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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. One objective of this study was to conduct a qualitative systematic review of some case-control studies and to examine the role of human papillomavirus (HPV) in the development of human cervical cancer (CC) 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 and cervical cancer? The method of the conditio sine qua non relationship was used to proof the hypothesis whether the presence of human papillomavirus guarantees the presence of cervical carcinoma. In other words, if human cervical cancer is present, then human papillomavirus 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 and cervical carcinoma. Significance was indicated by a p-value of less than 0.05. **Result:** The studies analyzed (sample size N = 7657) were able to provide strict evidence that human papillomavirus is a necessary condition (a conditio sine qua non) of cervical carcinoma. Furthermore, the studies analyzed provide impressive evidence of a cause-effect relationship (k = +0.723669245, p value < 0.00001) between human papillomavirus and cervical carcinoma. **Conclusion:** Human papillomavirus is the cause of human cervical carcinoma.

Keywords

Human Papillomavirus, Cervical Cancer, Cause Effect Relationship, Causality

1. 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 [1] [2] most common cancer in women worldwide, and is 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 [3]. Human papillomavirus is considered to be one of the most important risk factors in the development of cervical cancer while sexual transmission is the predominant route of HPV infection. 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.

2. Material and Methods

Human cervical cancer can be a deadly disease too. Identifying the cause of cervical cancer of is of strategic importance in public health.

2.1. 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 investigated the relationship between human papilloma virus and cervical cancer at least by polymerase chain reaction (PCR). The search in Pubmed was performed while using medical key words like "case control study" and "human papilloma virus" and "cervical carcinoma" and "PCR DNA" et cetera. The articles found where saved as a *.txt file while using Pubmed support (Menu: Send to, Choose Radio Button: File, Choose Format: Abstract (text). Click button "create file"). The created *.txt file was converted into a *.pdf file. The abstracts where studied within the *.pdf file. Those articles were considered for a review which provided access to data without any data access barrier.

2.2. The Data of the Studies Analyzed

Novel laboratory techniques [4] (Southern Blot hybridization, Immunohistochemistry (IHC), introduced by Coons [5] in 1941, *In-situ* hybridization (ISH), described in the year 1969 by Joseph G. Gall [6], Fluorescent ISH (FISH), RNA *in situ* hybridization (RNA ISH), Polymerase chain reaction (PCR), Nested PCR,

Quantitative polymerase chain reaction (QPCR) et cetera) can improve our understanding of the pathogenesis of diseases. In principle, it is possible to distinguish between benign and malignant cell populations (Immunohistochemistry (IHC)) or to distinguish virus in tumor cells from virus in non-tumor cells (*In situ* hybridization (ISH)) et cetera. Still, false positive or false negative results or bias is possible. In the light of thoughts like these, the data of the studies analyzed are presented by table (Table 1). The meaning of the abbreviations a_t, b_t, c_t, d_t, N_t of Table 1 (Table 1) and Table 2 (Table 2) are explained by a 2 by 2-table (Table 3).

Table 1. Human papillomavirus PCR DNA and human cervical cancer due to the studies analysed.

Author	Year	Country	a_t	b_t	c_t	d_t	$a_t + b_t + d_t$	$a_t + b_t + c_t + d_t = N_t$	$(a_t + b_t + d_t)/N_t$
								Sample size	(SINE)
Eluf-Neto *et al.*, 1994 [7]	1994	Brazil	167	38	32	187	392	424	0.924528302
Ngelangel *et al.*, 1998 [8]	1998	Philippines	333	35	23	346	714	737	0.968792402
Chichareon *et al.*, 1998 [9]	1998	Thailand	356	42	21	219	617	638	0.967084639
Chaouki *et al.*, 1998 [10]	1998	Morocco	176	38	10	147	361	371	0.973045822
Rolón *et al.*, 2000 [11]	2000	Paraguay	109	18	4	73	200	204	0.980392157
Franceschi *et al.*, 2003 [12]	2003	India	204	59	1	154	417	418	0.997607656
Asato *et al.*, 2004 [13]	2004	Japan	311	333	45	2916	3560	3605	0.987517337
Bernal *et al.*, 2008 [14]	2008	Spain	56	210	4	990	1256	1260	0.996825397
		Total	1712	773	140	5032	7517	7657	0.981716077

Table 2. Without a human papillomavirus infection no human cervical cancer.

Author	Year	Country	$a_t + b_t + d_t$	N_t	$(a_t + b_t + d_t)/N_t$	X^2 (Sine)	k	p value (k)
Eluf-Neto *et al.*, 1994 [7]	1994	Brazil	392	424	0.924528302	4.53082192	0.66941066	3.18104E−43
Ngelangel *et al.*, 1998 [8]	1998	Philippines	714	737	0.968792402	1.37195122	0.84304507	6.2931E−116
Chichareon *et al.*, 1998 [9]	1998	Thailand	617	638	0.967084639	1.75104167	0.79508743	1.04251E−89
Chaouki *et al.*, 1998 [10]	1998	Morocco	361	371	0.973045822	0.57484076	0.74972995	2.8642E−47
Rolón et al., 2000 [11]	2000	Paraguay	200	204	0.980392157	0.15909091	0.78631137	2.87949E−29
Franceschi *et al.*, 2003 [12]	2003	India	417	418	0.997607656	0.0016129	0.7432314	3.7933E−52
Asato *et al.*, 2004 [13]	2004	Japan	3560	3605	0.987517337	0.66877744	0.60055085	1.0309E−284
Bernal *et al.*, 2008 [14]	2008	Spain	1256	1260	0.996825397	0.01232394	0.39572399	8.05848E−45
		Total	7517	7657	0.981716077	9.07046076	0.723669245	
					Alpha =	0.05		
					Degrees of freedom =	8	Degr. of fr. =	1
					X^2 (Critical) SINE =	15.5073131	Chi crit. k =	3.841458821
					X^2 (Calculated) SINE =	9.07046076	X^2 calc. (k) =	4009.949276
							K =	0.723669245

Table 3. The sample space of a contingency table.

		Conditioned B_t (Human cervical carcinoma)		
		Yes = +1	**Not = +0**	**Total**
Condition A_t (HPV PCR DNA pos.)	Yes = +1	a_t	b_t	A_t
	Not = +0	c_t	d_t	$\underline{A}_t$
	Total	B_t	$\underline{B}_t$	N_t

2.3. Statistical Analysis

All statistical analyses were performed with Microsoft Excel version 14.0.7166.5000 (32-Bit) software (Microsoft GmbH, Munich, Germany). In order to simplify the understanding of this article, to increase the transparency for the reader and to correct some of the misprints of former publications, several of the following lines are repeated word by word and taken from former publications.

2.3.1. The 2 × 2 Table

The 2 × 2 table in this article is defined [15]-[37] in general more precisely (Table 3) as follows.

In general it is $(a_t + b_t) = A_t$, $(c_t + d_t) = \underline{A}_t$, $(a_t + c_t) = B_t$, $(b_t + d_t) = \underline{B}_t$ and $a_t + b_t + c_t + d_t = N_t$. Equally, it is $B_t + \underline{B}_t = A_t + \underline{A}_t = N_t$. In this context, it is $p(a_t) = p(A_t \cap B_t)$, $p(A_t) = p(a_t) + p(b_t)$ or in other words $p(A_t) = p(A_t \cap B_t) + p(b_t) = p(A_t \cap B_t) + p(A_t \cap \underline{B}_t)$ while $p(A_t)$ is not defined as $p(a_t)$. In the same context, it is $p(B_t) = p(a_t) + p(c_t) = p(A_t \cap B_t) + p(c_t)$ and equally that $p(\underline{B}_t) = 1 - p(B_t) = p(b_t) + p(d_t)$. Furthermore, the joint probability of A_t and B_t is denoted by $p(A_t \cap B_t)$. Thus far, it is $p(A_t \cap B_t) = p(A_t) - p(b_t) = p(B_t) - p(c_t)$ or in other words it follows that $p(B_t) + p(b_t) - p(c_t) = p(A_t)$. Define $\Lambda = p(b_t) - p(c_t)$, the famous Einstein's term under conditions of probability theory and we obtain $p(B_t) + \Lambda = p(A_t)$. In general, it is $p(a_t) + p(c_t) + p(b_t) + p(d_t) = 1$. These relationships are viewed by the table (Table 4) as follows.

2.3.2. Independence

In the case of independence of A_t and B_t it is

$$p(A_t \cap B_t) \equiv p(A_t) \times p(B_t) \tag{1}$$

2.3.3. Necessary Condition (Conditio Sine qua Non)

The mathematical formula of the *necessary* condition relationship (conditio sine quam non) [15]-[37] of a population was defined as

$$p(A_t \leftarrow B_t) \equiv \frac{a_t + b_t + d_t}{N_t} \equiv +1 \tag{2}$$

and used to proof the hypothesis: *without* A_t *no* B_t. In particular it is

Table 4. The probabilities of a contingency table.

		Conditioned B_t		Total
		Yes = +1	**No = +0**	
Condition A_t	Yes = +1	$p(a_t) = \mathrm{p}(A_t \cap B_t)$	$p(b_t)$	$p(A_t)$
	No = +0	$p(c_t)$	$p(d_t)$	$p(\underline{A}_t)$
	Total	$p(B_t)$	$p(\underline{B}_t)$	1

$$\begin{aligned} p(A_t \leftarrow B_t) &\equiv p(a_t) + p(b_t) + p(d_t) \\ p(A_t \leftarrow B_t) &\equiv p(A_t \cap B_t) + p(\underline{B}_t) \\ p(A_t \leftarrow B_t) &\equiv p(A_t \cap B_t) + (1 - p(B_t)) \\ p(A_t \leftarrow B_t) &\equiv +1 \end{aligned} \tag{3}$$

Scholium.

The study design and other factors can have an impact on bias with respect to the necessary condition. A different question worth asking concerns the relationship between the independence of an event A_t (a condition) and another event B_t (conditioned) and the necessary condition relationship. A fundamental question worth considering at this stage is whether is it possible that an event A_t is a necessary condition of event B_t an even if the event A_t (a necessary condition) is independent of an event B_t (the conditioned). In this context, the conditio sine qua non was defined as

$$p(A_t \leftarrow B_t) \equiv p(A_t \cap B_t) + p(\underline{B}_t) \equiv +1 \tag{4}$$

or as

$$p(A_t \leftarrow B_t) \equiv p(A_t \cap B_t) + (1 - p(B_t)) \equiv +1 \tag{5}$$

Under conditions where an event A_t is *independent* of an even B_t it is equally true that

$$p(A_t \cap B_t) \equiv p(A_t) \times p(B_t) \tag{6}$$

Rearranging equation before it is

$$p(A_t) \times p(B_t) + (1 - p(B_t)) \equiv +1 \tag{7}$$

or

$$p(A_t) \times p(B_t) \equiv p(B_t) \tag{8}$$

or

$$p(A_t) \equiv +1. \tag{9}$$

Only under conditions where $p(A_t) = 1$, theoretically it is possible to treat A_t as a necessary condition of B_t even if A_t is independent of B_t and vice versa, otherwise not. In other words, it is very difficult to treat a statistically significant conditio sine qua non relationship as very convincing if at the same time an

event A_t is independent of and event B_t and vice versa. While discussing the statistical significance of results with respect to a necessary condition (or a sufficient condition or a necessary and sufficient condition), such or similar arguments should be considered. Due to an inappropriate study design or other sources of possible bias, the statistical significance of a conditio sine qua non relationship should be treated with very great cautious if evidence is provided that at the same time the same investigated parameters are independent of each other.

2.3.4. The X^2 Goodness of Fit Test of a Necessary Condition

Under some circumstances, the rule three and other methods can be used to test the significance of a necessary condition. In this publication, the chi-square [38] goodness of fit test was used to determine whether sample data are consistent with a hypothesized (theoretical) distribution of a necessary condition. In particular, the hypotheses can take the following form.

H_0: The sample distribution does agree with the hypothetical (theoretical) distribution of a necessary condition.

H_A: The sample distribution does not agree with the hypothetical (theoretical) distribution of a necessary condition.

The X^2 Goodness-of-Fit Test can be shown schematically as

$$\chi^2 \equiv \sum_{t=+1}^{t=+N} \left(\frac{\left(\text{Observed}_t - \text{Expected}_t\right)^2}{\text{Expected}_t} \right) \tag{10}$$

The degrees of freedom are calculated as $N - 1$. Interestingly, if there is no discrepancy between an observed and a theoretical distribution at all, then the value of the calculated $X^2 = 0$. As the discrepancy between an observed and the theoretical distribution of a necessary condition becomes larger, the X^2 becomes larger. This X^2 values are evaluated by the known X^2 distribution. An adjustment (*Yate's correction for continuity*) can be used when there is one degree of freedom. When there is more than one degree of freedom, the same adjustment is not used. Applying this to the formula above, we find the X^2 Goodness-of-Fit Test *with continuity correction* shown schematically as

$$\chi^2 \equiv \sum_{t=+1}^{t=+N} \left(\frac{\left(\left|\text{Observed}_t - \text{Expected}_t\right| - \left(\frac{1}{2}\right) \right)^2}{\text{Expected}_t} \right) \tag{11}$$

Under circumstances, where the term ($|\text{Observed}_t - \text{Expected}_t|$) is less than 1/2, the continuity correction should be omitted. The theoretical (hypothetical) distribution of a necessary condition is shown schematically by the 2 × 2 table (**Table 5**).

The theoretical distribution of a necessary condition (conditio sine qua non) is determined by the fact that $c_t = 0$. The X^2 Goodness-of-Fit Test *with continuity correction* of a necessary condition (conditio sine qua non) is calculated as

Table 5. The theoretical distribution of a necessary condition (conditio sine qua non).

		Conditioned		Total
		Yes = +1	No = +0	
Condition	Yes = +1	a_t	b_t	$(a_t + b_t)$
	No = +0	$c_t = 0$	d_t	$(c_t + d_t)$
	Total	$(a_t + c_t)$	$(b_t + d_t)$	$(a_t + b_t + c_t + d_t)$

$$\chi^2(\text{SINE}) \equiv \left(\frac{\left(\left| (a+b) - (a+b) \right| - \left(\frac{1}{2} \right) \right)^2}{(a+b)} \right) + \left(\frac{\left(\left| (d) - (c+d) \right| - \left(\frac{1}{2} \right) \right)^2}{(c+d)} \right) = 0 + \left(\frac{\left(\left| d - (c+d) \right| - \left(\frac{1}{2} \right) \right)^2}{(c+d)} \right) \quad (12)$$

or more simplified as

$$\chi^2(\text{SINE}) \equiv \left(\frac{\left(\left| -c \right| - \left(\frac{1}{2} \right) \right)^2}{(c+d)} \right) + 0 \quad (13)$$

Under these circumstances, the degree of freedom is d.f. $= N - 1 = 2 - 1 = 1$. The *conditio sine qua non model* can be used widely and is one of the new and appropriate methods of analysis of binary outcome variables. In this context, *meta-analysis and systematic reviews* aims to combine effects estimated from several studies to achieve greater precision of the conclusions drawn and can provide us with more convincing and reliable evidence of some special aspects of medicine. In meta-analysis the heterogeneity between the studies can be modelled via the additive properties of the chi square distribution too. In general, let X_t denote n independent random variables which follow a chi-square distribution. The sum of these independent chi-square variates is itself a chi-square variate which is known as the additive property of independent chi-squares. There may be disadvantages in the use of the chi-square-goodness-of-fit test. Still, the chi square distribution, a continuous probability distribution, is related to the standard normal distribution and is a simple and good measure of model adequacy. However, a particular concern with the use of the chi-square-goodness-of-fit test is a priori justified if expected cell frequencies of a 2 × 2 table are too small (all are less than one).

2.3.5. The Mathematical Formula of the Causal Relationship *k*

Huxley [38] and Darwin [39] claimed more than a century ago that humans share recent common ancestors with the African apes. Modern molecular me-

thods have spectacularly confirmed their prediction. Genomic divergences between humans and other hominoids and especially our closest living evolutionary relatives the common chimpanzee (*Pan troglodytes*) and bonobo (*Pan paniscus* or pygmy chimpanzee) are very small but not zero. Ebersberger *et al.* [40], Fujiyama *et al.* [41] and other sequenced the chimpanzee genome. According to Ebersberger *et al.* "the chimpanzee genome were sequenced and compared to corresponding human DNA sequences ... the average sequence difference is low (1.24%)" [40]. The Chimpanzee Sequencing and Analysis Consortium calculated "the genome-wide nucleotide divergence between human and chimpanzee to be 1.23%" [42] and confirmed results from other and more limited studies. In other words, the difference between chimpanzee genome and compared to corresponding human DNA sequences is very small. Still there is a difference and this very small difference makes the difference. A chimpanzee is not a human being, a human being is not a chimpanzee. Even if both are similar and "relatives" both are equally not the same. The relationship between the mathematical formula of the causal relationship k [15]-[37] and the closest existing mathematical relatives, Pearson's measures of relationships, is similar to the circumstances aforementioned. In contrast to Pearson's product-moment correlation coefficient [43] or to Pearson's Phi [44] Coefficient (Mean Square Contingency Coefficient et cetera), the mathematical formula of the causal relationship k [15]-[37] is defined *at every single event*, *at every single Bernoulli trial t*, as

$$k\left({}_{R}U_{t},{}_{0}W_{t}\right)\equiv\frac{\left(p\left({}_{R}U_{t}\times{}_{0}W_{t}\right)-\left(p\left({}_{R}U_{t}\right)\times p\left({}_{0}W_{t}\right)\right)\right)}{\sqrt[2]{\left(p\left({}_{R}U_{t}\right)\times p\left({}_{R}\underline{U}_{t}\right)\right)\times\left(p\left({}_{0}W\right)\times p\left({}_{0}\underline{W}_{t}\right)\right)}} \tag{14}$$

where ${}_{R}U_{t}$ denotes the cause and ${}_{0}W_{t}$ denotes the effect while the chi-square distribution [45] can be applied to determine the significance of causal relationship k. This small difference makes the difference. Only under conditions where *the probability of events is constant from trial to trial*, we can extrapolate *from one Bernoulli trial to N Bernoulli trials* with some consequences one of which is that

$$k\left({}_{R}U_{t},{}_{0}W_{t}\right)\equiv\frac{N\times N\times\left(p\left({}_{R}U_{t}\times{}_{0}W_{t}\right)-\left(p\left({}_{R}U_{t}\right)\times p\left({}_{0}W_{t}\right)\right)\right)}{N\times N\times\sqrt[2]{\left(p\left({}_{R}U_{t}\right)\times p\left({}_{R}\underline{U}_{t}\right)\right)\times\left(p\left({}_{0}W\right)\times p\left({}_{0}\underline{W}_{t}\right)\right)}} \tag{15}$$

or that

$$k\left({}_{R}U_{t},{}_{0}W_{t}\right)\equiv\frac{\left(N\times N\times p\left({}_{R}U_{t}\times{}_{0}W_{t}\right)-\left(N\times p\left({}_{R}U_{t}\right)\times N\times p\left({}_{0}W_{t}\right)\right)\right)}{\sqrt[2]{\left(N\times p\left({}_{R}U_{t}\right)\times N\times p\left({}_{R}\underline{U}_{t}\right)\right)\times\left(N\times p\left({}_{0}W\right)\times N\times p\left({}_{0}\underline{W}_{t}\right)\right)}} \tag{16}$$

or at the end

$$k\left({}_{R}U_{t},{}_{0}W_{t}\right)\equiv\frac{\left(\left(N\times a_{t}\right)-\left({}_{R}U_{t}\times{}_{0}W_{t}\right)\right)}{\sqrt[2]{\left({}_{R}U_{t}\times{}_{R}\underline{U}_{t}\right)\times\left({}_{0}W\times{}_{0}\underline{W}_{t}\right)}} \tag{17}$$

where N is the sample size, $a_{t}=N\times p\left({}_{R}U_{t}\cap{}_{0}W_{t}\right)$, ${}_{R}U_{t}=N\times p\left({}_{R}U_{t}\right)$, ${}_{R}\underline{U}_{t}=N\times p\left({}_{R}\underline{U}_{t}\right)$, ${}_{0}W_{t}=N\times p\left({}_{0}W_{t}\right)$, ${}_{0}\underline{W}_{t}=N\times p\left({}_{0}\underline{W}_{t}\right)$. Several factors can have an impact on the calculated causal relationship k with the potential of bias.

Scholium.

Firstly, the relationship between condition and cause has an impact on the causal relationship k. A proper and deeper analysis of the relationship between cause and condition is beyond the scope of this article and can be found in literature [15]-[37]. We will be concerned with the latter sort of entity in this article from a pragmatically point of view. In the hope of casting light on the tricky problems of the relationship between condition and cause, the concept of independence is of use too. The question whether an event A_t can be a (necessary, sufficient, necessary and sufficient) condition of an event B_t even if both are independent of each other, is already answered few lines before. Still, under which circumstances can we treat an event as a cause or as the cause of another event? Can an event be a cause of another event without being a (necessary, sufficient, necessary and sufficient et cetera) condition of the same event? The concept of this article is restricted on its capacity to bring high degrees of conceptual exactness and rigour to questions like these but not incapable. Most authors who have written on the question of the relationship between condition and cause came to different conclusions. Currently still worthy of consideration is the remark of von Bar.

"Die erste Voraussetzung, welche erforderlich ist, damit eine Erscheinung als die Ursache einer anderen bezeichnet werden könne, ist, daß jene eine der Bedingungen dieser sein. Würde die zweite Erscheinung auch dann eingetreten sein, wenn die erste nicht vorhanden war, so ist sie in keinem Falle Bedingung und noch weniger Ursache. Wo immer eine Kausalzusammenhang behauptet wird, da muß er wenigstens diese Probe aushalten… Jede Ursache ist nothwendig auch eine Bedingung eines Ereignisses; aber nicht jede Bedingung ist Ursache zu nennen." [46]

Translated into English:

"The first requirement, which is required, thus that something could be called as the cause of another, is that the one has to be one of the conditions of the other. If the second something had occurred even if the first one did not exist, so it is by no means a condition and still less a cause. Wherever a causal relationship is claimed, the same must at least withstand this test… Every cause is necessarily also a condition of an event too; but not every condition is cause too."

From this statement, it could appear that there is a gap between what is a cause and what is a condition. Is it possible to generalize this finding? In probabilistic approaches to causation, it is obvious that a cause of an event is equally a condition of the same event too. Clearly, the same relationship must not be given the other way too. A condition of an event must not equally be a cause of the same event. In summary, the objections build on the contradiction between condition and cause are no longer justified. A cause is a condition of an event too but not necessarily vice versa. A condition of an event must not be equally the cause of the same event. Thus far, like other fundamental concepts, the concepts of necessary conditions, the concepts of sufficient conditions and the con-

cepts of necessary and sufficient conditions can be one of the handy tools to determine precisely whether a causal relationship is significant or not. A study which provides evidence of a significant causal relationship k without at the same time providing evidence of a significant necessary condition, or of a significant sufficient condition or of a significant necessary and sufficient condition should be treated with some cautious.

Secondly, a proper study design is necessary to use the mathematical formula of the causal relationship k with confidence otherwise bias is possible. For example, the probabilities of two events within a population are know precisely and shown schematically by the 2 × 2 table (Table 6).

The causal relationship k (Table 6) is calculated as $k = +0.314800094$. Using the conditional probabilities, we obtain the following picture (Table 7).

Now we perform a study A with a sample size of $n = 10{,}000$. The *verum group* is $n_{\text{Verum}} = n/2 = 5000$ and the *placebo group* is $n_{\text{Placebo}} = n/2 = 5000$. We do expect that the probabilities within the sample are the same like in the population. Under these conditions we obtain the following picture (Table 8).

Thus far, this study has provided the following data (Table 9).

Calculating the causal relationship k under these conditions, we obtain

$$k\left({}_{R}U_{t}, {}_{0}W_{t}\right) \equiv \frac{\left(\left(\left((10000)\times(4955)\right)\right)-\left(\left((5000)\times(4955)\right)\right)\right)}{\sqrt[2]{\left((4955)\times(5045)\right)\times\left((5000)\times(5000)\right)}} = +0.991031209 \quad (18)$$

Table 6. The probabilities within a population.

		Effect		Total
		Yes = +1	No = +0	
Cause	Yes = +1	0.99	0.009	0.999
	No = +0	0	0.001	0.001
	Total	0.99	0.1	1

Table 7. The data of the study A.

		Effect		Total
		Yes = +1	No = +0	
Cause	Yes = +1	(0.99/0.999)	(0.009/0.999)	1
	No = +0	0	(0.001/0.001)	1
	Total	(0.99/0.999)	(2-(0.99/0.999))	2

Table 8. The data of the study A.

		Effect		Total
		Yes = +1	No = +0	
Cause	Yes = +1	(0.99/0.999) × 5000	(0.009/0.999) × 5000	1 × 5000
	No = +0	0 × 5000	(0.001/0.001) × 5000	1 × 5000
	Total	(0.99/0.999) × 5000	(2-(0.99/0.999)) × 5000	2 × 5000

Table 9. The data of the study A.

		Effect		Total
		Yes = +1	No = +0	
Cause	Yes = +1	4955	45	5000
	No = +0	0	5000	5000
	Total	4955	5045	10,000

a causal relationship k of k = +0.991031209. The study with the sample size n = 10,000 should have obtained a causal relationship k = +0.314800094 while the same obtained a causal relationship k = +0.991031209. This example demonstrates that the study design as such can be a source of bias if inappropriate measures are taken. To reduce the bias, it makes sense to *consider the prevalence of a factor/an event within the population as much as possible as an essential part of study design*. According to the data above, the prevalence of a cause within the population is $p({}_{R}U_{t})$ = 0.999. The sample size of the study is still n = 10,000. Under these assumptions, the sample size of *the verum group* should be considered as $n_{\text{Verum}} = p\left({}_{R}U_{t}\right)\times n = 0.999\times 10000 = 9900$ while the sample size of *the placebo group* is $n_{\text{Placebo}} = p\left({}_{R}\underline{U}_{t}\right)\times n = 0.001\times 10000 = 1$ (Table 10).

The causal relationship k (Table 10) is calculated as k = +0.314800094. The situation does not really change if *a case control study* is regarded. If the same problem is analysed within a case control approach, this should not have any systematic influence on the probabilities (Table 11) of the sample studied.

Let us assume that the sample size of this case control study B is n = 1000, with 500 cases and 500 controls. We obtain the following data (Table 12).

The data of this case control study (Table 12) are demanding that the causal relationship k is equal to k = +0.229415734 while the same causal relationship k should be equal to k = +0.314800094 what motivates us to affirm the following conclusion. *Inappropriate study design can lead to severe bias*. Given the difficulty of the problems as associated with study design it is useful to adopt *a strategy of extreme caution under conditions* when the data of a study provide evidence of a significant cause effect relationship but fails in the same respect to provide some evidence of a significant necessary condition relationship or of a significant sufficient condition relationship or of a significant necessary and sufficient condition relationship otherwise conclusions may run into difficulties.

2.3.6. The Chi Square Distribution

The chi-squared distribution [38] 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 Table 13.

2.3.7. The X^2 Goodness of Fit Test of a Causal Relationship k

Under some circumstances the chi-square [45] goodness of fit test can be used to

Table 10. The impact of study design on the causal relationship *k*.

		Effect		Total
		Yes = +1	**No = +0**	
Cause	Yes = +1	0.99 × 10000	0.009 × 10000	9990
	No = +0	0 × 10000	0.001 × 10000	10
	Total	9900	100	10,000

Table 11. The data of the case control study B.

		Effect		Total
		Yes = +1	**No = +0**	
Cause	Yes = +1	(0.99/0.99)	(0.009/0.01)	(2-(0.001/0.01))
	No = +0	0	(0.001/0.01)	(0.001/0.01)
	Total	1	1	2

Table 12. The data of the case control study B.

		Effect		Total
		Yes = +1	**No = +0**	
Cause	Yes = +1	(0.99/0.99)) × 500	(0.009/0.01) × 500	950
	No = +0	0 × 500	(0.001/0.01) × 500	50
	Total	500	500	1000

Table 13. 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

test the significance of a causal relationship. Under conditions where *the probability of events is constant from trial to trial*, we expect a constant causal relationship k_t. In other words, at each Bernoulli trial t it is

$$\left|k\left({}_{R}U_{t}, {}_{0}W_{t}\right)\right| \equiv |1| \tag{19}$$

Performing N Bernoulli trials (Sample size N), the basic relationship will not change. It follows that

$$N \times \left|k\left({}_{R}U_{t}, {}_{0}W_{t}\right)\right| \equiv N \times |1| \tag{20}$$

or that

$$N \times \left|k\left({}_{R}U_{t}, {}_{0}W_{t}\right)\right| - N \times |1| = 0 \tag{21}$$

Simplifying equation we obtain

$$N \times \left(\left|k\left({}_{R}U_{t}, {}_{0}W_{t}\right)\right| - |1|\right) = 0 \tag{22}$$

Multiplying equation by itself it is

$$N \times \left(\left|k\left({}_{R}U_{t}, {}_{0}W_{t}\right)\right| - |1|\right) \times N \times \left(\left|k\left({}_{R}U_{t}, {}_{0}W_{t}\right)\right| - |1|\right) = 0 \times 0 \tag{23}$$

or

$$N^2 \times \left(\left|k\left({}_{R}U_{t}, {}_{0}W_{t}\right)\right| - |1|\right)^2 = 0 \tag{24}$$

Dividing equation by $N^* |1| = N$, we obtain

$$\frac{N^2 \times \left(\left|k\left({}_{R}U_{t}, {}_{0}W_{t}\right)\right| - |1|\right)^2}{N} = \frac{0}{N} = 0 \tag{25}$$

or

$$N \times \left(\left|k\left({}_{R}U_{t}, {}_{0}W_{t}\right)\right| - |1|\right)^2 = 0 \tag{26}$$

or the X^2 value as

$$\chi^2 = N \times \left(\left|k\left({}_{R}U_{t}, {}_{0}W_{t}\right)\right| - |1|\right)^2 = 0 \tag{27}$$

The chi square (X^2) statistic can be used to investigate whether the observed distribution of the causal relationship differ from the theoretical expected distribution of the causal relationship. The table (Table 8) contains the critical values of the chi-square distribution (degrees of freedom, df = 1). Upper-tail and lower-tail critical values of the chi-square distribution with v degrees of freedom are provided by software packages.

3. Results

3.1. Without the Presence of Human Papillomavirus DNA No Human Cervical Cancer

Claims.

Null hypothesis:

The presence of human papillomavirus DNA is a necessary condition (a condi-

tio sine qua non) of human cervical cancer. In other words, the sample distribution agrees with the hypothetical (theoretical) distribution of a necessary condition.

Alternative hypothesis:

The presence of human papillomavirus DNA is not a necessary condition (a conditio sine qua non) of human cervical cancer. In other words, the sample distribution does not agree with the hypothetical (theoretical) distribution of a necessary condition.

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

Proof.

The data reviewed by this article which investigated the relationship between the presence of human papillomavirus DNA and human cervical cancer are viewed by the table (Table 1). Altogether, 8 studies with $N = 7657$ cases and controls were meta-analyzed while the level of significance was alpha = 0.05. Under these circumstances (degrees of freedom = 8, alpha = 0.05) the calculated Chi-square value (Chi-square Goodness-of-Fit Test with continuity correction) of a necessary condition (conditio sine qua non) is equal to X^2 Calculated (SINE) = 9.070460764. The critical Chi square can be obtained (degrees of freedom = 8, alpha = 0.05) as X^2 Critical = 15.50731306. In particular, due to the data of the studies meta-analyzed, human papillomavirus DNA and human cervical cancer are not independent (degrees of freedom = 1, Chi-square value calculated = 4009.949276) of each other. The detailed calculations are shown by the table (Table 2). Furthermore, the calculated Chi square value of the necessary condition (X^2 Calculated (SINE) = 9.070460764) is less than the critical Chi square value (X^2 Critical =15.50731306). Due to this evidence, we do not reject the null hypothesis in favor of the alternative hypotheses. The data as published by studies presented by the table (Table 1) do support our Null hypothesis that the sample distribution of the studies analyzed agrees with the hypothetical (theoretical) distribution of a necessary condition. In point of fact, the presence of human papillomavirus DNA is a necessary condition (a conditio sine qua non) of human cervical cancer. In other words, without the presence of human papillomavirus DNA no human cervical cancer.

Q. e. d.

3.2. Human Papillomavirus Is the Cause of Human Cervical Cancer

Claims.

Null hypothesis: (no causal relationship, $k = 0$)

There is no causal relationship between human papillomavirus and human cervical cancer.

Alternative hypothesis: (causal relationship, $k \neq 0$)

There is a causal relationship between human papillomavirus and human cervical cancer.

Conditions.

Alpha level = 5%. The two tailed critical Chi square value (degrees of free-

dom = 1) for alpha level 5% is 3.841458821.

Proof.

The data for this hypothesis test are illustrated in the 2 × 2 table (Table 14).

The causal relationship k (HPV DNA, Human cervical cancer) is calculated [15]-[37] as

$$k\left(\text{HPV DNA}, \text{CC}\right)=\frac{\left(\left(7657\times 1712\right)-\left(2458\times 1852\right)\right)}{\sqrt[2]{\left(1852\times 5805\right)\times\left(2485\times 5172\right)}}=+0.723669245$$

The value of the test statistic k = +0.723669245 is equivalent to a calculated [15]-[37] chi-square value of

$$\chi^2_{\text{Calculated}}=7657\times\left(\frac{\left(\left(7657\times 1712\right)-\left(2458\times 1852\right)\right)}{\sqrt[2]{\left(1852\times 5805\right)\times\left(2485\times 5172\right)}}\right)\times\left(\frac{\left(\left(7657\times 1712\right)-\left(2458\times 1852\right)\right)}{\sqrt[2]{\left(1852\times 5805\right)\times\left(2485\times 5172\right)}}\right)$$

$$\chi^2_{\text{Calculated}}=7657\times 0.723669245\times 0.723669245$$

$$\chi^2_{\text{Calculated}}=4009.949276$$

The chi-square statistic, uncorrected for continuity, is calculated as X^2 = 4009.949276 and thus far equivalent to a p value of $p < 0.00001$. The calculated chi-square statistic exceeds the critical chi-square value of 3.841458821 (Table 13). Consequently, we reject the null hypothesis and accept the alternative hypotheses. There is a highly significant causal relationship between (k = +0.723669245, p value < 0.00001) human papillomavirus and human cervical cancer. The result is significant at $p < 0.00001$.

Q. e. d.

4. 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

Table 14. The causal relationship between HPV and cervical cancer.

		Human cervical cancer		Total
		Yes	No	
Human papillomavirus PCR DNA	Yes	1712	773	2485
	No	140	5032	5172
	Total	1852	5805	**7657**
	$p\left(A_t \leftarrow B_t\right)=$	0.981716077		
	$X^2\left(A_t \leftarrow B_t\right)=$	9.070460764		
	$k\left(A_t B_t\right)=$	0.723669245		
	p value (k)<	0.00001		

specimens of cervical cancer, while there was no significant variation in HPV positivity among countries and 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 [47] [48]. 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. In point of fact, the studies presented (**Table 2**) support strong evidence for the hypothesis that HPV is a necessary condition cervical cancer. In other words, *without* HPV infection *no* cervical cancer. Only the study of Eluf-Neto *et al*., 1994 [7] failed on this point. In this context, PCR technology is highly sensitive. Still, contaminated specimens may have induced false (positive) results, particularly in the earliest PCR based studies. Thus far, 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 [49] [50]. With the development of technology and science, the methods for detecting HPV DNA should become increasingly sensitive. 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. Future and more precise studies should avoid contamination as much as possible while taking the aforementioned and other factors into account. In particular, all studies presented provide strong evidence (**Table 2**) that there is a highly significant (**Table 14**) cause-effect relationship between HPV and cervical cancer. As with other sciences, general topics relating to matters like methodology and explanation are still very much present and numerous potential limitations can be acknowledged in the present meta/re-analysis of the studies above. More than that, the sample size of the studies analyzed was equal to $N = 7657$ while a highly precise and accurate molecular PCR-technology was used to investigate the relationship between HPV and CC which cannot be ignored. Besides of all, as long as other studies are not able to provide a better and more convincing explanation of the etiology of human cervical cancer it appears to be more than justified to accept the following and inescapable conclusion.

5. Conclusion

Human papillomavirus is the cause of human cervical cancer.

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