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Gastric Cancer and Epstein-Barr Virus Infection: A Systematic Review of ISH Based Studies

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Abstract

Background: Epstein-Barr virus (EBV) has an important role in the oncogenesis of several malignant diseases. Reports even demonstrated the presence of Epstein-Barr virus in gastric carcinoma (GC). However, the pathogenic role of EBV in GC is uncertain. The present investigation was carried out to investigate a possible causal relationship between GC and EBV.

Statistical Analysis: The method of the *conditio sine qua non* relationship was used to proof the hypothesis whether gastric cancer is a necessary condition (a conditio sine qua non) of the presence of EBV in human gastric tissues. In other words *without* GC *no* EBV in human stomach. The mathematical formula of the causal relationship k was used to proof the hypothesis, whether there is a cause effect relationship between gastric cancer and EBV. Significance was indicated by a p-value (two sided) of less than 0.05.

Results: In toto 26 ISH based studies with a sample size of N = 11860 were re-analyzed. All the studies analyzed support the null-hypothesis *without* GC *no* EBV positivity in human stomach. In other words, gastric cancer itself is a conditio sine qua non of EBV positivity in stomach tissues while the cause effect relationship between gastric cancer and EBV was highly significant.

Conclusions: Epstein-Barr virus is neither a cause, nor the cause of human gastric cancer.

Keywords: gastric cancer, Epstein-Barr virus, cause effect relationship, causality

1. Introduction

Gastric cancer (Parkin, 2005) is one of the most common causes of cancer death worldwide. Meanwhile gastric carcinogenesis is identified as being caused by an infection with the bacterium Helicobacter pylori (HP) which has been established as the cause of gastric cancer (Barukčić, 2017; Barukčić, 2018). However, besides of HP as the cause of GC (Barukčić, 2017; Barukčić, 2018) Epstein-Barr virus (EBV) has been demonstrated in about 10% (Kume et al., 1999) of the malignant epithelial cells of gastric cancer (Shibata & Weiss, 1992; Ohfuji et al, 1996; Vasef et al., 1996; Harn et al., 1995). In point of fact, an increasing amount of literature suggests that gastric cancer is associated to Epstein–Barr virus infection (Burke et al., 1990; Moritani et al., 1996; Akiba et al., 2008). Epstein-Barr virus (EBV) is an ubiquitous human herpesvirus, and over 90% of adults human population (Mandell et al., 2005) has serological evidence of previous viral infection. Although human immune system in most cases is able to control EBV infection to a large extent the virus is not completely cleared. Epstein-Barr virus establishes latency by infecting resting B cells (Decker et al., 1996; Babcock et al., 1998; Babcock et al., 1999) and activating the same to continuously proliferating lymphoblasts. At least with each such subsequent exposure to EBV effectively a greater number of memory B cells persist (Airoldi et al., 2004; Gatto & Brink, 2010). Finally, EBV persists for life and continues to replicate (Ressing et al., 2015) in human host. The clinical implications of these findings, however, remain unclear especially with respect to gastric cancer.

2. Material and Methods

2.1 Search Strategy

Detection of Epstein-Barr virus DNA in human tissues may be achieved by various methods; in-situ hybridization (ISH) is one of these methods. In-situ hybridization (ISH) is a technique described in the year 1969 by Joseph G. Gall (Gall & Pardue, 1969) which allows a precise localization of a specific EBV DNA segment within an adequately preserved histologic specimen. The sensitivity and specificity of the in situ hybridization for diagnosis of specific EBV segments has been reported as being 94% and 69% (Fanaian et al., 2009). In-situ hybridization can distinguish especially EBV in the cytoplasm and/or nuclei of tumor cells from EBV in other cells such as lymphocytes. Thus far, for the questions addressed in this paper, PubMed was searched especially for appropriate ISH based studies conducted in any country which investigated the relationship between GC and EBV. The search in PubMed was performed while using some medical key words like “gastric cancer” and “EBV” and “ish” and “review” 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 bottom “create file”). The created *.txt file was converted into a *.pdf file. The abstracts were studied within the *.pdf file. Those articles were considered for a review which provided access to data without any data access barrier; no data access restrictions were accepted. Additionally, appropriate review (Chen et al., 2015) articles and references published were checked. Furthermore, studies were excluded if data were self-contradictory or insufficient to calculate the necessary measures of relationship.

2.2 The Data of the Studies Analyzed

The studies reviewed in this publication investigated histological specimens of gastric carcinomas of various histological subtypes for the presence of Epstein-Barr virus while using the highly sensitive in situ hybridization technique. The non-dysplastic epithelial cells, the adjacent normal gastric epithelium/mucosa, or the reactive inflammatory infiltrate or non-neoplastic gastric epithelium of the same histological specimens analyzed were used as a *control group* too. The data of the studies reviewed in this publication are presented in more detail by several tables (**Table 1, Table 2**).

Table 1. Summary of the data analyzed

		EBV positivity by ISH <B>		
		Yes	No	Total
Gastric cancer	Yes	504	5426	5930
<A>	No	**5**	5925	5930
	Total	509	11351	11860
		k =	**+0.207598682**	
		p value (k) <	**0.00001**	
		WITHOUT <A>	NO <B>.	
		p (SINE) =	0.999578415	
		X^2(SINE) =	**0.805570462**	

Table 2. The data of the ISH studies considered for a meta-analysis

Study Id	Year	Country	N	a_t	b_t	c_t	d_t	p(SINE)	X^2(Sine)	k	X^2(k)	p value (k)
Shibata et al. (Shibata et al., 1992)	1992	USA	276	22	116	0	138	1	0,01136	0,294	23,91	1,01182E-06
Tokunaga et al. (Tokunaga et al., 1993)	1993	Japan	1940	67	903	0	970	1	0,00373	0,189	69,40	8,05237E-17
Imai et al.(Imai et al., 1994)	1994	Japan	2000	70	930	0	1000	1	0,00357	0,190	72,54	1,63775E-17
Ott et al.(Ott et al., 1994)	1994	Germany	78	7	32	0	39	1	0,03571	0,314	7,69	0,005552329
Yuen et al.(Yuen et al., 1994)	1994	China	148	7	67	0	74	1	0,03571	0,223	7,35	0,006715542
Harn et al.(Harn et al., 1995 et al)	1995	Taiwan	110	6	49	0	55	1	0,04167	0,240	6,35	0,011763607
Moritani et al.(Moritani et al., 1996)	1996	Japan	264	15	117	0	132	1	0,01667	0,245	15,90	6,66513E-05
Gulley et al.(Gulley et al., 1996)	1996	USA	190	11	84	0	95	1	0,02273	0,248	11,68	0,000633123
Selves et al.(Selves et al., 1996)	1996	France	118	5	54	0	59	1	0,05000	0,210	5,22	0,022312649
Galetsky et al.(Galetsky et al., 1997)	1997	Russia	412	18	188	0	206	1	0,01389	0,214	18,82	1,43477E-05
Kume et al.(Kume et al 1999)	1999	Japan	688	40	304	0	344	1	0,00625	0,248	42,47	7,18064E-11
Gurtsevich et al.(Gurtsevich et al., 1999)	1999	Russia	368	17	167	0	184	1	0,01471	0,220	17,82	2,42389E-05
Wan et al.(Wan et al 1999)	1999	China	116	6	52	0	58	1	0,04167	0,234	6,33	0,011889502
Chapel et al. (Chapel et al 2000)	2000	France	112	7	49	0	56	1	0,03571	0,258	7,47	0,006285182
Corvalan et al.(Corvalan et al., 2001)	2001	Chile	370	31	154	0	185	1	0,00806	0,302	33,83	5,99958E-09
Kang et al.(Kang et al., 2002)	2002	Korea	466	21	212	0	233	1	0,01190	0,217	21,99	2,7393E-06
Oda et al.(Oda et al., 2003)	2003	Japan	194	5	92	0	97	1	0,05000	0,163	5,13	0,023484924
Ishii et al.(Ishii et al., 2004)	2004	Japan	266	19	114	0	133	1	0,01316	0,277	20,46	6,08417E-06
Wang et al.(Wang et al., 2004)	2004	China	370	13	172	0	185	1	0,01923	0,191	13,47	0,000241971
Lopes et al.(Lopes et al., 2004)	2004	Brasil	106	6	47	0	53	1	0,04167	0,245	6,36	0,011672154

Herrera-Goepfert et al. (2005)	2005	Mexico	660	24	306	2	328	0,997	0,08654	0,171	19,38	1,07191E-05
Alipov et al.(Alipov et al., 2005)	2005	Japan	278	14	125	0	139	1	0,01786	0,230	14,74	0,000123242
Luo et al.(Luo et al., 2005)	2005	China	344	11	161	0	172	1	0,02273	0,182	11,36	0,000749071
von Rahden et al.(von Rahden et al., 2006)	2006	Germany	164	5	77	0	82	1	0,05000	0,177	5,16	0,023149754
Truong et al.(Truong et al., 2009)	2009	USA	470	12	223	0	235	1	0,02083	0,162	12,31	0,000449475
Chen et al.(Chen et al., 2010)	2010	China	1352	45	631	3	673	0,998	0,13021	0,168	38,10	6,71151E-10
		Total	11860	504	5426	5	5925	0.999	0.80557		515.2	
					Alpha =				0.05	Alpha =		0.05
					Degrees of freedom (D. f.) =				26	D. f. =		26
					X² (Critical SINE) =				38.89	X² (Critical k) =		38.89
					X² (Calculated SINE) =				0.80557	X² (Calc. k) =		515.2
										p value (k) <		0.0001

2.3 Statistical Analysis

All statistical analyses were performed with Microsoft Excel ® version 14.0.7166.5000 (32-Bit) software (Microsoft GmbH, Munich, Germany). All P values are two-sided; significance was indicated by a P value of less than 0.05. The following statistical tools and techniques were used to analyze the data.

2.3.1 The 2x2 Table

The 2x2 table in this article is defined (Barukčić, 1989; Barukčić, 1997; Barukčić, 2005; Barukčić, 2006; Barukčić, 2006; Barukčić, 2009; Barukčić, 2017) in general more precisely (**Table 3**) as follows.

Table 3. The sample space of a contingency table

		Conditioned B_t		
		Yes = +1	*Not = +0*	*Total*
Condition A_t	Yes =+1	$\mathbf{a_t}$	$\mathbf{b_t}$	A_t
	Not = +0	$\mathbf{c_t}$	$\mathbf{d_t}$	$\mathbf{\underline{A}_t}$
	Total	B_t	$\underline{B}_t$	N_t

In general it is (a+b) = A_t, (c+d) = $\underline{A}_t$, (a+c) = B_t, (b+d) = $\underline{B}_t$ 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 $p(A_t)= p(A_t \cap B_t)+p(A_t \cap \underline{B}_t)$ while $p(A_t)$ is not defined as $p(a_t)$. In the same context, it should be considered that $p(B_t) = p(a_t)+p(c_t) = p(A_t \cap B_t) +p(c_t)$ and equally that $p(\underline{B}_t) = 1- p(B_t) =p(b_t)+p(d_t)$. In point of fact, the joint probability of A_t and B_t is denoted by $p(A_t \cap B_t)$. 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.

Table 4. The probabilities of a contingency table

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

2.3.2 Independence

Data as such can be continuous, ordinal, or categorical. Still, in the case of independence of A_t and B_t it is according to Kolmogoroff (Kolmogoroff, 1933)

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

2.3.3 Exclusion (A_t Excludes B_t and Vice Versa Relationship)

The mathematical formula of the exclusion relationship (A_t excludes B_t and vice versa) of a population was defined as (Barukčić, 1989; Barukčić, 1997; Barukčić, 2005; Barukčić, 2006; Barukčić, 2011; Barukčić, 2012; Barukčić, 2016; Barukčić, 2017; Barukčić, 2018)

$$p(A_t \mid B_t) \equiv \frac{b_t + c_t + d_t}{N_t} \equiv 1 - p(a_t) \equiv p(b_t) + p(c_t) + p(d_t) \equiv p(c_t) + (1 - p(B_t)) \equiv p(b_t) + (1 - p(A_t)) \equiv +1 \quad (2)$$

and used to proof the hypothesis: A_t *excludes* B_t and vice versa.

2.3.4 Sufficient Condition (Conditio Per Quam; Material Conditional)

A given disease (i.e. effect) can be caused by only one causal mechanism but this must not be the case. A causal relationship can be described in terms of sufficient conditions/causes and points to the possibility of multicausality. The mathematical formula of the sufficient condition relationship (conditio per quam) (Barukčić, 1989; Barukčić, 1997; Barukčić, 2005; Barukčić, 2006; Barukčić, 2011; Barukčić, 2012; Barukčić, 2016; Barukčić, 2017; Barukčić, 2018) of a population was defined as

$$p(A_t \rightarrow B_t) \equiv p(A_t \cap B_t) + p(\underline{A}_t) \equiv p(A_t \cap B_t) + (1 - p(A_t)) \equiv p(a_t) + p(c_t) + p(d_t) \equiv p(d_t) + p(B_t) \equiv \frac{a_t + c_t + d_t}{N_t} \equiv +1 \quad (3)$$

and used to proof the hypothesis: *if* A_t *then* B_t .

2.3.5 Necessary Condition (Conditio Sine Qua Non)

Causation is an essential concept in human medicine and corresponds not only with major approaches to causation found in the philosophical literature but has consequences which reach far beyond medicine itself. A necessary event is an event (i. e. condition/cause) without which another event (i.e. conditioned/effect) cannot occur. The formula of the necessary condition (conditio sine qua non) relationship (Barukčić, 1989; Barukčić, 1997; Barukčić, 2005; Barukčić, 2006; Barukčić, 2011; Barukčić, 2012; Barukčić, 2016; Barukčić, 2017; Barukčić, 2018) was derived as

$$p(A_t \leftarrow B_t) \equiv p(A_t \cap B_t) + p(\underline{B}_t) \equiv p(A_t \cap B_t) + (1 - p(B_t)) \equiv p(a_t) + p(b_t) + p(d_t) \equiv \frac{a_t + b_t + d_t}{N} \equiv +1 \quad (4)$$

and used to proof the hypothesis: *without* A_t *no* B_t.

2.3.6 Necessary and Sufficient Condition (Material Biconditional)

The *necessary and sufficient condition* relationship (Barukčić, 1989; Barukčić, 1997; Barukčić, 2005; Barukčić, 2006; Barukčić, 2011; Barukčić, 2012; Barukčić, 2016; Barukčić, 2017; Barukčić, 2018) was defined as

$$p(A_t \leftrightarrow B_t) \equiv p(A_t \cap B_t) + p(\underline{A}_t \cap \underline{B}_t) \equiv \frac{a_t + d_t}{N} \equiv +1 \quad (5)$$

2.4 The Data of a Study are Self-Contradictory

The conclusions of studies concerned with causality are potentially endangered by the quality of the data, by nonrandom systematic error in the design or conduct of a study (bias), by confounding, by measurement errors, by an inappropriate design of a study and incorrect 'cut off'-values of measured factors, by the statistics used and other factors too. Regardless of terminology, especially the bias caused by different confounders may result in an underestimation or an overestimation of the exposure effect. In practice, one way to address confounding is to identify and control confounders, randomization, blinding and matching (Kocher & Zurakowski, 2004) can decrease confounding. In point of fact, empirical or study data as such must meet some formal theoretical and mathematical requirements to be of use to prove causality from data alone. Otherwise and for preliminary purposes the same data must be regarded as self-contradictory and must be treated as inappropriate for causal analysis or labelled as potentially and significantly determined by known or unknown confounders. The standard to prove cause-effect relationships is set higher than the standard to suggest only an association. Strictly speaking, it is very unlikely to establish a significant causal relationship from data which are self-contradictory.

2.4.1 The X^2 Goodness of Fit Test of a Necessary Condition

Under conditions where the chi-square (Pearson, 1900) goodness of fit test cannot be used it is possible to use an approximate and conservative (one sided) confidence interval as discussed by Rumke (Rumke, 1975), Louis

(Louis, 1981), Hanley et al. (Hanley & Lippman-Hand, 1983) and Jovanovic (Jovanovic & Levy, 1997) known as the rule of three. According to the definition of the conditio sine qua non relationship it is

$$p(A_t \cap B_t) + (1 - p(B_t)) \equiv +1 \tag{6}$$

or

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

or

$$p(A_t \cap B_t) - p(B_t) \equiv 0 \tag{8}$$

or

$$p(A_t \cap B_t) \equiv p(B_t) \tag{9}$$

Multiplying equation before by the population or sample size N, it is

$$N \times p(A_t \cap B_t) \equiv N \times p(B_t) \tag{10}$$

or

$$N \times p(A_t \cap B_t) - N \times p(B_t) = 0 \tag{11}$$

Multiplying equation by itself yields

$$(N \times p(A_t \cap B_t) - N \times p(B_t)) \times (N \times p(A_t \cap B_t) - N \times p(B_t)) = 0 \times 0 \tag{12}$$

Dividing by $N \times p(B_t)$ we obtain

$$\frac{(N \times p(A_t \cap B_t) - N \times p(B_t))^2}{N \times p(B_t)} = 0 \tag{13}$$

which is equivalent with

$$\frac{(a_t - (B_t))^2}{(B_t)} = \frac{(a_t - (a_t + c_t))^2}{(B_t)} = \frac{(c_t)^2}{(B_t)} = 0 \tag{14}$$

Adding $\mathbf{(((b_t+d_t)-(b_t+d_t))^2/(b_t+d_t)) = 0}$ yields

$$\frac{(c_t)^2}{(B_t)} + 0 = 0 + 0 = 0 \tag{15}$$

Using Yates continuity correction (Yates, 1934), the chi-square value of a conditio sine qua non distribution follows as

$$\chi^2 (A_t \leftarrow B_t) \equiv \frac{\left(c_t - \left(\frac{1}{2}\right)\right)^2}{(B_t)} + 0 = 0 \tag{16}$$

This definition of the X^2 distribution of a *conditio sine qua non* distribution (degrees of freedom = 2-1=1) is more precise than already published (Barukčić, 2018) formulas and can be used to prove whether the data of a study do support a conditio-sine qua non Null-hypothesis: *without* A_t *no* B_t. Even if the data support such a null-hypothesis, the question is justified, can we rely on such a result? In other words, it is necessary to search for contradictions within the data itself. From the definition of the conditio sine qua non above it is

$$p(A_t \leftarrow B_t) \equiv p(A_t \cap B_t) + (1 - p(B_t)) \equiv +1 \tag{17}$$

or at the end

$$p(A_t \cap B_t) = p(B_t) \tag{18}$$

There are circumstances, where the two factors A_t and B_t investigated are independent of each other. In other words, the causal relationship between A_t and B_t is equal to **k(A_t , B_t) =0** or it is

$$p(A_t \cap B_t) \equiv p(A_t) \times p(B_t) \tag{19}$$

If a conditio sine qua non is given, it is equally **p(A_t, B_t) = p(B_t)**.Rearranging the equation before, we obtain

$$p(B_t) \equiv p(A_t) \times p(B_t) \tag{20}$$

and at the end after division by p(B_t)

$$1 \equiv p(A_t) \tag{21}$$

In other words, due to formal mathematical requirements, the data of a study must be treated as self-contradictory if the data of the same study do support a significant conditio sine qua non relationship between the two factors A_t and B_t while at the same time the same data do support the hypothesis too, that the two factors A_t and B_t are independent of each other. Such data are inappropriate to establish a cause effect relationship.

Under conditions where the causal relationship between the two factors A_t and B_t **k(A_t , B_t) < 0** while there is a significant conditio sine qua non relationship between the two factors A_t and B_t investigated, the data must be treated as self-contradictory too and cannot be used for causal analysis. If the causal relationship is **k(A_t, B_t) < 0**, then it is

$$p(A_t \cap B_t) < p(A_t) \times p(B_t) \tag{22}$$

If a significant conditio sine qua non relationship is given, then it is **p(A_t, B_t) = p(B_t)**. Rearranging the equation above, we obtain

$$p(B_t) < p(A_t) \times p(B_t) \tag{23}$$

or at the end

$$1 < p(A_t) \tag{24}$$

Still, *there is no probability which is greater than 1*. In other words, data which support a significant negative causal relationship and equally a significant conditio sine qua non relationship are self-contradictory (**Table 5**) and inappropriate for causal analysis.

Table 5. Conditio sine qua non in more detail.

		Signifiant *conditio sine qua non* relationship	
		Yes	No
Significant causal relationship	k > 0	Data ok.	Data ok. (IMP?)
	k = 0	**Contradiction!**	Data ok. (no relationship)
	k < 0	**Contradiction!**	Data ok. (EXCL?)

2.4.2 The X² Goodness of Fit Test of a Sufficient Condition (Conditio per Quam)

Pearson's chi-square (Pearson, 1900) goodness of fit test cannot be used under any (Barnard, 1947; Gorroochurn, 2016) circumstances. Under which possible circumstances is it the case that Pearson's chi-square goodness of fit test is of use can be found in literature (Yamane, 1964). The rule of three discussed by Rumke (Rumke, 1975), Louis (Louis, 1981), Hanley et al. (Hanley & Lippman-Hand, 1983) and Jovanovic (Jovanovic & Levy, 1997) is an approximate and conservative (one sided) confidence interval and of use in this context too. According to the definition of the conditio per quam relationship it is

$$p\left(A_t \cap B_t\right)+\left(1-p\left(A_t\right)\right) \equiv +1 \tag{25}$$

or

$$p\left(A_t \cap B_t\right)+1-p\left(A_t\right) \equiv +1 \tag{26}$$

or

$$p\left(A_t \cap B_t\right)-p\left(A_t\right) \equiv 0 \tag{27}$$

or

$$p\left(A_t \cap B_t\right) \equiv p\left(A_t\right) \tag{28}$$

Multiplying equation before by the population or sample size N, it is

$$N \times p\left(A_t \cap B_t\right) \equiv N \times p\left(A_t\right) \tag{29}$$

or

$$N \times p\left(A_t \cap B_t\right)-N \times p\left(A_t\right)=0 \tag{30}$$

The square operation yields

$$\left(N \times p\left(A_t \cap B_t\right)-N \times p\left(A_t\right)\right) \times\left(N \times p\left(A_t \cap B_t\right)-N \times p\left(A_t\right)\right)=0 \times 0 \tag{31}$$

Dividing by $N \times p(B_t)$ we obtain

$$\frac{\left(N \times p\left(A_t \cap B_t\right)-N \times p\left(A_t\right)\right)^2}{N \times p\left(A_t\right)}=0 \tag{32}$$

which is equivalent with

$$\frac{\left(a_t-\left(A_t\right)\right)^2}{\left(A_t\right)}=\frac{\left(a_t-\left(a_t+b_t\right)\right)^2}{\left(A_t\right)}=\frac{\left(b_t\right)^2}{\left(A_t\right)}=0 \tag{33}$$

Adding $(((c_t+d_t)-(c_t+d_t))^2/(c_t+d_t)) = 0$ yields

$$\frac{\left(a_t\right)^2}{\left(A_t\right)}+0=0+0=0 \tag{34}$$

Using Yates continuity correction (Yates, 1934), the chi-square value of a conditio sine qua non distribution follows as

$$\chi^2\left(A_t \rightarrow B_t\right) \equiv \frac{\left(a_t-\left(\frac{1}{2}\right)\right)^2}{\left(A_t\right)}+0=0 \tag{35}$$

This definition of the X^2 distribution of a *conditio per quam* (Barukčić, 2018) distribution (degrees of freedom d.f. = 2-1=1) can be used to prove whether the data of a study do support a conditio per quam Null-hypothesis: *if* A_t *then* B_t. Even if the data of a certain study do support such a null-hypothesis, the question is justified, can we rely on the quality of the data of a study and at the end on such a result? In other words, it is necessary to search for formal contradictions within the data itself. From the definition of the conditio per quam relationship above it is

$$p\left(A_t \rightarrow B_t\right) \equiv p\left(A_t \cap B_t\right)+\left(1-p\left(A_t\right)\right) \equiv +1 \tag{36}$$

or at the end

$$p(A_t \cap B_t) = p(A_t) \quad (37)$$

There are circumstances, where the two factors A_t and B_t investigated are independent of each other. In other words, the causal relationship between A_t and B_t is equal to $\mathbf{k(A_t, B_t) = 0}$ or it is

$$p(A_t \cap B_t) \equiv p(A_t) \times p(B_t) \quad (38)$$

Under circumstances of a conditio per quam relationship it is equally $\mathbf{p(A_t, B_t) = p(A_t)}$ and we obtain

$$p(A_t) \equiv p(A_t) \times p(B_t) \quad (39)$$

or at the end after dividing by $\mathbf{p(A_t)}$

$$1 \equiv p(B_t) \quad (40)$$

In other words, due to formal aspects, the data of a study must be treated as self-contradictory if the data of the same study do support a significant *conditio per quam* relationship between the two factors A_t and B_t while the same data do support the hypothesis too, that the two factors A_t and B_t are independent of each other. Such data are inappropriate to establish a cause effect relationship. Under conditions where the causal relationship between the two factors A_t and B_t is $\mathbf{k(A_t, B_t) < 0}$ while there is a significant conditio per quam relationship between the two factors A_t and B_t investigated, the data must be treated as self-contradictory too and cannot be used for causal analysis. If the causal relationship is $\mathbf{k(A_t, B_t) < 0}$, then it is

$$p(A_t \cap B_t) < p(A_t) \times p(B_t) \quad (41)$$

If a significant conditio per quam relationship is given, then it is $\mathbf{p(A_t, B_t) = p(A_t)}$. Rearranging equation above, we obtain

$$p(A_t) < p(A_t) \times p(B_t) \quad (42)$$

or at the end after dividing by $\mathbf{p(A_t)}$

$$1 < p(B_t) \quad (43)$$

Again, *there is no probability which is greater than 1*. In other words, data which support a significant negative causal relationship and equally a significant conditio per quam relationship are self-contradictory (**Table 6**) and inappropriate for causal analysis.

Table 6. Conditio per quam in more detail.

		Signifiant *conditio per quam* relationship	
		Yes	No
Significant causal relationship	k > 0	Data ok.	Data ok. (SINE?)
	k = 0	**Contradiction!**	Data ok. (no relationship)
	k < 0	**Contradiction!**	Data ok. (EXCL?)

2.4.3 The X² Goodness of Fit Test of the Exclusion Relationship (Exclusio)

The justification of inferences or procedures which extrapolate from sample data to the population or general facts is a central problem of statistics itself. The problem of induction is not addressed, nor is the article concerned with details to justify the correctness of statistical methods. Despite disagreements, it is insightful to recall that the relation between data and hypotheses is of use to determine how believable a hypothesis is and a way to avoid invalid inference. But, as can be imagined, insufficient statistical methods (i.e. risk ratio) used to analyze data but also confounding has influence on a valid inference especially in studies concerned with causality and it is hard to avoid incorrect conclusions in principle. A good study design has the potential for reducing confounding but does not guarantee valid inference. Still, hypotheses can be evaluated in the light of empirical facts while using some specific statistical methods. The chi square is such a statistical method which can be used for discrete distributions like the binomial distribution and the Poisson distribution but requires a sufficient sample size (n >30) in order to be valid. The *chi-square Goodness of fit test* compares how well an *empirical distribution* fits a theoretical distribution. The null hypothesis of Chi-Square goodness of fit test (Yamane, 1964) assumes that there is no significant difference between an empirical distribution and a theoretical distribution. In contrast to this, the chi-square test for independence compares two sets of data. For continuous distributions, the Kolmogorov-Smirnov (Sachs, 1992) and Anderson-Darling goodness of fit tests

(Sachs, 1992) are used. Under conditions where the chi-square goodness of fit test (Pearson, 1900) cannot be used it is possible to use an approximate and conservative (one sided) confidence interval known as *the rule of three* (Rumke, 1975; Hanley et al. 1983; Louis, 1981; Jovanovic et al., 1997). According to the definition of the *exclusion relationship* it is and has to be that

$$p(b_t)+p(c_t)+p(d_t) \equiv +1 \tag{44}$$

Rearranging this equation, we obtain

$$p(b_t)=1-p(c_t)-p(d_t)=1-\left(p(c_t)+p(d_t)\right) \equiv 1-p(\underline{A}_t)=p(A_t) \tag{45}$$

and

$$p(c_t)=1-p(b_t)-p(d_t) \equiv 1-\left(p(b_t)+p(d_t)\right)=1-p(\underline{B}_t)=p(B_t) \tag{46}$$

The chi square goodness of fit test of the exclusion relationship can be derived as follows.

$$\begin{aligned}
N \times p(b_t) &= N \times p(A_t) \\
\left(N \times p(b_t)-N \times p(A_t)\right) &= 0 \\
\left(N \times p(b_t)-N \times p(A_t)\right) \times \left(N \times p(b_t)-N \times p(A_t)\right) &= 0 \times 0 \\
\frac{\left(N \times p(b_t)-N \times p(A_t)\right)^2}{N \times p(A_t)} &= \frac{0}{N \times p(A_t)}=0
\end{aligned} \tag{47}$$

$$\chi^2(b_t)=\frac{\left(N \times p(b_t)-N \times p(A_t)\right)^2}{N \times p(A_t)}=\frac{(b_t-(a_t+b_t))^2}{A_t}=\frac{(-(a_t))^2}{A_t} = 0$$

and as

$$\chi^2(b_t)=\frac{(-(a_t)-0,5)^2}{A_t} = 0$$

$$\begin{aligned}
N \times p(c_t) &= N \times p(B_t) \\
\left(N \times p(c_t)-N \times p(B_t)\right) &= 0 \\
\left(N \times p(c_t)-N \times p(B_t)\right) \times \left(N \times p(c_t)-N \times p(B_t)\right) &= 0 \times 0 \\
\frac{\left(N \times p(c_t)-N \times p(B_t)\right)^2}{N \times p(B_t)} &= \frac{0}{N \times p(B_t)}=0
\end{aligned} \tag{48}$$

$$\chi^2(b_t)=\frac{\left(N \times p(c_t)-N \times p(B_t)\right)^2}{N \times p(B_t)}=\frac{(c_t-(a_t+c_t))^2}{B_t}=\frac{(-(a_t))^2}{B_t} = 0$$

$$\chi^2(c_t)=\frac{(-(a_t)-0,5)^2}{B_t} = 0$$

The chi square value with degree of freedom d.f. = 2-1=1of the exclusion relationship with a continuity correction can be calculated as

$$\chi^2(\text{EXCL})=\frac{(-(a_t)-0,5)^2}{A_t}+\frac{(-(a_t)-0,5)^2}{B_t} \tag{49}$$

This definition of the X² distribution of an *exclusion* distribution (degrees of freedom d.f.= 2-1=1) is already discussed in literature (Barukčić, 2018). The null-hypothesis A_t *excludes* B_t *and vice versa* can be tested while using the chi square distribution. Even if the data of a study support the null-hypothesis A_t *excludes* B_t *and vice versa*, the question is justified, can we rely on such a result? In other words, are there any contradictions present within the analyzed data itself? From the definition of the A_t *excludes* B_t *and vice versa* relationship above it is

$$p(b_t)+p(c_t)+p(d_t) \equiv +1 \tag{50}$$

or at the end

$$p(b_t)=1-p(c_t)-p(d_t)=1-(p(c_t)+p(d_t))\equiv 1-p(\underline{A}_t)=p(A_t) \tag{51}$$

and

$$p(c_t)=1-p(b_t)-p(d_t)\equiv 1-(p(b_t)+p(d_t))=1-p(\underline{B}_t)=p(B_t) \tag{52}$$

There are circumstances, where the two factors A_t and B_t investigated are *independent* of each other. In other words, the causal relationship between A_t and B_t is equal to $\mathbf{k(A_t, B_t)=0}$ or it is

$$p(A_t \cap B_t)\equiv p(A_t)\times p(B_t) \tag{53}$$

Under conditions of an exclusion relationship it is $\mathbf{p(c_t) = p(B_t)}$ **and** $\mathbf{p(b_t) = p(A_t)}$. Thus far, rearranging the equation before, we obtain

$$p(A_t \cap B_t)\equiv p(b_t)\times p(c_t) \tag{54}$$

Under conditions of an exclusion relationship it is $\mathbf{p(A_t, B_t) = 0}$. Thus far, it is

$$0\equiv p(b_t)\times p(c_t) \tag{55}$$

In other words, under conditions where the causal relationship between the two factors A_t and B_t is $k(A_t, B_t) = 0$ and where the same two factors A_t and B_t are equally excluding each other it is equally true that $p(A_t, B_t) = 0$ and that $p(c_t)\times p(b_t) = 0$. Under these circumstances it is $p(B_t) = p(A_t, B_t) + p(c_t) = 0$ or $p(A_t) = p(A_t, B_t) + p(b_t) = 0$. Such data are inappropriate for causal analysis. Data which support the hypothesis that two factors A_t and B_t investigated are *independent* of each other and equally that the same two factors A_t and B_t investigated are *excluding* each other are self-contradictory and inappropriate to establish a cause effect relationship. Furthermore, under conditions of a significant positive causal relationship between the two factors A_t and B_t is $\mathbf{k(A_t, B_t) > 0}$ and a significant exclusion relationship between the same two factors A_t and B_t investigated too, the data must be treated as self-contradictory and cannot be used for causal analysis. If the causal relationship is $k(A_t, B_t) > 0$, then it is

$$p(A_t \cap B_t) > p(A_t)\times p(B_t) \tag{56}$$

Under conditions of an exclusion relationship it is $\mathbf{p(A_t, B_t) = 0}$. Thus far, rearranging the equation before, we obtain

$$0 > p(A_t)\times p(B_t) \tag{57}$$

Under conditions where $k(A_t, B_t) > 0$ it is equally $\mathbf{p(A_t) > 0}$ **and** $\mathbf{p(B_t) > 0}$. Thus far, it is possible and allowed to divide by $p(A_t)\times p(B_t)$. Dividing by $p(A_t)\times p(B_t)$ we obtain

$$\frac{0}{p(A_t)\times p(B_t)} > \frac{p(A_t)\times p(B_t)}{p(A_t)\times p(B_t)} \tag{58}$$

In general, under these conditions we must accept

$$+0 > +1 \tag{59}$$

which is a logical contradiction. Thus far, data which forces us to accept that there is a causal relationship which is $k(A_t, B_t) > 0$ and that equally the same two factors A_t and B_t investigated are *excluding* of each other are self-contradictory and inappropriate for causal analysis. In other words, the mathematical formula of the causal relationship k (Barukčić, 1989; Barukčić, 1996; Barukčić, 2005; Barukčić, 2006; Barukčić, 2009; Barukčić, 2017; Barukčić, 2018) is defined *at every single event t*, *at every single Bernoulli trial t*, as

$$k(A_t,B_t)\equiv \frac{(p(a_t)-(p(A_t)\times p(B_t)))}{\sqrt[2]{(p(A_t)\times p(\underline{A}_t))\times(p(B_t)\times p(\underline{B}_t))}} \tag{60}$$

where A_t denotes the cause and B_t denotes the effect. Under conditions where there is a significant cause and effect relationship and equally a significant exclusion relationship it is $\mathbf{p(a_t) = p(A_t, B_t) = 0}$ and it follows that

$$k(A_t,B_t)\equiv \frac{(0-(p(A_t)\times p(B_t)))}{\sqrt[2]{(p(A_t)\times p(\underline{A}_t))\times(p(B_t)\times p(\underline{B}_t))}} < 0 \tag{61}$$

In other words, an exclusion relationship demands a causal relationship which is $k(A_t, B_t) < 0$ and vice versa. Otherwise there is evidence that the data used are self-contradictory (**Table 7**) and it is difficult to consider the same data for causal analysis.

Table 7. Exclusion relationship in more detail.

		Signifiant exclusion relationship	
		Yes	No
Significant causal relationship	$k > 0$	**Contradiction!**	Data ok. (SINE? IMP?)
	$k = 0$	**Contradiction!**	Data ok. (no relationship?)
	$k < 0$	Data ok.	Data ok. (A_t OR B_t?)

2.4.4 The Mathematical Formula of the Causal Relationship k

The mathematical formula of the causal relationship k (Barukčić, 1989; Barukčić, 1997; Barukčić, 2005; Barukčić, 2006; Barukčić, 2006; Barukčić, 2009; Barukčić, 2017) is defined *at every single event t*, *at every single Bernoulli trial t*, as

$$k(A_t, B_t) \equiv \frac{(p(A_t \times B_t) - (p(A_t) \times p(B_t)))}{\sqrt[2]{(p(A_t) \times p(\underline{A}_t)) \times (p(B_t) \times p(\underline{B}_t))}} \tag{62}$$

where A_t denotes the cause and B_t denotes the effect. The chi-square distribution (Pearson K, 1900) can be applied to determine the significance (Barukčić, 2016) of causal relationship k. Correlation (Bravais, 1846; Pearson, 1896; Wright, 1921) is not causation, causation is not correlation. The relationship between correlation and causation (Wright, 1921) is discussed in many publications. This does not necessarily imply that repeating itself over and over again may contribute anything new to further scientific progress. Under conditions where a random variable A_t is a cause of the random variable B_t and *only* a necessary condition too, the chi square value of the causal relationship can be simplified as follows.

$$\chi(k) \equiv N \times k(A_t, B_t)^2 \equiv N \times \frac{N \times N \times (p(A_t \times B_t) - (p(A_t) \times p(B_t)))^2}{N \times N \times (p(A_t) \times p(\underline{A}_t)) \times (p(B_t) \times p(\underline{B}_t))} \tag{63}$$

where A_t denotes the cause and B_t denotes the effect. Under conditions where A_t is equally a necessary condition of B_t it is

$$p(A_t \cap B_t) \equiv p(B_t) \tag{64}$$

Substituting this relationship into the equation before we obtain

$$\chi(k) \equiv N \times k(A_t, B_t)^2 \equiv N \times \frac{N \times N \times (p(B_t) - (p(A_t) \times p(B_t)))^2}{N \times N \times (p(A_t) \times p(\underline{A}_t)) \times (p(B_t) \times p(\underline{B}_t))} \tag{65}$$

or the relationship

$$\chi(k) \equiv N \times k(A_t, B_t)^2 \equiv N \times \frac{N \times N \times (p(B_t) \times (1 - p(A_t)))^2}{N \times N \times (p(A_t) \times p(\underline{A}_t)) \times (p(B_t) \times p(\underline{B}_t))} \tag{66}$$

or the relationship

$$\chi(k) \equiv N \times k(A_t, B_t)^2 \equiv N \times \frac{N \times N \times p(B_t)^2 \times (1 - p(A_t))^2}{N \times N \times (p(A_t) \times p(\underline{A}_t)) \times (p(B_t) \times p(\underline{B}_t))} \tag{67}$$

Equation can be simplified as

$$\chi(k) \equiv N \times k(A_t, B_t)^2 \equiv N \times \frac{N \times N \times p(B_t) \times (1 - p(A_t))}{N \times N \times (p(A_t) \times) \times (\times p(\underline{B}_t))} = \frac{N \times p(B_t) \times N \times (1 - p(A_t))}{N \times p(A_t) \times N \times p(\underline{B}_t)} \tag{68}$$

or at the end as

$$\chi(k) \equiv N \times k(A_t, B_t)^2 \equiv N \times \frac{B_t \times \underline{A}_t}{A \times \underline{B}_t} = \frac{E(B_t) \times E(A_t)}{E(A_t) \times E(\underline{B}_t)} \tag{69}$$

Under conditions where a random variable A_t is a cause of the random variable B_t and *only* a sufficient condition too, it has to be that

$$p(A_t \cap B_t) \equiv p(A_t) \tag{70}$$

and the chi square value of the causal relationship can be derived as

$$\chi(k) \equiv N \times k(A_t, B_t)^2 \equiv N \times \frac{A_t \times \underline{B}_t}{B \times \underline{A}_t} = \frac{E(A_t) \times E(B_t)}{E(B_t) \times E(\underline{A}_t)} \tag{71}$$

Another simple form of a X^2 square goodness of fit test can be derived as follows. Under conditions of independence it is

$$p(A_t \cap B_t) \equiv p(A_t) \times p(B_t) \tag{72}$$

or

$$p(A_t \cap B_t) - p(A_t) \times p(B_t) = 0 \tag{73}$$

or

$$\left(p(A_t \cap B_t) - p(A_t) \times p(B_t)\right) \times \left(p(A_t \cap B_t) - p(A_t) \times p(B_t)\right) = 0 \times 0 = 0 \tag{74}$$

or

$$\frac{\left(p(A_t \cap B_t) - p(A_t) \times p(B_t)\right)^2}{p(A_t) \times p(B_t)} = 0 \tag{75}$$

If the probability changes from trial ***t*** to trial *t*, we obtain

$$\chi^2 = \sum_{t=+1}^{N} \frac{\left(p(A_t \cap B_t) - p(A_t) \times p(B_t)\right)^2}{p(A_t) \times p(B_t)} = 0 \tag{76}$$

If the probability is constant form trial to trial it is

$$\chi^2 = N \times \frac{\left(p(A_t \cap B_t) - p(A_t) \times p(B_t)\right)^2}{p(A_t) \times p(B_t)} = 0 \tag{77}$$

Table 8. 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

3. Results

3.1 Without Gastric Cancer no EBV DNA in Human Gastric Tissues

The studies presented provided no self-contradictory data (**Table 2**) and were considered for further analysis.

Claims.

Null Hypothesis:

Gastric cancer is a necessary condition (a conditio sine qua non) of Epstein-Barr virus DNA in gastric tissues. In other words, *without* gastric cancer *no* EBV in human gastric tissues.

Alternative Hypothesis:

Gastric cancer is a necessary condition (a conditio sine qua non) of Epstein-Barr virus DNA in gastric tissues. In other words, *without* gastric cancer *no* EBV in human gastric tissues.

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

Proof.

The *conditio sine qua non* relationship between gastric cancer and Epstein - Barr virus was investigated by several studies (**Table 2**). The data as presented by **Table 2** were not self-contradictory. All the 26 studies analyzed support the Null-hypothesis *without* gastric cancer *no* EBV positivity in human gastric tissues (X^2 (Critical SINE) =38.89, X^2 (Calculated SINE) =0.80557)). In the same context, the studies provided evidence of a highly significant cause effect relationship between GC and EBV (Degrees of freedom = 26, X^2 (Critical k)=38.89, X^2 (Calc. k)=515.2, p value (k) <0.0001). In general, *without* GC *no* EBV in human gastric tissues.

Q. e. d.

3.2 The Causal Relationship between Gastric Cancer and Epstein-Barr Virus

Claims.

Null Hypothesis:

Gastric cancer and Epstein-Barr virus are not causally related, both are independent of each other. k = 0.

Alternative Hypothesis:

Gastric cancer and Epstein-Barr virus are causally related, both are not independent of each other $k \neq 0$.

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

Proof.

The data illustrated by **Table 2** investigated the presence of EBV DNA and in human gastric tissues by ISH technology. The sample size of the studies considered for a re-analysis was N= 11860. All 26 studies analysed were not self-contradictory and provide support of a highly significant cause effect relationship between GC and EBV (Degrees of freedom = 26, X^2 (Critical k) = 38.89, X^2 (Calc. k) = 515.2, p value (k) <0.0001). In other words, there is a highly significant cause effect relationship between GC and EBV. **Q. e. d.**

4. Discussion

In summary, the findings of the tissue-based ISH studies analyzed in this publication strongly suggest a highly significant cause effect relationship between gastric cancer and EBV infection and may cast serious doubt on the causal relationship between Helicobacter pylori and gastric cancer (Barukčić, 2017; Barukčić, 2018) in principle. To better understand these results, it's necessary to be more precise and to take into account several important factors. First and foremost, it is important to bear in mind the core objectives; what is the cause, what is the effect? In other words, *is EBV a cause or the cause of GC* or vice versa, *is GC a cause or the cause of EBV in detected in tissues*? The presence of EBV within normal gastric tissues and in a minority (Gulley et al., 1996; Oda et al., 2003) of gastric carcinoma (Luqmani et al., 2001) cases deserves wider investigation. In fact, even if EBV is usually benign, EBV may infect a resting, mature B cell and activate it (Fields et al., 1990) to become a proliferating B lymphoblast thus that an EBV reactivation (Meij et al., 1999) reflected by aberrant IgG, IgM, IgA antibody responses can occur. Nevertheless, EBV can survive and persists in memory B cells, which act as a reservoir for the virus (Decker et al., 1996; Babcock et al., 1998; Babcock et al., 1998) in the peripheral blood of human host for life while well controlled by host's immune system. EBV is present in human host before infecting gastric carcinoma tissues through the reactivated EBV-carrying lymphocytes (Oda et al., 2003) which is one of the main reasons (Zhang et al., 2014) of its crucial role in gastric carcinogenesis. Our results suggest a highly significant causal relationship between GC and EBV. In the same respect, without gastric cancer no Epstein-Bar virus infection in gastric cancer tissues or in other words the presence of EBV in gastric cancer tissues is the effect of gastric cancer. These results of this publication indicate that EBV infection plays no etiologic role (von Rahden et al., 2006) in gastric cancer. Still, therapeutic vaccines for cancer and chronic infectious diseases like EBV may achieve consistent efficacy and a great effort in the development of vaccines is necessary.

5. Conclusion

Without gastric cancer *no* EBV in gastric cancer tissues. EBV is neither a cause nor the cause of gastric cancer.

References

Airoldi, I., Raffaghello, L., Cocco, C., Guglielmino, R., Roncella, S., Fedeli, F., … Pistoia, V. (2004). Heterogeneous expression of interleukin-18 and its receptor in B-cell lymphoproliferative disorders deriving from naive, germinal center, and memory B lymphocytes. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research*, *10*(1 Pt 1), 144-154.

Akiba, S., Koriyama, C., Herrera-Goepfert, R., & Eizuru, Y. (2008). Epstein-Barr virus associated gastric carcinoma: Epidemiological and clinicopathological features. *Cancer Science*, *99*, 195-201. https://doi.org/10.1111/j.1349-7006.2007.00674.x

Alipov, G., Nakayama, T., Nakashima, M., Wen, C. Y., Niino, D., Kondo, H., ... Sekine, I. (2005). Epstein-Barr virus-associated gastric carcinoma in Kazakhstan. *World Journal of Gastroenterology*, *11*, 27-30. https://doi.org/10.3748/wjg.v11.i1.27

Armitage, P., & Colton, T. (Eds.) (2005). *Encyclopedia of biostatistics* (2nd ed.). Chichester, West Sussex, England, Hoboken, NJ: John Wiley.

Babcock, G. J., Decker, L. L., Freeman, R. B., & Thorley-Lawson, D. A. (1999). Epstein-Barr Virus–Infected Resting Memory B Cells, Not Proliferating Lymphoblasts, Accumulate in the Peripheral Blood of Immunosuppressed Patients. *J. Exp. Medv.*, *190*, 567-576. https://doi.org/10.1084/jem.190.4.567

Babcock, G. J., Decker, L. L., Volk, M., & Thorley-Lawson, D. A. (1998) EBV Persistence in Memory B Cells In Vivo. *Immunity*, *9*, 395-404. https://doi.org/10.1016/S1074-7613(00)80622-6

Barukčić, I. (1989). *Die Kausalität* (1. Aufl.). Hamburg: Wiss.-Verl.

Barukčić, I. (1997). *Die Kausalität* (2., völlig überarb. Aufl.). Wilhelmshaven: Scientia.

Barukčić, I. (2005). *Causality: New statistical methods*. Norderstedt, Germany: Books on Demand GmbH.

Barukčić, I. (2005). *Causality: New statistical methods*. Norderstedt, Germany: Books on Demand GmbH.

Barukčić, I. (2006). *Causality: New statistical methods* (2. Aufl.). Norderstedt: Books on Demand.

Barukčić, I. (2009). *Causality I. A theory of energy, time and space* (5. ed., 14. rev).

Barukčić, I. (2009). *Causality II. A theory of energy, time and space* (5. ed., 13. rev).

Barukčić, I. (2011). The Equivalence of Time and Gravitational Field. *Physics Procedia*, *22*, 56-62. https://doi.org/10.1016/j.phpro.2011.11.008

Barukčić, I. (2016). The Mathematical Formula of the Causal Relationship k. *International Journal of Applied Physics and Mathematics*, *6*, 45-65. https://doi.org/10.17706/ijapm.2016.6.2.45-65

Barukčić, I. (2016). Unified Field Theory. *Journal of Applied Mathematics and Physics*, *4*, 1379-1438. https://doi.org/10.4236/jamp.2016.48147

Barukčić, I. (2017). Anti Bohr — Quantum Theory and Causality. *International Journal of Applied Physics and Mathematics*, *7*, 93-111. https://doi.org/10.17706/ijapm.2017.7.2.93-111

Barukčić, I. (2017). *Die Kausalität*. Norderstedt: Books on Demand.

Barukčić, I. (2017). Helicobacter pylori — The Cause of Human Gastric Cancer. *Journal of Biosciences and Medicines*, *5*, 1-9. https://doi.org/10.4236/jbm.2017.52001

Barukčić, I. (2017). *Theoriae causalitatis principia mathematica*. Norderstedt: Books on Demand.

Barukčić, I. (2018). Epstein Bar Virus — The Cause of Hodgkin's Lymphoma. *Journal of Biosciences and Medicines*, *6*, 75-100. https://doi.org/10.4236/jbm.2018.61008

Barukčić, I. (2018). Fusobacterium nucleatum —The Cause of Human Colorectal Cancer. *Journal of Biosciences and Medicines*, *06*, 31-69. https://doi.org/10.4236/jbm.2018.63004

Barukcic, I. (2018). Helicobacter Pylori is the Cause of Gastric Cancer. *Modern Health Science*, *1*, p43.

https://doi.org/10.30560/mhs.v1n1p43

Barukčić, I. (2018). Human Papillomavirus — The Cause of Human Cervical Cancer. *Journal of Biosciences and Medicines*, *6*, 106-125. https://doi.org/10.4236/jbm.2018.64009

Barukčić, I. (2018). Mycobacterium Avium Subspecies Paratuberculosis: The Cause Of Croh's Disease. *Modern Health Science*, *1*, p19. https://doi.org/10.30560/mhs.v1n1p19

Barukčić, K., & Barukčić, I. (2016). Epstein Barr Virus—The Cause of Multiple Sclerosis. *Journal of Applied Mathematics and Physics*, *4*, 1042-1053. https://doi.org/10.4236/jamp.2016.46109

Bienaymé, I. J. (1846). Sur les probabilités des erreurs d'après la méthode des moindres carrés. *Journal De Mathématiques Pures Et Appliquées*, *1*(17), 33-78.

Bolboacă, S. D., Jäntschi, L., Sestraş, A. F., Sestraş, R. E., & Pamfil, D. C. (2011). Pearson-Fisher Chi-Square Statistic Revisited. *Information*, *2*, 528-545. https://doi.org/10.3390/info2030528

Bravais, A. (1846). Analyse mathématique sur les probabilités des erreurs de situation d'un point. *Mémoires Présentées Par Divers Savants À L'Académie Royale Des Sciences De L 'Institut De France*, *9*, 255-332.

Burke, A. P., Yen, T. S., Shekitka, K. M., & Sobin, L. H. (1990). Lymphoepithelial carcinoma of the stomach with Epstein-Barr virus demonstrated by polymerase chain reaction. *Modern Pathology: An Official Journal of the United States and Canadian Academy of Pathology, Inc*, *3*(3), 377-380.

Chapel, F., Fabiani, B., Davi, F., Raphael, M., Tepper, M., Champault, G., & Guettier, C. (2000). Epstein-Barr virus and gastric carcinoma in Western patients: comparison of pathological parameters and p53 expression in EBV-positive and negative tumours. *Histopathology*, *36*(3), 252-261.

Chen, J. N., Ding, Y. G., Feng, Z. Y., Li, H. G., He, D., Du, H., … Shao, C. K. (2010). Association of distinctive Epstein-Barr virus variants with gastric carcinoma in Guangzhou, southern China. *Journal of Medical Virology*, *82*, 658-667. https://doi.org/10.1002/jmv.21731

Chen, X. Z., Chen, H., Castro, F. A., Hu, J. K., & Brenner, H. (2015). Epstein-Barr virus infection and gastric cancer: a systematic review. *Medicine*, *94*, e792. https://doi.org/10.1097/MD.0000000000000792

Clopper, C. J., & Pearson, E. S. (1934). The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial. *Biometrika*, *26*, 404-413. https://doi.org/10.1093/biomet/26.4.404

Corvalan, A., Koriyama, C., Akiba, S., Eizuru, Y., Backhouse, C., Palma, M., … Tokunaga, M. (2001). Epstein-Barr virus in gastric carcinoma is associated with location in the cardia and with a diffuse histology: A study in one area of Chile. *International Journal of Cancer*, *94*(4), 527-530.

Decker, L. L., Klaman, L. D., & Thorley-Lawson, D. A. (1996). Detection of the latent form of Epstein-Barr virus DNA in the peripheral blood of healthy individuals. *Journal of Virology*, *70*(5), 3286-3289.

Dixon, F. J., Talmage, D. W., Maurer, P. H., & Deichmiller, M. (1952). The half-life on homologous gamma globulin (antibody) in several species. *The Journal of Experimental Medicine*, *95*(5), 313-318.

Fanaian, N. K., Cohen, C., Waldrop, S., Wang, J., & Shehata, B. M. (2009). Epstein-Barr virus (EBV)-encoded RNA: automated in-situ hybridization (ISH) compared with manual ISH and immunohistochemistry for detection of EBV in pediatric lymphoproliferative disorders. *Pediatric and Developmental Pathology: The Official Journal of the Society for Pediatric Pathology and the Paediatric Pathology Society*, *12*, 195-199. https://doi.org/10.2350/07-07-0316.1

Fisher, R. A. (1922). On the Interpretation of χ 2 from Contingency Tables, and the Calculation of P. *Journal of the Royal Statistical Society*, *85*, 87-94. https://doi.org/10.2307/2340521

Fukayama, M., Hayashi, Y., Iwasaki, Y., Chong, J., Ooba, T., Takizawa, T., … Hirai, K. (1994). Epstein-Barr virus-associated gastric carcinoma and Epstein-Barr virus infection of the stomach. *Laboratory Investigation; a Journal of Technical Methods and Pathology*, *71*(1), 73-81.

Galetsky, S. A., Tsvetnov, V. V., Land, C. E., Afanasieva, T. A., Petrovichev, N. N., Gurtsevitch, V. E., & Tokunaga, M. (1997). Epstein-Barr-virus-associated gastric cancer in Russia. *International Journal of Cancer*, *73*(6), 786-789.

Gall, J. G., & Pardue, M. L. (1969). FORMATION AND DETECTION OF RNA-DNA HYBRID MOLECULES IN CYTOLOGICAL PREPARATIONS *Proceedings of the National Academy of Sciences of the United States of America*, *63*(2), 378-383.

Gatto, D., & Brink, R. (2010). The germinal center reaction. *The Journal of Allergy and Clinical Immunology*, *126*, 898-907; quiz 908-9. https://doi.org/10.1016/j.jaci.2010.09.007

Gorroochurn, P. (2016). KARL PEARSON'S CHI-SQUARED GOODNESS-OF-FIT TEST. In P. Gorroochurn (Ed.), *Classic topics on the history of modern mathematical statistics: From Laplace to more recent times* (pp. 293-347). Hoboken, New Jersey: John Wiley & Sons Inc. https://doi.org/10.1002/9781119127963.ch3

Gorroochurn, P. (Ed.) (2016). *Classic topics on the history of modern mathematical statistics: From Laplace to more recent times*. Hoboken, New Jersey: John Wiley & Sons Inc.

Gulley, M. L., Pulitzer, D. R., Eagan, P. A., & Schneider, B. G. (1996). Epstein-Barr virus infection is an early event in gastric carcinogenesis and is independent of bcl-2 expression and p53 accumulation. *Human Pathology*, *27*(1), 20-27.

Gurtsevich, V. E., Galetskiĭ, S. A., Nered, S. N., Novikova, E. V., Iakovleva, L. S., Land, C. E., … Tokunaga, M. (1999). Obnaruzhenie i kharakteristika opukholeĭ zheludka, assotsiirovannykh s virusom gerpesa épsteĭn-barr [Detection and characterization of gastric carcinoma associated with epstein-barr herpes virus]. *Vestnik Rossiiskoi Akademii Meditsinskikh Nauk*, (3), 56-59.

Hanley, J. A. (1983). If Nothing Goes Wrong, Is Everything All Right? *JAMA*, *249*, 1743. https://doi.org/10.1001/jama.1983.03330370053031

Harn, H. J., Chang, J. Y., Wang, M. W., Ho, L. I., Lee, H. S., Chiang, J. H., & Lee, W. H. (1995). Epstein-Barr virus-associated gastric adenocarcinoma in Taiwan. *Human Pathology*, *26*(3), 267-271.

Harn, H. J., Ho, L. I., Chung, W. H., Lin, J. J., Lee, H. S., & Lee, W. H. (1995). Epstein-Barr virus-associated typical gastric carcinoma detected by in situ hybridization and polymerase chain reaction. *Journal of Clinical Gastroenterology*, *20*(3), 253-254.

Henrickson, S. E. (2018) To EBV or not to EBV: Rational vaccine design for a common infection. *Science Immunology*, *3*. https://doi.org/10.1126/sciimmunol.aat9661

Herrera-Goepfert, R., Akiba, S., Koriyama, C., Ding, S., Reyes, E., Itoh, T., … Eizuru, Y. (2005). Epstein-Barr virus-associated gastric carcinoma: Evidence of age-dependence among a Mexican population. *World Journal of Gastroenterology*, *11*, 6096-6103. https://doi.org/10.3748/wjg.v11.i39.6096

Hill, A. B. (1965). The environment and disease: association or causation? *Proceedings of the Royal Society of Medicine*, *58*, 295-300. https://doi.org/10.1177/0141076814562718

Imai, S., Koizumi, S., Sugiura, M., Tokunaga, M., Uemura, Y., Yamamoto, N., … Osato, T. (1994). Gastric carcinoma: monoclonal epithelial malignant cells expressing Epstein-Barr virus latent infection protein. *Proceedings of the National Academy of Sciences of the United States of America*, *91*(19), 9131-9135.

Ishii, H. H., Gobe, G. C., Yoneyama, J., Mukaide, M., & Ebihara, Y. (2004). Role of p53, apoptosis, and cell proliferation in early stage Epstein-Barr virus positive and negative gastric carcinomas. *Journal of Clinical Pathology*, *57*, 1306-1311. https://doi.org/10.1136/jcp.2003.015081

Jovanovic, B. D., & Levy, P. S. (1997). A Look at the Rule of Three. *The American Statistician*, *51*, 137-139. https://doi.org/10.1080/00031305.1997.10473947

Kang, G. H., Lee, S., Kim, W. H., Lee, H. W., Kim, J. C., Rhyu, M. G., & Ro, J. Y. (2002). Epstein-barr virus-positive gastric carcinoma demonstrates frequent aberrant methylation of multiple genes and constitutes CpG island methylator phenotype-positive gastric carcinoma. *The American Journal of Pathology*, *160*, 787-794. https://doi.org/10.1016/S0002-9440(10)64901-2

Kocher, M. S., & Zurakowski, D. (2004). Clinical epidemiology and biostatistics: A primer for orthopaedic surgeons. *The Journal of Bone and Joint Surgery. American Volume*, *86-A*(3), 607-620.

Kolmogoroff, A. (1933). *Grundbegriffe der Wahrscheinlichkeitsrechnung*. *Ergebnisse der Mathematik und Ihrer Grenzgebiete: Vol. 2*. Berlin, Heidelberg, s.l.: Springer Berlin Heidelberg. Retrieved from https://doi.org/10.1007/978-3-642-49888-6

Kume, T., Oshima, K., Shinohara, T., Takeo, H., Yamashita, Y., Shirakusa, T., & Kikuchi, M. (1999). Low rate of apoptosis and overexpression of bcl-2 in Epstein-Barr virus-associated gastric carcinoma. *Histopathology*, *34*(6), 502-509.

Lancaster, H. O., & Seneta, E. (2005). Chi-Square Distribution. In P. Armitage & T. Colton (Eds.), *Encyclopedia of biostatistics* (2nd ed.). Chichester, West Sussex, England, Hoboken, NJ: John Wiley. https://doi.org/10.1002/0470011815.b2a15018

Leemis, L. M., & Trivedi, K. S. (1996). A Comparison of Approximate Interval Estimators for the Bernoulli Parameter. *The American Statistician*, *50*, 63. https://doi.org/10.2307/2685046

Lopes, L. F., Bacchi, M. M., Elgui-de-Oliveira, D., Zanati, S. G., Alvarenga, M., & Bacchi, C. E. (2004). Epstein-Barr virus infection and gastric carcinoma in São Paulo State, Brazil. *Brazilian Journal of Medical and Biological Research = Revista Brasileira De Pesquisas Medicas E Biologicas*, *37*(11), 1707-1712.

Louis, T. A. (1981). Confidence Intervals for a Binomial Parameter after Observing No Successes. *The American Statistician*, *35*, 154. https://doi.org/10.1080/00031305.1981.10479337

Luo, B., Wang, Y., Wang, X. F., Liang, H., Yan, L. P., Huang, B. H., & Zhao, P. (2005). Expression of Epstein-Barr virus genes in EBV-associated gastric carcinomas. *World Journal of Gastroenterology*, *11*, 629-633. https://doi.org/10.3748/wjg.v11.i5.629

Luqmani, Y. A., Linjawi, S. O., & Shousha, S. (2001). Detection of Epstein-Barr virus in gastrectomy specimens. *Oncology Reports*, *8*(5), 995-999.

Mandell, G. L., Douglas, R. G., & Bennett, J. E. (2005). *Mandell, Douglas, and Bennett's principles and practice of infectious diseases* ([6. - 8. ed.]). Philadelphia, Pa.: Elsevier.

Moritani, S., Kushima, R., Sugihara, H., & Hattori, T. (1996). Phenotypic characteristics of Epstein-Barr-virus-associated gastric carcinomas. *Journal of Cancer Research and Clinical Oncology*, *122*(12), 750-756.

Neyman, J. (1937). Outline of a Theory of Statistical Estimation Based on the Classical Theory of Probability. *Philosophical Transactions of the Royal Society a: Mathematical, Physical and Engineering Sciences*, *236*, 333–380. https://doi.org/10.1098/rsta.1937.0005

Oda, K., Koda, K., Takiguchi, N., Nunomura, M., Seike, K., & Miyazaki, M. (2003). Detection of Epstein-Barr virus in gastric carcinoma cells and surrounding lymphocytes. *Gastric Cancer: Official Journal of the International Gastric Cancer Association and the Japanese Gastric Cancer Association*, *6*, 173-178. https://doi.org/10.1007/s10120-003-0247-2

Ohfuji, S., Osaki, M., Tsujitani, S., Ikeguchi, M., Sairenji, T., & Ito, H. (1996). Low frequency of apoptosis in Epstein-Barr virus-associated gastric carcinoma with lymphoid stroma. *International Journal of Cancer*, *68*(6), 710-715.

Ott, G., Kirchner, T., & Müller-Hermelink, H. K. (1994). Monoclonal Epstein-Barr virus genomes but lack of EBV-related protein expression in different types of gastric carcinoma. *Histopathology*, *25*(4), 323-329.

Parkin, D. M., Bray, F., Ferlay, J., & Pisani, P. (2005). Global cancer statistics, 2002. *CA: A Cancer Journal for Clinicians*, *55*(2), 74-108.

Pearson, K. (1896). Mathematical Contributions to the Theory of Evolution. III. Regression, Heredity, and Panmixia. *Philosophical Transactions of the Royal Society a: Mathematical, Physical and Engineering Sciences*, *187*, 253-318. https://doi.org/10.1098/rsta.1896.0007

Pearson, K. (1900). X. 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. *The London, Edinburgh, and Dublin Philosophical Magazine and Journal of Science*, *50*, 157-175. https://doi.org/10.1080/14786440009463897

Pearson, K. (1904). On the theory of contingency and its relation to association and normal correlation. *London*, 1-46. Retrieved from https://archive.org/details/cu31924003064833

Ressing, M. E., van Gent, M., Gram, A. M., Hooykaas, M. J. G., Piersma, S. J., & Wiertz, E. J. H. J. (2015). Immune Evasion by Epstein-Barr Virus. *Current Topics in Microbiology and Immunology*, *391*, 355-381. https://doi.org/10.1007/978-3-319-22834-1_12

Rumke, C. L. (1975). Implications of the Statement: No Side Effects Were Observed. *The New England Journal of Medicine*, *292*, 372-373. https://doi.org/10.1056/NEJM197502132920723

Sachs, L. (1992). *Angewandte Statistik: Anwendung statistischer Methoden* (Siebente, völlig neu bearbeitete Auflage). Berlin, Heidelberg: Springer. Retrieved from http://dx.doi.org/10.1007/978-3-662-05747-6

Selves, J., Bibeau, F., Brousset, P., Meggetto, F., Mazerolles, C., Voigt, J. J., … Delsol, G. (1996). Epstein-Barr virus latent and replicative gene expression in gastric carcinoma. *Histopathology*, *28*(2), 121-127.

Shibata, D., & Weiss, L. M. (1992). Epstein-Barr virus-associated gastric adenocarcinoma. *The American*

Journal of Pathology, *140*(4), 769-774.

Shousha, S., & Luqmani, Y. A. (1994). Epstein-Barr virus in gastric carcinoma and adjacent normal gastric and duodenal mucosa. *Journal of Clinical Pathology*, *47*(8), 695-698.

Tokunaga, M., Land, C. E., Uemura, Y., Tokudome, T., Tanaka, S., & Sato, E. (1993). Epstein-Barr virus in gastric carcinoma. *The American Journal of Pathology*, *143*(5), 1250-1254.

Truong, C. D., Feng, W., Li, W., Khoury, T., Li, Q., Alrawi, S., … Tan, D. (2009). Characteristics of Epstein-Barr virus-associated gastric cancer: A study of 235 cases at a comprehensive cancer center in U.S.A. *Journal of Experimental & Clinical Cancer Research: CR*, *28*, 14. https://doi.org/10.1186/1756-9966-28-14

Vasef, M. A., Weiss, L. M., Chen, Y. Y., & Medeiros, L. J. (1996). Gastric lymphoepithelioma-like carcinoma and jejunal B-cell MALT lymphoma with large cell transformation. Demonstration of EBV with identical LMP gene deletions in the carcinoma and large cell lymphoma. *American Journal of Clinical Pathology*, *105*(5), 560-566.

Von Rahden, Burkhard H. A. von, Langner, C., Brücher, B. L. D. M., Stein, H. J., & Sarbia, M. (2006). No association of primary adenocarcinomas of the small bowel with Epstein-Barr virus infection. *Molecular Carcinogenesis*, *45*, 349-352. https://doi.org/10.1002/mc.20163

Wan, R., Gao, M. Q., Gao, L. Y., Chen, B. F., & Cai, Q. K. (1999). In situ detection of Epstein-Barr virus in gastric carcinoma tissue in China highrisk area. *World Journal of Gastroenterology*, *5*, 531-532. https://doi.org/10.3748/wjg.v5.i6.531

Wang, Y., Luo, B., Zhao, P., & Huang, B. H. (2004). Expression of Epstein-Barr virus genes in EBV-associated gastric carcinoma. *Ai Zheng = Aizheng = Chinese Journal of Cancer*, *23*(7), 782-787.

Wiener, A. S. (1951) The half-life of passively acquired antibody globulin molecules in infants. *The Journal of Experimental Medicine*, *94*(3), 213-221.

Wright, S. (1921). Correlation and Causation. *Journal of Agricultural Research*, *20*, 557-585.

Yamane, T. (Ed.) (1964). *Statistics. An introductory analysis*: Harper International Edition.

Yates, F. (1934). Contingency Tables Involving Small Numbers and the χ 2 Test. *The Journal of the Royal Statistical Society (Supplement)*, *1*, 217-235. https://doi.org/10.2307/2983604

Yuen, S. T., Chung, L. P., Leung, S. Y., Luk, I. S., Chan, S. Y., & Ho, J. (1994). In situ detection of Epstein-Barr virus in gastric and colorectal adenocarcinomas. *The American Journal of Surgical Pathology*, *18*(11), 1158-1163.

Zhang, R., Li, F., Li, H., Yu, J., & Ren, X. (2014). The clinical significance of memory T cells and its subsets in gastric cancer. *Clinical & Translational Oncology: Official Publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico*, *16*, 257-265. https://doi.org/10.1007/s12094-013-1066-5

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