothesis. We accept the alternative hypothesis and reject the null hypothesis.

In other words, without the presence of human papillomavirus (HPV) in human cervical tissues there is presence of human cervical carcinoma. Human papillomavirus is not a conditio sine qua non (a necessary condition) of human cervical carcinoma.

Q. e. d.

Highly significant cause-effect relationship between human papillomavirus and human cervical carcinoma due to Rolón et al. (Rolón et al., 2000)

Claims.

Null hypothesis (H_0): (no causal relationship)

There is not a highly significant causal relationship between human papillomavirus and cervical carcinoma.

H_0: k = 0.

Alternative hypothesis (H_A): (causal relationship)

There is a highly significant causal relationship between human papillomavirus and cervical carcinoma.

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 Rolón et al. (Rolón et al., 2000) and illustrated in the 2 × 2 table (Table 14). The causal relationship k(human papillomavirus, cervical carcinoma) is calculated (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) as

$$\mathrm{k}\left(\text{Human papillomavirus [HPV]}, \text{Cercival cancer [CC]}\right) = \frac{\left(\left(204\times109\right)-\left(127\times113\right)\right)}{\sqrt[2]{\left(127\times77\right)\times\left(113\times91\right)}} = +0{,}786311372$$

The value of the test statistic k = +0,786311372 is equivalent to a calculated chi-square value of

$$\chi^2_{\text{Calculated}} = 204\times\frac{\left(\left(204\times109\right)-\left(127\times113\right)\right)}{\sqrt[2]{\left(127\times77\right)\times\left(113\times91\right)}}\times\frac{\left(\left(204\times109\right)-\left(127\times113\right)\right)}{\sqrt[2]{\left(127\times77\right)\times\left(113\times91\right)}}$$

$$\chi^2_{\text{Calculated}} = 204\times\left(+0{,}786311372\right)\times\left(+0{,}786311372\right)$$

$$\chi^2_{\text{Calculated}} = 126{,}1302571$$

The calculated chi-square statistic, uncorrected for continuity, is 126,1302571 and equivalent to a p value of less than 0,000001. 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 hypotheses. According to the data as obtained by Rolón et al. there is a highly significant causal relationship (Rolón et al., 2000) between human papillomavirus and human cervical carcinoma (k=+0,786311372, p value < 0,000001).

Q. e. d.

Discussion

The nature of the relationship between HPV and cervical cancer has been exhaustively investigated over more than 20 years. Several studies which have unequivocally shown that HPV-DNA can be detected in about 95% to 100% of adequate specimens of cervical cancer, support the claim that HPV is a necessary condition cervical cancer. The most reviews available have consistently concluded that there is a strong evidence of an association between HPV and cervical cancer (Bosch et al., 2002; Bosch et al., 2013). Still, the cause or a cause of cervical cancer still remains unclear and is not identified without any doubt. To re-evaluate the role of HPV in the etiology of cervical cancer, we re-analyzed some outstanding HPV DNA polymerase chain reaction based case control studies. All studies presented (Table 15) provide strong evidence that **there is a highly significant cause-effect relationship between HPV and cervical cancer** (All p values < 0,000001).

Table 15. Overview of the results achieved.

Study	Country	Year	N	**p** Sine qua non	p Critical	Signif.	**Causal relationship**	p-value	significant
Study of Franceschi et al.	India	2003	418	0,99760766	0,99282297	*	+0,7432314	p < 0,000001	***
Study of Asato et al.	Japan	2004	3605	0,99760766	0,99916782	(*)	+0,60055086	p < 0,000001	***
Study of Bernal et al.	Spain	2008	1260	0,9968254	0,99761905	(*)	+0,39572399	p < 0,000001	***
Study of Ngelangel et al.	Philippines	1998	737	0,9687924	0,99592944		+0,84304507	p < 0,000001	***
Study of Chichareon et al.	Thailand	1998	638	0,96708464	0,99529781		+0,79508743	p < 0,000001	***
Study of Eluf-Neto et al.	Brazil	1994	424	0,9245283	0,99292453		+0,66941066	p < 0,000001	***
Study of Chaouki et al.	Morocco	1998	371	0,97304582	0,99191375		+0,74972995	p < 0,000001	***
Study of et al. Rolón et al.	Paraguay	2000	204	0,98039216	0,98529412	(*)	+0,78631137	p < 0,000001	***

In point of fact, besides of the secured cause-effect relationship between HPV and CC, several studies failed to provide evidence that HPV is a necessary condition (a conditio sine qua non) of CC. In particular, only the study of Franceschi et al. (Franceschi et al., 2003) was able to provide evidence that **HPV is a conditio sine qua non (a necessary condition) of human cervical cancer**. It is worth to mention that certain especially methodological factors may have contributed to the numerous problems as associated with the different studies above. In this context, ignoring factors like varying inclusion criteria, the possibility of contaminated specimens, the dependence of detection rates of

HPV using different HPV type-specific PCR primers some detailed investigations of few cervical cancer specimens that appeared to be HPV-DNA negative suggest that these were largely false negatives (Bosch et al., 1995; Walboomers et al., 1999). PCR technology is highly sensitive and contaminated specimens of the studies above may have induced false positive results, particularly in the earliest PCR based studies. With the development of technology and science as such, the methods for detecting HPV DNA should become increasingly more sensitive. Furthermore, it is reasonable to assume that the detection rates of HPV using special HPV type PCR primers may be higher compared with those using other PCR primers. 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. But even the specificity and sensitivity of the in situ hybridization (ISH) technology may depend on the target used. Future studies should avoid contamination as much as possible while taking the aforementioned and other factors into account. Numerous potential limitations can be acknowledged in the present meta/re-analysis of the studies above. Still, according to Franceschi et al. (Franceschi et al., 2003), **human papillomavirus is a condition sine qua non of human cervical cancer** while the study of Asato et al. (Asato et al., 2004) and the study of Bernal et al. (Bernal et al., 2008) were very close of being significant. In this context, it appears not be justified to ignore the result of the study of Franceschi et al. (Franceschi et al., 2003). In the light of this publication, the tremendous global impact of human papillomavirus (HPV) on the patients, their families, and human communities is no longer justified. Cancer prevention is no longer only a theoretical desire. Preventing cervical cancer is possible and has the potential to save millions of lives. For lessening the burden of cervical cancer it is useful to implement concrete strategies to address barriers to vaccine acceptance and access. In this context it is necessary to address several fundamental questions. Does it make sense to offer a preventive HPV vaccination at all? Is it allowed to refuse a HPV vaccination to males or females who already had some contact with HPV?

Viruses as such are not primarily only destructive, pathogen, life-threating and deadly. The other side of every virus is a constructive and progressive moment too. Viral sequences can be found in the genomes of various organisms (Moelling, 2013). Thus far, viruses appear to play a fundamental role in driving evolution forward. An unnecessary prophylactic vaccination can have a massive impact on the creative side of viruses and the potential role of viruses during the further history of life, genome composition, genetic diversity and on progress in evolution as such. In contrast to thoughts like this, is it justified to refuse a HPV vaccination to males or females who already had some contact with HPV especially after the reproductive goals in life are achieved? Since more than 140 different HPV genotypes have been recognized and fully sequenced (Tommasino, 2014) it is not very probable that every patient who is HPV positive has been infected by all different HPV genotypes. A HPV testing before HPV vaccination is cost-expensive, a waste of time and money. In contrast to possible side effects of an unnecessary HPV vaccination, the global threat by HPV is unimaginable high. Until questions like the before are clarified for sure, everyone should get an access to a low-cost and highly effective HPV vaccination.

Conclusion

Human papillomavirus is the cause of human cervical cancer.

References

1. Agresti A, Coull BA,. Approximate is better than “exact” for interval estimation of binomial proportions. The American Statistician. **1998**; 52: 119–126. http://dx.doi.org/10.2307/2685469
2. Asato T, Maehama T, Nagai Y, Kanazawa K, Uezato H, Kariya K,. A large case-control study of cervical cancer risk associated with human papillomavirus infection in Japan, by nucleotide sequencing-based genotyping. J. Infect. Dis. 2004; **189**: 829-32. https://doi.org/10.1086/382896
3. Astorga ML,. Diodorus Cronus and Philo of Megara: Two Accounts of the Conditional. Rupkatha Journal on Interdisciplinary Studies in Humanities. 2015; **7**, 9-16.
4. Bailey HH, Chuang LT, duPont NC, Eng C, Foxhall LE, Merrill JK, Wollins DS, Blanke CD,. American Society of Clinical Oncology Statement: Human Papillomavirus Vaccination for Cancer Prevention. Journal of Clinical Oncology. 2016; **34**: 1803-12. https://doi.org/10.1200/JCO.2016.67.2014
5. Barnard GA,. A New Test for 2 × 2 Tables. Nature. 1945; **156**: 783-784. https://doi.org/10.1038/156783b0
6. Barnard GA,. Significance Tests for 2 × 2 Tables. Biometrika. 1947; **34**: 123-138. https://doi.org/10.1093/biomet/34.1-2.123
7. Barukčić I,. Die Kausalität. Hamburg: Wissenschaftsverlag, 1989. pp. 218.
8. Barukčić I,. Die Kausalität. Wilhelmshaven: Scientia, 1997. pp. 374.
9. Barukčić I,. Causality. New Statistical Methods. Hamburg-Norderstedt: Books on Demand, 2005. pp. 488.
10. Barukčić I,. Causality. New Statistical Methods, Second English Edition. Hamburg-Norderstedt: Books on Demand, 2006a. pp. 488.
11. Barukčić I,. New method for calculating causal relationships. Proceeding of XXIIIrd International Biometric Conference. 2006b July 16-21; McGill University, Montréal, Québec, Canada. p. 49.
12. Barukčić I,. Causality I. A Theory of Energy, Time and Space. Morrisville: Lulu, 2011a. pp. 648.
13. Barukčić I,. Causality II. A Theory of Energy, Time and Space. Morrisville: Lulu, 2011b. pp. 376.
14. Barukčić I,. The deterministic relationship between cause and effect. International International Biometric Conference, Kobe, JAPAN, 26 - 31 August 2012.

https://www.biometricsociety.org/conference-abstracts/2012/programme/p1-5/P-1/249-P-1-30.pdf

15. Barukčić I,. The Mathematical Formula of the Causal Relationship k. International Journal of Applied Physics and Mathematics. 2016a; **6**: 45-65. https://doi.org/10.17706/ijapm.2016.6.2.45-65
16. Barukčić K, Barukčić I,. Epstein Barr Virus - The Cause of Multiple Sclerosis. Journal of Applied Mathematics and Physics. 2016b; **4**: 1042-53. https://doi.org/10.4236/jamp.2016.46109
17. Barukčić I,. Unified Field Theory. Journal of Applied Mathematics and Physics. 2016c; **4**: 1379-1438. https://doi.org/10.4236/jamp.2016.48147
18. Barukčić I,. Anti Bohr - Quantum Theory and Causality. International Journal of Applied Physics and Mathematics. 2017a; **7**: 93-111. https://doi.org/10.17706/ijapm.2017.7.2.93-111
19. Barukčić I,. Helicobacter pylori-The Cause of Human Gastric Cancer. Journal of Biosciences and Medicines. 2017b; **5**: 1-19. https://doi.org/10.4236/jbm.2017.52001
20. Barukčić I,. Theoriae causalitatis principia mathematica. Hamburg-Norderstedt: Books on Demand, 2017c. pp. 244. https://www.bod.de/buchshop/theoriae-causalitatis-principia-mathematica-ilija-barukcic-9783744815932
21. Bernal M, Burillo I, Mayordomo JI, Moros M, Benito R, Gil J,. Human papillomavirus (HPV) infection and intraepithelial neoplasia and invasive cancer of the uterine cervix: a case-control study in Zaragoza, Spain. Infectious Agents and Cancer. 2008; **29**: 1-4. https://doi.org/10.1186/1750-9378-3-8
22. Bochenski JM,. A history of formal logic, Translated and edited by Ivo Thomas. Notre Dame: University of Notre Dame Press. 1961; pp. 14/15.
23. Bosch FX, Manos M, Muñoz N, Sherman M, Jansen A, Peto J, et al. Prevalence of human papillomavirus in cervical cancer: a worldwide perspective. Journal of the National Cancer Institute. 1995; 87: 796-802. https://doi.org/10.1093/jnci/87.11.796
24. Bosch FX, Lorincz A, Munoz N, Meijer CJ, Shah KV,. The causal relation between human papillomavirus and cervical cancer. J Clin Pathol 2002; **55**: 244-65. http://jcp.bmj.com/content/55/4/244

25. Bosch FX, de Sanjosé S,. Chapter 1: Human Papillomavirus and Cervical Cancer-Burden and Assessment of Causality. Journal of the National Cancer Institute Monographs, 2013; **2003**: 3-13. https://doi.org//10.1093/oxfordjournals.jncimonographs.a003479
26. Chaouki N, Bosch FX, Muñoz N, Meijer CJ, El Gueddari B, El Ghazi A, Deacon J, Castellsagué X, Walboomers JM,. The viral origin of cervical cancer in Rabat, Morocco. International Journal of Cancer. 1998; **75**: 546-54. https://doi.org/10.1002/(SICI)1097-0215(19980209)75:4<546::AID-IJC9>3.0.CO;2-T
27. Chichareon S, Herrero R, Muñoz N, Bosch FX, Jacobs MV, Deacon J, Santamaria M, Chongsuvivatwong V, Meijer CJ, Walboomers JM,. Risk factors for cervical cancer in Thailand: a case-control study. Journal of the National Cancer Institut. 1998; **90**: 50-7. https://doi.org/10.1093/jnci/90.1.50
28. Clopper C, Pearson ES,. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika. 1934; **26**: 404-413. http://dx.doi.org/10.1093/biomet/26.4.404
29. Colón-López V, Ortiz AP, Del Toro-Mejías LM, García H, Clatts MC and Palefsky J,. Awareness and knowledge of human papillomavirus (HPV) infection among high-risk men of Hispanic origin attending a sexually transmitted infection (STI) clinic. BMC Infect Dis. 2012; **12**: 346. https://doi.org/10.1186/1471-2334-12-346
30. de Villiers EM, Wagner D, Schneider A, Wesch H, Miklaw H, Wahrendorf J, Papendick U, zur Hausen H,. Human papillomavirus infections in women with and without abnormal cervical cytology. Lancet. 1987; **2**: 703-706. https://doi.org/10.1016/j.canep.2010.12.006
31. Eluf-Neto J, Booth M, Muñoz N, Bosch FX, Meijer CJ, Walboomers JM,. Human papillomavirus and invasive cervical cancer in Brazil. British Journal of Cancer. 1994; **69**: 114-9. https://doi.org/10.1038/bjc.1994.18
32. Fisher RA,. On the interpretation of X^2 from contingency tables, and the calculation of P. Journal of the Royal Statistical Society. 1922; 85: 87-94. https://doi.org/10.2307/2340521
33. Franceschi S, Rajkumar T, Vaccarella S, Gajalakshmi V, Sharmila A, Snijders PJ, Muñoz N, Meijer CJ, Herrero R,. Human papillomavirus and risk factors for cervical cancer in Chennai, India: a case-control study. *Int J Cancer*. 2003; **107:** 127-133. https://doi.org/10.1002/ijc.11350
34. Hill AB,. The Environment and Disease: Association or Causation? *Proceedings of the Royal Society of Medicine*. 1965; **58**: 295-300. https://doi.org/10.1177/0141076814562718

35. Jovanovic BD, Levy PS,. A Look at the Rule of Three. The American Statistician. 1997; **51**: 137-139. https://doi.org/10.1080/00031305.1997.10473947
36. Leemis LM, Trivedi KS,. A Comparison of Approximate Interval Estimators for the Bernoulli Parameter. The American Statistician. 1996; **50**: 63-68. https://doi.org/10.2307/2685046
37. Louis TA. Confidence Intervals for a Binomial Parameter After Observing No Successes. The American Statistician. 1981; **35**: 154. https://doi.org/10.1080/00031305.1981.10479337
38. Moelling K,. What contemporary viruses tell us about evolution: a personal view. Archives of Virology. 2013; **158**: 1833-1848. https://doi.org/10.1007/s00705-013-1679-6
39. Ngelangel C, Muñoz N, Bosch FX, Limson GM, Festin MR, Deacon J, Jacobs MV, Santamaria M, Meijer CJ, Walboomers JM,. Causes of cervical cancer in the Philippines: a case-control study. Journal of the National Cancer Institute. 1998; **90**:43-9. https://doi.org/10.1093/jnci/90.1.43
40. Neyman, J,. Outline of a Theory of Statistical Estimation Based on the Classical Theory of Probability. Philosophical Transactions of the Royal Society A. 1937; **236**: 333–380. https://doi.org/10.1098/rsta.1937.0005
41. Pearson K,. VII. Mathematical contributions to the theory of evolution.- III. Regression, heredity, and panmixia. Philosophical Transactions of the Royal Society of London. Ser. A. 1896; **187**: 253-18. https://doi.org/10.1098/rsta.1896.0007
42. Pearson K,. On the Criterion That a Given System of Deviations from the Probable in the Case of a Correlated System of Variables Is Such That It Can Be Reasonably Supposed to Have Arisen from Random Sampling. Philosophical Magazine Series. 1900; **5**: 157-175. http://dx.doi.org/10.1080/14786440009463897
43. Pearson K,. Mathematical contributions to the theory of evolution. - XIII. On the Theory of Contingency and Its Relation to Association and Normal Correlation. London, Dulau and Co., 1904. pp. 1-35. https://archive.org/details/cu31924003064833
44. Pisani P, Parkin M, Baray F, Ferlay J Estimates of the worldwide mortality from 25 cancers in 1990. International Journal of Cancer. 1999; **83**: 18-29. https://doi.org/10.1002/(SICI)1097-0215(19990924)83:1<18::AID-IJC5>3.0.CO;2-M
45. Pisani P, Bray F, Parkin DM Estimates of the world-wide prevalence of cancer for 25 sites in the adult population. International Journal of Cancer. 2002; **97**: 72-81. https://doi.org/10.1002/ijc.1571

46. Rolón PA, Smith JS, Muñoz N, Klug SJ, Herrero R, Bosch X, Llamosas F, Meijer CJ, Walboomers JM,. Human papillomavirus infection and invasive cervical cancer in Paraguay. International Journal of Cancer. 2000; **85**:486-91. https://doi.org/10.1002/(SICI)1097-0215(20000215)85:4<486::AID-IJC7>3.0.CO;2-S

47. Rumke CL,. Implications of the Statement: No Side Effects Were Observed. N Engl J Med. 1975; **292**: 372-373. https://doi.org/10.1056/NEJM197502132920723

48. Thompson ME Reviews. Causality. New statistical methods. I. Barukcic. Short book review. International Statistical Institute. 2006; **26**: 6. http://isi.cbs.nl/sbr/images/V26-1_Apr06.pdf

49. Tommasino M,. The human papillomavirus family and its role in carcinogenesis. Semin Cancer Biol. 2014; **26**: 13-21, https://doi.org/10.1016/j.semcancer.2013.11.002

50. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A Global cancer statistics, 2012. CA Cancer J Clin. 2015; **65**: 87-108. https://doi.org/10.3322/caac.21262

51. Walboomers JMM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, ShahKV, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol. 1999; **189**:12–19. https://doi.org/10.1002/(SICI)1096-9896(199909)189:1<12::AID-PATH431>3.0.CO;2-F