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RESEARCH ARTICLE

Helicobacter Pylori is the Cause of Human Gastric Cancer

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Disclosure
The authors report no conflicts of interest.

ABSTRACT
Background—Helicobacter pylori (HP) infection has been repeatedly reported to be associated with human gastric cancer (GC). However, Epstein Bar virus (EBV) has been found in gastric cancer tissues too. It is therefore not surprising that it proved difficult to establish a causal relationship between Helicobacter pylori and gastric cancer. A systematic review and meta-analysis of observational studies was performed to re-investigate the relationship between Helicobacter pylori and gastric cancer.
Material and methods—The electronic database PubMed was searched for titles and abstracts of studies which investigated the relationship between HP and GC. Four eligible Japanese studies were included in this meta-analysis (196 incident gastric cancers among a total of 14792 individuals). The data available were analysed by new statistical methods. This study considers 5% as a reasonable cut-off for statistical significance.
Results—The studies reviewed provided highly significant evidence that a HP infection is a necessary condition of GC. In everyday language, **without** a helicobacter pylori infection, **no** human gastric cancer (P Value < .004). In the same respect, the causal relationship between HP and GC was highly significant too.
Conclusion—In a systematic review and meta-analysis, it was possible to establish a causal relationship between HP and GC. Helicobacter pylori is the cause of human gastric cancer.

Keywords: Helicobacter pylori; human gastric cancer; cause effect relationship;

INTRODUCTION

Helicobacter pylori shares a very intimate coevolutionary history with humans for longer than previously thought[1,2] and is meanwhile a valuable tool for tracking[3,4] human migration over more than the last 100,000 years and possibly longer. In point of fact, HP, first described by Marshall and Warren[5] in the 1980s, is a spiral-shaped gram-negative human gastric bacterium able to withstand harsh environmental conditions. The global prevalence[6] of HP infection is varying between 24.4% and 70.1%. It has been repeatedly reported that the prevalence of HP is particularly higher in countries with inferior socioeconomic conditions[7]. Various authors favour the faecal-oral and oral-oral transmissions[8] of HP while even the sexual transmission[9] route of HP has been discussed too. In particular, well established and growing evidence indicates that this microorganism is mainly related with different extra gastric manifestations[10] and several gastroduodenal disturbances like peptic ulcer[5], mucosa- associated lymphoid tissue lymphoma[11,12] (MALT), and even human gastric cancer[13,14]. "There is sufficient evidence in humans for the carcinogenicity of infection with Helicobacter pylori... Infection with Helicobacter pylori is carcinogenic to humans (Group 1)."[15(p220)]

Even against the backdrop of various systematic review[16] and meta-analysis[17] of the relationship between HP and GC, an ultimate and generally accepted solution of the nature of the relationship between HP and GC is still not in sight. Uncertainty grew in particular as a result of the fact that Epstein-Barr virus (EBV), discovered 1964 by Michael Anthony Epstein, Bert Geoffrey Achong and Yvonne M. Barr[18], has been demonstrated in about 10% of the malignant epithelial cells of gastric cancer[19] too. Thus far, the contradictions came to a head by a systematic review and meta-analysis of Chen et al. which came to the conclusion that "... tissue-based ISH methods strongly suggest an association between EBV infection and gastric cancer ..."[20]. It seems to be our human fate to deal with never-ending contradictions. Therefore it is certainly natural, human and understandable that it burns sometimes on our soul to ask even at this place a recurring question once again. **Which came first, the chicken or the egg**[21]? In other words, is HP a pathogen which changes or damages human gastric mucosa i.e. in order to survive in exceptionally harsh living conditions or is it more likely that HP itself is only a kind of a secondary invader of an already pre-damaged human gastric mucosa? Finally, with this background in mind, it is not the intent of this article to provide another systematic[22,23] review and meta-analysis of the relationship between HP and GC based on maximum articles possible. This work has already been done several times before by various[24,25] authors, including Barukčić[13,14] himself. The primary task of this article is to provide a final, reliable and credible clarification of the causal relationship between HP and GC and to overcome any thinkable doubt with regard to this relationship by reviewing some excellent and extraordinary studies while equally disproving the causative significance of EBV in relation to gastric cancer.

MATERIAL AND METHODS

Material

This meta-analysis was performed in a manner consistent with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [22] (PRISMA) guideline.

Search strategy

The published literature was identified by searching the electronic database PubMed. The search strategy was as follows: (Helicobacter pylori[MeSH Term]) AND (gastric cancer[MeSHTerm]) AND (IgG[MeSHTerm]). Reference lists of the identified articles were manually screened by the author in order to identify further relevant studies. In toto, 538 titles and abstracts were identified and screened against inclusion criteria.

Inclusion criteria

Systematic errors (bias) or random errors are determined by various factors and are present to some degree in all experimental i.e. interventional (Phase I-IV study, Intervention study, Field study, Group study) and observational i.e. noninterventional (Prospective study, Case-control study, Cohort Study, Cross-sectional study) research. Therefore, it is not surprising that the design of a medical study and the choice of a study type are major determinants of the quality of the data of a study and of its clinical value. In order to prevent us from being confronted with erroneous statistically significant results which could negatively influence future studies and which could possibly lead to completely wrong expectations, several effective counter-measures are necessary. One of these counter-measures is the use of a more robust mathematical-logical methodology as partially presented in this publication. Clarity can be provided too by lowering the significance level α for every single test performed. A clinical study based on a randomized controlled trial (RCT) cannot always be conducted. Observational studies can be a valuable alternative to randomized

controlled trial in such circumstances. However, the potential weaknesses of observational data need to be counteracted and can be reduced i. e. by increasing the sample size. Prospective not exclusively immunoglobulin G (IgG) based studies with more than 1000 participants were included. In order to reduce the impact of bias or random error of IgG based observational studies with smaller sample size, IgG based observational studies with less than 3000 participants were excluded. There was no restriction on age, sex or ethnicity et cetera of the enrolled subjects.

Data sources and studies

After exclusion of inappropriate records, the following studies were included in this review and meta-analysis. In this part, it is A = $E(U_t)$ and B = $E(W_t)$.

Uemura et al. [26] at the Kure Kyosai Hospital, Japan, investigated the relationship between HP and GC by *a prospective, long-term study* of a large group of patients with a mean duration of follow-up of 7.8 years. The base-line data and the statistical analysis are shown by **table 3**. The exact one-sided right tailed P Value according to the hypergeometric distribution is P Value = 0.0006161496354787965 and has been calculated as

$$p(X \geq a) = 1 - \sum_{i=0}^{a-1} \frac{\binom{A}{i}\binom{N-A}{B-i}}{\binom{N}{B}}$$

$$= 1 - \sum_{i=0}^{36-1} \frac{\binom{1246}{i}\binom{1526-1246}{36-i}}{\binom{1526}{36}}$$

Table 3: HP and GC (Study Uemura et al., 2001)

		Gastric cancer		
		YES	NO	
HP positive	YES	36	1210	1246
	NO	0	280	280
		36	1490	1526

STATISTICAL ANALYSIS.

Causal relationship k = + 0.07368483
P Value right tailed (HGD) = 0.0006161496
p (without HP no GC) = 1.0000000000
χ^{-2} (SINE — B_t) = 0.0000
χ^{-2} (SINE — $\underline{A}_t$) = 0.0000
P Value right tailed (HGD) = 0.0006
P Value (SINE) = 0.0000000000

RELATIVE RISK (RR).

RR (nc) = Div. by zero

RR (sc) = +1.2314

ADDITIONAL MEASURES.

OR = +0.2071
IOR = +0.2247

STUDY DESIGN.

p(IOU)= +0.159895151
p(IOI)= +0.792922674

Kazumasa Miki[27] used *serum anti-Helicobacter pylori immunoglobulin antibodies* to evaluate the relationship between HP and GC. The base-line data of the study of Kazumasa Miki and the statistical analysis are shown in **table 4.** The exact one-sided right tailed P Value according to the hypergeometric distribution is P Value = 0.0018314551185057003 and has been calculated as

$$p(X \geq a) = 1 - \sum_{i=0}^{a-1} \frac{\binom{A}{i}\binom{N-A}{B-i}}{\binom{N}{B}}$$

$$= 1 - \sum_{i=0}^{59-1} \frac{\binom{4210}{i}\binom{5290-4210}{63-i}}{\binom{5290}{63}}$$

Table 4: HP and GC (Study Kazumasa Miki, 2011)

		Gastric cancer		
		YES	NO	
HP positive	YES	59	4151	4210
	NO	4	1076	1080
		63	5227	5290

STATISTICAL ANALYSIS.

Causal relationship k =	+ 0.0383122936
P Value right tailed (HGD) =	0.0018314551
p (without HP no GC) =	**0.9992438563**
χ^{-2} (SINE — B_t) =	0.2540
χ^{-2} (SINE — $\underline{A}_t$) =	0.0148
P Value right tailed (HGD) =	0.0018
P Value (SINE) =	0.0007558579

RELATIVE RISK (RR).

RR (nc) =	+3.7838
RR (sc) =	+1.1793

ADDITIONAL MEASURES.

OR =	+0.2146
IOR =	+0.1768

STUDY DESIGN.

p(IOU)=	+0.192249527
p(IOI)=	+0.783931947

Yoshida et al.[28] measured *serum HP antibody titres* using enzyme-linked immunosorbent assay (ELISA) in order to investigate the relationship between Helicobacter pylori and gastric cancer. In general, it is more or less difficult to confirm an accurate cut-off value to diagnose HP infection while using some commercial serology kits. Gastric cancer cases have been reported with present/past HP infection while the serum HP-IgG antibody titres were below the cut-off value[26]. An inappropriate cut-off value might contribute decisively to overlook many gastric cancer subject which are effectively HP positive. Yoshida et al.[28] classified subjects as HP-infected, (HP antibody titre > 50 U/ml); HP-

negative (HP antibody titre < 30 U/ml) and indeterminate (HP antibody titre ≥ 30 U/ml but ≤ 50 U/ml) their own way. The sensitivity and specificity of the ELISA used Yoshida et al.[28] has been 93,5% and 92,5%. The original data of the study of Yoshida et al. and the statistical analysis are illustrated by **table 5**. The exact one-sided right tailed P Value according to the hypergeometric distribution is P Value = 0.0007194143339914171 and has been calculated as

$$p(X \geq a) = 1 - \sum_{i=0}^{a-1} \frac{\binom{A}{i}\binom{N-A}{B-i}}{\binom{N}{B}}$$

$$= 1 - \sum_{i=0}^{81-1} \frac{\binom{3738}{i}\binom{4655-3738}{87-i}}{\binom{4655}{87}}$$

Table 5: HP and GC (Study Yoshida et al., 2014)

		Gastric cancer		
		YES	NO	
HP positive	YES	81	3657	3738
	NO	6	911	917
		87	4568	4655

STATISTICAL ANALYSIS.

Causal relationship k =	+0.0444235636
P Value right tailed (HGD) =	0.0007194143
p (without HP no GC) =	**0.9987110634**
χ^{2} (SINE — B_t) =	0.4138
χ^{2} (SINE — $\underline{A}_t$) =	0.0393
P Value right tailed (HGD) =	0.0007
P Value (SINE) =	0.0012881063

RELATIVE RISK (RR).

RR (nc) =	+3.3118
RR (sc) =	+1.1630

ADDITIONAL MEASURES.

OR =	+0.2131
IOR =	+0.1594

STUDY DESIGN.

p(IOU)=	+0.1783029
p(IOI)=	+0.784317938

Shuto et al.[29] conducted *a prospective GC screening study* in residents of a rural city in Japan. Endoscopy in positive HP patients detected 10 GC cases out of a total of 3321 patients. The original data of the study of Shuto et al. and the statistical analysis are illustrated by **table 6**. The exact one-sided right tailed P Value according to the hypergeometric distribution is P Value = 0.00354621182756425 and has been calculated as

$$p(X \geq a) = 1 - \sum_{i=0}^{a-1} \frac{\binom{A}{i}\binom{N-A}{B-i}}{\binom{N}{B}}$$

$$= 1 - \sum_{i=0}^{10-1} \frac{\binom{1891}{i}\binom{3321-1891}{10-i}}{\binom{3321}{10}}$$

Table 6: HP and GC (Study Shuto et al., 2017)

		Gastric cancer		
		YES	NO	
HP positive	YES	10	1881	1891
	NO	0	1430	1430
		10	3311	3321

STATISTICAL ANALYSIS.

Causal relationship k =	+0.0477906199
P Value right tailed (HGD) =	0.0035462118
p (without HP no GC) =	**1.0000000000**
χ^{2} (SINE — B_t) =	0.0000
χ^{2} (SINE — $\underline{A}_t$) =	0.0000
P Value right tailed (HGD) =	0.0035
P Value (SINE) =	0.0000000000

RELATIVE RISK (RR).

RR (nc) =	Div. by zero
RR (sc) =	+1.7602

ADDITIONAL MEASURES.

OR =	+0.4336
IOR =	+0.7562

STUDY DESIGN.

p(IOU)=	+0.427582054
p(IOI)=	+0.566395664

Ethics and dissemination

The ethical approval is not required because no primary data are collected.

Methods

Basic Definitions

In the following, we will describe in more detail the logical-mathematical methods used to analyze the data in this study. A more extended and detailed philosophical, logical and other scientific justification as well as the mathematical proofs of the methods which are described next can be found in detail[30] elsewhere[31–35].

Definition: Cause U_t

Let U_t denote a cause (Latin: causa; German: Ursache) or a condition or an event et cetera at a (certain period of) time / Bernoulli[36] trial t. Let $p(U_t)$ denote the probability of U_t at the same (certain period of) time / Bernoulli trial t. Let $E(U_t)$ denote the expectation value of U_t at the same (certain period of) time / Bernoulli trial t. In general, it is

$$p(U_t) = \frac{E(U_t)}{(U_t)} = \frac{(U_t) \times E(U_t)}{(U_t) \times (U_t)} = \frac{E(U_t^{\,2})}{(U_t)^2} = \frac{E(U_t) \times E(U_t)}{(U_t) \times E(U_t)} = \frac{E(U_t)^2}{E(U_t^{\,2})}$$

or

$$p(U_t)^2 = \frac{E(U_t)^2}{(U_t)^2}$$

or

$$1 - p(U_t) = \frac{(U_t) \times \big(1 - p(U_t)\big)}{(U_t)} = \frac{(U_t) - E(U_t)}{(U_t)} = 1 - \frac{E(U_t)}{(U_t)} = \frac{E\big(\underline{U_t}\big)}{(U_t)}$$

The variance of U_t at one single Bernoulli trial t is given as

$$\begin{gathered}\sigma(U_t)^2 = E\big({U_t}^2\big) - E(U_t)^2 \\ = \big((U_t)^2 \times p(U_t)\big) - \big((U_t)^2 \times p(U_t)^2\big) \\ = (U_t)^2 \times p(U_t) \times \big(1 - p(U_t)\big) \\ = (U_t) \quad \times p(U_t) \times (U_t) \quad \times \big(1 - p(U_t)\big) \\ = E(U_t) \times E\big(\underline{U_t}\big)\end{gathered}$$

Furthermore, it is

$$(U_t) = \frac{\sigma(U_t)}{\sqrt[2]{p(U_t) \times \big(1 - p(U_t)\big)}}$$

The relationship before is normalized as

$$\frac{E(U_t)^2}{E\big({U_t}^2\big)} + \frac{\sigma(U_t)^2}{E\big({U_t}^2\big)} = +1$$

In contrast to *Chebyshev*'s[35,37] inequality, the exact probability of a single event is given as

$$p(U_t) = \frac{E(U_t)^2}{E\big({U_t}^2\big)} = 1 - \frac{\sigma(U_t)^2}{E\big({U_t}^2\big)} = 1 - \frac{\sigma(U_t)^2}{(U_t) \times E(U_t)}$$

Under conditions, where an associated *standard error* on the mean is given by the relation

$$\sigma\big(\overline{U}_t\big) = \frac{\sigma(U_t)}{\sqrt[2]{(U_t)}}$$

the exact probability of a single event is given as

$$p(U_t) = 1 - \frac{\sigma(U_t)^2}{E\big({U_t}^2\big)} = \ 1 - \frac{\sigma\big(\overline{U}_t\big)^2}{E(U_t)}$$

Definition: Effect W_t

Let W_t denote an effect (Latin: effectum; German: Wirkung) or a conditioned or another event et cetera at a (certain period of) time / Bernoulli[36] trial t. Let $p(W_t)$ denote the probability of W_t at the same (certain period of) time / Bernoulli trial t. Let $E(W_t)$ denote the expectation value of W_t at the same (certain period of) time / Bernoulli trial t. In general, it is

$$p(W_t) = \frac{E(W_t)}{(W_t)} = \frac{(W_t) \times E(W_t)}{(W_t) \times (W_t)} = \frac{E\big({W_t}^2\big)}{(W_t)^2} = \frac{E(W_t) \times E(W_t)}{(W_t) \times E(W_t)} = \frac{E(W_t)^2}{E\big({W_t}^2\big)}$$

or

$$p(W_t)^2 = \frac{E(W_t)^2}{(W_t)^2}$$

or

$$1 - p(W_t) = 1 - \frac{E(W_t)}{(W_t)} = \frac{(W_t) - E(W_t)}{(W_t)} = \frac{(W_t) \times \left(1 - p(W_t)\right)}{(W_t)} = \frac{E\left(\underline{W_t}\right)}{(W_t)}$$

The variance of W_t at one single Bernoulli trial t is given as

$$\begin{gathered}\sigma(W_t)^2 = E\left({W_t}^2\right) - E(W_t)^2 \\ = \left((W_t)^2 \times p(W_t)\right) - \left((W_t)^2 \times p(W_t)^2\right) \\ = (W_t)^2 \times p(W_t) \times \left(1 - p(W_t)\right) \\ = (W_t) \times p(W_t) \times (W_t) \times \left(1 - p(W_t)\right) \\ = E(W_t) \times E\left(\underline{W_t}\right)\end{gathered}$$

Furthermore, it is

$$(W_t) = \frac{\sigma(W_t)}{\sqrt[2]{p(W_t) \times \left(1 - p(W_t)\right)}}$$

Definition: Cause and effect (U_t , W_t)

Let (U_t , W_t) denote cause and effect at a (certain period of) time / Bernoulli[36] trial t. Let p(U_t , W_t) denote the joint probability of cause and effect at the same (certain period of) time / Bernoulli trial t. Furthermore, let E(U_t , W_t) denote the expectation value of cause and effect at the same (certain period of) time / Bernoulli trial t. In general, it is

$$p(U_t, W_t) = \frac{E(U_t, W_t)}{(U_t, W_t)}$$

or

$$p(U_t, W_t)^2 = \frac{E(U_t, W_t)^2}{(U_t, W_t)^2}$$

or

$$1 - p(U_t, W_t) = 1 - \frac{E(U_t, W_t)}{(U_t, W_t)} = \frac{(U_t, W_t) - E(U_t, W_t)}{(U_t, W_t)}$$

The co-variance of cause and effect at one single Bernoulli trial t is given as

$$\begin{gathered}\sigma(U_t, W_t) = E(U_t, W_t) - \left(E(U_t) \times E(W_t)\right) \\ = \left((U_t, W_t) \times p(U_t, W_t)\right) - \left((U_t) \times p(W_t) \times (W_t) \times p(W_t)\right) \\ = (U_t, W_t) \times \left(p(U_t, W_t) - \left(p(U_t) \times p(W_t)\right)\right)\end{gathered}$$

Furthermore, it is

$$(U_t, W_t) = \frac{\sigma(U_t, W_t)}{\sqrt[2]{p(U_t, W_t) - \left(p(U_t) \times p(W_t)\right)}}$$

Extended Definitions

The coincidence or the occurrence of cause and effect at a (certain period of) time / Bernoulli[36] trial t is given as

$$p(a_t) = p(U_t, W_t)$$

In the following, we consider the following identities. It is

$$p(U_t) = p(a_t) + p(b_t)$$

and

$$p(\underline{U_t}) = p(c_t) + p(d_t)$$

and

$$p(W_t) = p(a_t) + p(c_t)$$

and

$$p(\underline{W_t}) = p(b_t) + p(d_t)$$

and

$$p(a_t) + p(b_t) + p(c_t) + p(d_t) = p(U_t) + p(\underline{U_t}) = p(W_t) + p(\underline{W_t}) = +1$$

The basic relationships as described before are illustrated by the following contingency table (table 1).

Table 1: The relationship between cause and effect.

		Effect		
		YES	NO	
Cause	YES	$p(a_t)$	$p(b_t)$	$p(U_t)$
	NO	$p(c_t)$	$p(d_t)$	$p(\underline{U_t})$
		$p(W_t)$	$p(\underline{W_t})$	+1

Conditions

Definition: Conditio sine qua non

Conditio sine qua non or the necessary[38,39] condition relationship between cause and effect, denoted as p ($U_t \leftarrow W_t$), at a (certain period of) time / Bernoulli[36] trial t is defined as

$$p(U_t \leftarrow W_t) = p(a_t) + p(b_t) + p(d_t) = p(U_t) + p(d_t) = p(a_t) + p(\underline{W_t}) = +1$$

Example. *Without* gaseous oxygen (U_t), *no* human life (W_t).

Under conditions of a Binomial distribution with a population or sample size N, it is

$$E(U_t \leftarrow W_t) = N \times p(U_t \leftarrow W_t) = N \times \big(p(a_t) + p(b_t) + p(d_t)\big)$$
$$= \big(E(a_t) + E(b_t) + E(d_t)\big) = N$$

Definition: Conditio per quam

Conditio per quam or the sufficient[40] condition relationship between cause and effect, denoted as p ($U_t \rightarrow W_t$), at a (certain period of) time / Bernoulli[36] trial t is defined as

$$p(U_t \rightarrow W_t) = p(a_t) + p(c_t) + p(d_t) = p(W_t) + p(d_t) = p(a_t) + p(\underline{U_t}) = +1$$

Example. *If* it is raining (U_t), *then* the street is wet (W_t).

Definition: Necessary and sufficient conditions

A necessary and sufficient condition relationship between cause and effect, denoted as p (U_t <-> W_t), at a (certain period of) time / Bernoulli[36] trial t is defined as

$$p(U_t \leftrightarrow W_t) = p(a_t) + p(d_t) = +1$$

Definition: Either or conditions

An either U_t or W_t condition relationship between cause and effect at a (certain period of) time / Bernoulli[36] trial t is defined as

$$p(U_t > -< W_t) = p(b_t) + p(c_t) = +1$$

Definition: Exclusion relationship

An exclusion[41] relationship between cause and effect or U_t excludes W_t at a (certain period of) time / Bernoulli[36] trial t is defined as

$$p(U_t \uparrow W_t) = p(b_t) + p(c_t) + p(d_t) = +1 - p(a_t) = +1$$

Example. Being a man (U_t) and being a pregnant human being (W_t) excludes each other. Another example. A year-long use of the drug atorvastatin[42(p24)] (U_t) excludes lung cancer (W_t) ($p(U_t \uparrow W_t) =$ **0,9994**4391; P Value = 0,00055594) almost as effective as BionTech's ® mRNA[41(p9)] Cvoid-19 vaccine[35(p9)] (U_t) excludes Covid-19 infection (W_t) ($p(U_t \uparrow W_t) =$ **0,9998**1625; P Value = 0.0001837475309).

Under conditions of a Binomial distribution table 1 is multiplied by the population or the sample size N and becomes table 2.

Table 2: Cause and effect under condition's of a Binomial distribution.

		Effect		
		YES	NO	
Cause	YES	$E(a_t)$	$E(b_t)$	$E(U_t)$
	NO	$E(c_t)$	$E(d_t)$	$E(\underline{U}_t)$
		$E(W_t)$	$E(\underline{W}_t)$	N

Definition: The Chi-square goodness of fit test of a necessary condition relationship

Under some certain circumstances, a hypothesis about the conditio sine qua non relationship between cause (U_t) and effect (W_t) can be tested by the chi-square distribution, first described by the German statistician Friedrich Robert Helmert[43] and later rediscovered by Karl Pearson[44] in the context of a goodness of fit test. The Chi-square goodness of fit test of a conditio sine qua relationship (degrees of freedom 1) has been derived[35] as

$$\chi^2(U_t \leftarrow W_t) = \frac{E(c_t)^2}{E(B_t)^2} + 0$$

and equally as

$$\chi^2(U_t \leftarrow W_t) = \frac{E(c_t)^2}{E(\underline{A}_t)^2} + 0$$

The calculated chi-square value is compared with a theoretical chi-square value at a certain level of significance. The use of Yate's[45] continuity correction was neglected in this regard.

Definition: The left-tailed P Value of a necessary condition relationship

The left-tailed P Value of a necessary condition relationship calculated for a larger sample size has been derived[46] as

$$P\,Value_{left\,tailed}(U_t \leftarrow W_t) = 1 - e^{-(1-p(U_t \leftarrow W_t))} = 1 - e^{-(E(c_t)/N)}$$

Definition: Risk ratio RR_{nc} (U_t , W_t)

Under some circumstances, the original risk ratio[47–49] between cause (U_t) and effect (W_t), denoted as RR_{nc} (U_t , W_t), provides some slight and inferior evidence of a **necessary condition** (RR_{nc} (U_t , W_t) > +1) or of a mutually exclusive relationship (RR_{nc} (U_t , W_t) < +1) and is defined as

$$RR_{nc}(U_t, W_t) = \frac{E(a_t) \times E(\underline{U_t})}{E(c_t) \times E(U_t)}$$

Definition: Risk ratio RR_{sc} (U_t , W_t)
Furthermore, under some circumstances, the extended risk ratio[47–49] between cause (U_t) and effect (W_t), denoted as RR_{sc} (U_t , W_t), provides some slight and inferior evidence of a **sufficient**[49(p18)] **condition** (RR_{sc} (U_t , W_t) > +1) and equally of a mutually exclusive relationship (RR_{sc} (U_t , W_t) < +1) and is defined as

$$RR_{sc}(U_t, W_t) = \frac{E(a_t) \times E(\underline{B_t})}{E(b_t) \times E(B_t)}$$

Under conditions where the quality of data is very restricted or where the study design is very problematic, or due to other justifiable reasons, a statistically significant RR_{nc} (U_t , W_t) with RR_{nc} (U_t , W_t) > +1 and a statistically significant RR_{sc} (U_t , W_t) with RR_{sc} (U_t , W_t) > +1 calculated on the same data body would point to some very slight extent to the possibility of a necessary and sufficient condition which itself is a very vague and purely preliminary pre-stage of a causal relationship between the factors investigated.

Definition: Odds ratio OR(U_t , W_t)
The Odds [50–52] ratio, a re-formulation of Yule'Q[53], between cause (U_t) and effect (W_t), denoted as OR(U_t , W_t) is defined as

$$OR(U_t, W_t) = \frac{E(a_t) \times E(d_t)}{E(b_t) \times E(c_t)}$$

Definition: Index of relationship IOR(U_t , W_t)
The index[54] of relationship, denoted as IOR(U_t , W_t), between cause (U_t) and effect (W_t), is a very simple and robust mathematical alternative to risk ratio and odds ratio, and defined as

$$IOR(U_t, W_t) = \frac{N \times E(a_t)}{E(U_t) \times E(W_t)} - 1$$

Study design
Definition: Index[55] of unfairness (IOU)
The index of unfairness between cause (U_t) and effect (W_t) is denoted as IOU(U_t , W_t) and defined as

$$IOU(U_t, W_t) = \frac{E(U_t) + E(W_t)}{N} - 1$$

The p(IOU(U_t , W_t)) is given as

$$p\big(IOU(U_t, W_t)\big) = Absolute\left(\frac{E(U_t) + E(W_t)}{N} - 1\right)$$

A design[56] of a study which aims to support an investigation of a necessary or of a sufficient condition relationship between cause (U_t) and effect (W_t) or both relationships between cause (U_t) and effect (W_t) should assure as much as possible a p(IOU(U_t , W_t)) near to zero or at best p(IOU(U_t , W_t)) = 0.

Definition: Index[55] of independence (IOI)
The index of independence[57] between cause (U_t) and effect (W_t) is denoted as IOI(U_t , W_t) and defined as

$$IOI(U_t, W_t) = \frac{E(U_t) + E(\underline{W_t})}{N} - 1$$

The p(IOI(U_t , W_t)) is given as

$$p\big(IOI(U_t, W_t)\big) = Absolute\left(\frac{E(U_t) + E(\underline{W_t})}{N} - 1\right)$$

A study which aims to investigate a causal[57] relationship between cause (U_t) and effect (W_t) or a mutually exclusive relationship between cause (U_t) and effect (W_t) should be designed such that p(IOI(U_t , W_t)) is as much as possible near to zero or at best p(IOI(U_t , W_t)) = 0.

Causal relationship k

Definition: Causal relationship k

Let U_t denote a cause (Latin: causa; German: Ursache) or a condition or an event et cetera at a (certain period of) time / Bernoulli[36] trial t. Let p(U_t) denote the probability of U_t at the same (certain period of) time / Bernoulli trial t. Let W_t denote an effect (Latin: effectum; German: Wirkung) or a conditioned or another event et cetera at a (certain period of) time / Bernoulli[36] trial t. Let p(W_t) denote the probability of W_t at the same (certain period of) time / Bernoulli trial t. Let (U_t , W_t) denote cause and effect at a (certain period of) time / Bernoulli trial t. Let p(U_t , W_t) denote the joint probability of cause U_t and effect W_t at the same (certain period of) time / Bernoulli trial t. The causal relationship k(U_t , W_t) between cause (U_t) and effect (W_t) is derived and proofed[30–35] at every single run of an experiment t, at the same (certain period of) time / Bernoulli trial t, as

$$k(U_t, W_t) = \frac{p(U_t, W_t) - \big(p(U_t) \times p(W_t)\big)}{\sqrt[2]{\Big(p(U_t) \times \big(1 - p(U_t)\big)\Big) \times \Big(p(W_t) \times \big(1 - p(W_t)\big)\Big)}}$$

The statistical significance of the causal relationship can be tested by the Chi-square distribution, by the hyper-geometric[58,59] distribution and by other distributions. Usually, the hyper-geometric distribution (HGD) is practically applied only in analysis of small samples (Fisher's[51] test) but actually the same distribution is valid for all sample sizes. However, according to the central limit theorem[60], for a large sample size (n>30), the sampling distribution is approximately normal. Multi-causality[61], causal chains[31], time series[32] (after A comes B, B before A et cetera), n-dimensional[32] probability functions and conditions, n-dimensional[32] cumulative distribution functions and causality, causality under conditions of Einstein's general[62] theory of relativity and much more can be found in literature.

Statistical methods

The *causal*[35] *relationship k* between HP and GC has been tested. The *necessary condition*[35] (SINE) relationship (conditio sine qua non) has been used to test the hypothesis: **without** HP infection **no** GC. The index of relationship[54] (IOR) indicated whether there could be any kind of a relationship between HP and GC at all. The relative risk (RR (nc))[49], used for demonstrational purposes only, provided some evidence of a necessary condition relationship. The relative risk[47] (RR (sc))[49], used for demonstrational purposes only, provided some evidence of a sufficient condition relationship. Odds[51] ratio (OR) has been listed for completeness only. The quality of the *study design* was assessed by an index of unfairness[55] (IOU) and an index of independence[63] (IOI). The *P Values* have been calculated for each single study. The Chi-square itself is sensitive[64] to large sample size. Therefore, the Chi-square goodness of fit test of a necessary condition relationship to test the discrepancy between observed values and the values expected under the model in question has been used for demonstration purposes only. The P Value has been calculated according to the hypergeometric[58,59] distribution and based on the law of large numbers[46]. The significance level is set to $\alpha = 0.05$. The Null-hypothesis: without HP infection no GC has been rejected, if P Value > 0.0125.

Bonferroni Correction

The given significance level $\alpha = 0.05$ may be appropriate for each individual statistical test but not for the set of all investigations being performed simultaneously. Theoretically, there are circumstances under which it may appear

reasonable to avoid a lot of spurious positive results. One measure in this regard is the need to lower the alpha value in order to account for the number of tests being performed. One of the most simplest and conservative approaches to this issue is the Bonferroni[65] correction. Let $\alpha = 0.05$ denote the significance level for the entire set of **n** tests being performed on a data body. Let α_i denote the alpha value for each single test. In this publication, the alpha value for each single test is given as $\alpha_i = \alpha / n = 0.05 / 4 = 0.0125$. In other words, only P Values less than 0.0125 will be considered as statistically significant.

RESULTS

Without HP infection no human gastric cancer

Claim.
Null-hypothesis:
The relationship **without** a helicobacter pylori infection **no** human gastric cancer is true.
Alternative-hypothesis:
The relationship without a helicobacter pylori infection no human gastric cancer is not true.
P-Value: 0.0125 (for each single study)
Proof.
Various studies have been conducted in this regard, while the data of the studies of Uemura et al. [26] (table 3), Kazumasa Miki[27] (table 4), Yoshida et al.[28] (table 5) and Shuto et al.[29] (table 6) were re-calculated again. The studies of Uemura et al. [26] (P Value = 0.0006161496354787965), Kazumasa Miki[27] (P Value = 0.0018314551185057003), Yoshida et al.[28] (P Value = 0.00071941433399914171) and Shuto et al.[29] (P Value = 0.00354621182756425) impressed with a P Value of less than 0.0125. In other words, the data available do not allow us to reject the null-hypothesis. It is proofed that **without** a helicobacter pylori infection **no** human gastric cancer (P Value < 0.004).

Quod erat demonstrandum.

HP infection is the cause of human gastric cancer

The study design of the studies of Uemura et al. [26] (p (IOI) = +0.792922674), Kazumasa Miki[27] (p (IOI) = 0.783931947), Yoshida et al.[28] (p (IOI) = 0.784317938) and Shuto et al.[29] (p (IOI) = 0.566395664) was highly or even extremely unfair and not suitable enough to test a cause-effect relationship between helicobacter pylori and gastric cancer. Yet despite these significant and systematic restrictions and shortcomings, all studies were able to provide evidence of a highly significant causal relationship between a helicobacter pylori infection and human gastric cancer while the sample size has been impressive enough.

Claim.
Null-hypothesis:
The relationship a helicobacter pylori infection is the cause of human gastric cancer is not true.
Alternative-hypothesis:
The relationship a helicobacter pylori infection is the cause of human gastric cancer is true.
P-Value: 0.0125 (for each single study)
Proof.

The studies of Uemura et al. [26] (k = +0.07368483; P Value = 0.0006161496354787965), Kazumasa Miki[27] (k = +0.0383122936; P Value = 0.0018314551185057003), Yoshida et al.[28] (k = +0,0444235636 ; P Value = 0.00071941433399914171) and Shuto et al.[29] (k = +0.0477906199; P Value = 0.00354621182756425) provided evidence of a highly significant, positive causal relationship k between a helicobacter pylori infection und human gastric cancer with a P Value of less than 0.0125. In other words, the data available do not allow us to accept the null-hypothesis. We have no other option in the end but to reject the null-hypothesis and to accept the alternative hypothesis: a helicobacter pylori infection is the cause of human gastric cancer (P Value < 0.004).

Quod erat demonstrandum.

Without GC no EBV infection of human gastric carcinoma tissues

Epstein–Barr virus infection has been found frequently in tissues of gastric carcinoma[66] cases. More and more, EBV positivity in gastric cancer tissues has been taken as an counter-argument to the thesis of the causation of gastric cancer by helicobacter pylori. Chen et al. performed a systematic review on the relationship EBV and GC and published that EBV "… positivity determined by in situ[67,68] hybridization (ISH) was significantly higher in cancer tissues (range 5.0%–17.9%) than in adjacent mucosa from the same patients or biopsies from all control groups".[20] Unfortunately, the group around Chen et al. did not sufficiently enough appreciated the fact, whether EBV is the cause of GC or whether EBV is only a secondary invader of GC tissues.

Epstein–Barr virus[18] (EBV) is a double-stranded deoxyribonucleic[69] acid (DNA) human γ-herpes[70] virus (HHV4) with a 170-kb-large[71] genome which encodes for various proteins and

non-coding RNAs. After a generally asymptomatic primary EBV infection of mainly B-cells and epithelial cells usually during childhood, EBV resides latently[72] in resting B[73] cells for a lifetime[74]. However, under normal circumstances, an EBV infection is controlled by human immune system and individuals carrying EBV do not suffer from the viral infection. At the end, more than 95% of the adult population worldwide are infected by EBV at some time during their life span while **EBV seroprevalence increases**[75] **with age**. It is therefore in no way surprising that even more than 90% of all gastric cancer patients might be seropositive for EBV too. What does all this have to do with the relationship between EBV and GC? Unfortunately, the key role of human immune[76] responses to any cancer progression is still not known in detail despite reports of tumour infiltrating[77] immune cells which date back to 1863. As previously outline before, EBV itself resides latently[72] in resting B[73] cells for a lifetime[74]. Thus far, tumour-infiltrating B-cells[78] with EBV on board might enter gastric carcinoma tissues. In this case, EBV would not be the cause of human gastric cancer but only a secondary invader of already existing gastric carcinoma tissues. However, even the most beautiful theoretical considerations become still a little more beautiful assumed that at least a hint of a proof for a certain thesis can be presented. In the meantime, the question whether EBV is either the cause of gastric cancer or only a secondary[79] invader of gastric cancer tissues has been answered very convincingly. EBV is a secondary invader of gastric cancer tissues. In other words, **without** gastric cancer **no** EBV positivity of gastric cancer tissues.

DISCUSSION

In previous meta-analyses which evaluated the relationship between HP and GC, the significance of EBV with respect to GC has not been discussed to a necessary extent. This meta-analysis is the first to re-evaluate the relationship between HP and GC while considering the significance of EBV with respect to GC in narrative style. The epistemological shockwaves producing publication of Chen et al. "strongly suggest an association between EBV infection and gastric cancer"[20]. However, it was possible to invalidate this factually unfounded scientific attitude, elsewhere[79] and at this place too. In point of fact, this review was designed to reject the null hypothesis: without HP, no GC, without taking any losses into account. Particularly for this reason, only studies with very large sample sizes were considered for meta-analysis while the significance level for each single study was decreased. Nevertheless, and despite all the artificially erected massive barriers, it was not possible to reject the null hypothesis: **without** HP infection **no** GC. Nonetheless, it is not very surprising that even the striking evidence provided by this publication is based on some limitations. The studies presented in this publication, with the exception of the study of Shuto et al., 2017, are largely characterized by a study design that allow us to identify a necessary condition ($p(IOU) < 0.25$) relationship. It is however worth noting that, under conditions of very unfair ($p(IOU) > 0.25$), discriminatory and disadvantageous study design, even the study of Shuto et al. has been able to provide evidence of a highly significant necessary condition relationship ($p(SINE) = 1$; P Value = 0.0035462118) between HP and GC and equally of a causal relationship k between HP and GC too. Nevertheless, a critical reader may still be somewhat reserved and not fully convinced by the evidence presented in this publication. The studies based on *serum anti-Helicobacter pylori immunoglobulin antibodies* (Yoshida et al.[28], Kazumasa Miki[27]) were very convincing in the evidence provided but did not reach the very high level of significance of the prospective studies. This is factually comprehensible as the sensitivity and specificity of the kit used will have been one important factor in this context. Furthermore, none of the studies presented could provide evidence of a sufficient condition relationship between HP and GC. Such a sceptical remark would be understandable but is in itself still not conclusive. The study design of the studies analyzed has been very discriminatory in relation to the analysis of causal relationships. This is indicated by a highly or even extremely unfair index of independence (IOI) of the studies analysed ($p(IOI) > 0.78$; $p(IOI)$ of Shuto et al. was 0.56). It should be noted, however, that despite of this massive systematic disadvantage, all studies provided evidence of a highly significant causal relationship k between HP and GC. To put it in a nutshell, we cannot help but must refer to the *prospective* study of Uemura[26] et al., 2001 and to the *prospective* study of Shuto[29] et al., 2017 which weigh heavily in this respect. Another very important point on this matter is worth of consideration. Helicobacter pylori itself is known to be one dominant species of the human gastric microbiome and equally the most common[80] bacterial infection worldwide. Colonization with HP might cause a persistent local inflammatory response of the stomach. The mechanisms[81] through which HP manipulates the local human immune system in order to survive on the long run within the gastric niche is not the topic of this investigation. Nonetheless, at the end, a small proportion of HP infected individuals can develop even clinically

significant outcomes like a gastric malignancy. Thus far, there is good reason to believe that HP eradication[82] in the long term has the potential to significantly[83] decrease[84] GC prevalence in the population and will provide additional evidence of the causal relationship between HP and GC as already proven in this publication. In the light of the above and in the absence of any reference to the Henle[85] - Koch[86] postulates, it may be permitted to refer to this potentially last possible critical point, the lack of any reference to the Henle - Koch postulates in this publication. We will not be able to settle the issue of any epistemological validity of Henle-Koch postulate definitively at this place even if the same deserve a detailed reflection in the weeks, months and years ahead. Thus far and without beating around the bush, it is useful and necessary to point out that any reference to the Henle - Koch postulates would be rather misleading, since it is not the task of this publication to clarify whether gastric cancer is an infectious bacterial disease or not. At the end of this investigation we would like to bring the issue discussed to the point and would like to solve the same briefly, rapidly and efficiently, without wasting any time further. We were able to prove the key role of HP in the development of GC beyond any reasonable doubt under extraordinarily stringent and highly discriminatory study conditions.

CONCLUSION

The counterarguments based on the role of EBV in the pathogenesis of gastric cancer have been invalidated. We have convincing evidence for supposing that **without** HP infection, **no** GC (P Value < .004). Moreover, it is justified to believe that Helicobacter pylori is the cause of human gastric cancer.

Conflicts of Interest Statement

The author have no conflicts of interest to declare.

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References

1. Montano V, Didelot X, Foll M, et al. Worldwide Population Structure, Long-Term Demography, and Local Adaptation of Helicobacter pylori. *Genetics*. 2015;200(3):947-963. doi:10.1534/genetics.115.176404
2. Moodley Y, Linz B, Bond RP, et al. Age of the association between Helicobacter pylori and man. *PLoS Pathog*. 2012;8(5):e1002693. doi:10.1371/journal.ppat.1002693
3. Yamaoka Y. Helicobacter pylori typing as a tool for tracking human migration. *Clin Microbiol Infect*. 2009;15(9):829-834. doi:10.1111/j.1469-0691.2009.02967.x
4. Maixner F, Krause-Kyora B, Turaev D, et al. The 5300-year-old Helicobacter pylori genome of the Iceman. *Science*. 2016;351(6269):162-165. doi:10.1126/science.aad2545
5. Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet*. 1984;1(8390):1311-1315. doi:10.1016/s0140-6736(84)91816-6
6. Hooi JKY, Lai WY, Ng WK, et al. Global Prevalence of Helicobacter pylori Infection: Systematic Review and Meta-Analysis. *Gastroenterology*. 2017;153(2):420-429. doi:10.1053/j.gastro.2017.04.022
7. Coelho LGV, Marinho JR, Genta R, et al. IV th brazilian consensus conference on helicobacter pylori infection. *Arq Gastroenterol*. 2018;55(2):97-121. doi:10.1590/S0004-2803.201800000-20
8. Sjomina O, Pavlova J, Niv Y, Leja M. Epidemiology of Helicobacter pylori infection. *Helicobacter*. 2018;23 Suppl 1:e12514. doi:10.1111/hel.12514
9. Sgambato D, Visciola G, Ferrante E, et al. Prevalence of Helicobacter pylori infection in sexual partners of H. pylori-infected subjects: Role of gastroesophageal reflux. *United European Gastroenterol J*. 2018;6(10):1470-1476. doi:10.1177/2050640618800628
10. Mladenova I, Durazzo M. Transmission of Helicobacter pylori. *Minerva Gastroenterol Dietol*. 2018;64(3):251-254. doi:10.23736/S1121-421X.18.02480-7
11. Ata AA, Kamel IA. Primary reticulum cell sarcoma of the liver. A case report. *J Egypt Med Assoc*. 1965;48(7):514-521.
12. Violeta Filip P, Cuciureanu D, Sorina Diaconu L, Maria Vladareanu A, Silvia Pop C. MALT lymphoma: epidemiology, clinical diagnosis and treatment. *J Med Life*. 2018;11(3):187-193. doi:10.25122/jml-2018-0035
13. Barukčić I. Helicobacter pylori—The Cause of Human Gastric Cancer. *Journal of Biosciences and Medicines*. 2017;5(2):1-9. doi:10.4236/jbm.2017.52001
14. Barukčić I. Helicobacter Pylori is the Cause of Gastric Cancer. *Modern Health Science*. 2018;1(1):43-50. doi:10.30560/mhs.v1n1p43
15. IARC. Schistosomes, liver flukes and Helicobacter pylori. *IARC Monogr Eval Carcinog Risks Hum*. 1994;61:1-241.
16. Rokkas T, Rokka A, Portincasa P. A systematic review and meta-analysis of the role of Helicobacter pylori eradication in preventing gastric cancer. *Ann Gastroenterol*. 2017;30(4):414-423. doi:10.20524/aog.2017.0144
17. Ford AC, Yuan Y, Moayyedi P. Helicobacter pylori eradication therapy to prevent gastric cancer: systematic review and meta-analysis. *Gut*. 2020;69(12):2113-2121. doi:10.1136/gutjnl-2020-320839
18. Epstein MA, Achong BG, Barr YM. Virus Particles in Cultured Lymphoblasts from Burkitt's Lymphoma. *Lancet*. 1964;283(7335):702-703. doi:https://doi.org/10.1016/S0140-6736(64)91524-7
19. Kume T, Oshima K, Shinohara T, et al. Low rate of apoptosis and overexpression of bcl-2 in Epstein-Barr virus-associated gastric carcinoma. *Histopathology*. 1999;34(6):502-509. doi:10.1111/j.1365-2559.1999.00686.x
20. Chen XZ, Chen H, Castro FA, Hu JK, Brenner H. Epstein-Barr virus infection and gastric cancer: a systematic review. *Medicine (Baltimore)*. 2015;94(20):e792. doi:10.1097/MD.0000000000000792
21. Dombre C, Guyot N, Moreau T, et al. Egg serpins: The chicken and/or the egg dilemma. *Semin Cell Dev Biol*. 2017;62:120-132. doi:10.1016/j.semcdb.2016.08.019
22. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. *Open Med*. 2009;3(3):e123-130.
23. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med*. 2009;6(7):e1000100. doi:10.1371/journal.pmed.1000100
24. Ishaq S, Nunn L. Helicobacter pylori and gastric cancer: a state of the art review. *Gastroenterol Hepatol Bed Bench*. 2015;8(Suppl 1):S6-S14.
25. Eslick GD. Helicobacter pylori infection causes gastric cancer? A review of the epidemiological, meta-analytic, and experimental evidence. *World J Gastroenterol*. 2006;12(19):2991-2999. doi:10.3748/wjg.v12.i19.2991

26. Uemura N, Okamoto S, Yamamoto S, et al. Helicobacter pylori infection and the development of gastric cancer. *N Engl J Med*. 2001;345(11):784-789. doi:10.1056/NEJMoa001999
27. Miki K. Gastric cancer screening by combined assay for serum anti-Helicobacter pylori IgG antibody and serum pepsinogen levels - "ABC method." *Proc Jpn Acad Ser B Phys Biol Sci*. 2011;87(7):405-414. doi:10.2183/pjab.87.405
28. Yoshida T, Kato J, Inoue I, et al. Cancer development based on chronic active gastritis and resulting gastric atrophy as assessed by serum levels of pepsinogen and Helicobacter pylori antibody titer. *Int J Cancer*. 2014;134(6):1445-1457. doi:10.1002/ijc.28470
29. Shuto M, Fujioka T, Matsunari O, et al. Association between Gastric Cancer Risk and Serum Helicobacter pylori Antibody Titers. *Gastroenterol Res Pract*. 2017;2017:1286198. doi:10.1155/2017/1286198
30. Barukčić I. The Mathematical Formula of the Causal Relationship k. *IJAPM*. 2016;6(2):45-65. doi:10.17706/ijapm.2016.6.2.45-65
31. Barukčić I. *Die Kausalität*. 1. Aufl. Wiss.-Verl; 1989.
32. Barukčić I. *Die Kausalität*. 2., völlig überarb. Aufl. Scientia; 1997.
33. Barukčić I. *Theoriae Causalitatis Principia Mathematica*. Second edition. Books on Demand GmbH; 2021.
34. Barukčić I. Causal relationship k. *International Journal of Mathematics Trends and Technology IJMTT*. 2020;66(10):76-115.
35. Barukčić I. The causal relationship k. *MATEC Web Conf*. 2021;336(2):09032. doi:10.1051/matecconf/202133609032
36. Uspensky JV. *Introduction to Mathematical Probability*. 1st Edition. McGraw-Hill; 1937.
37. Tschébychef PL. Des valeurs moyennes. *Journal de Mathématiques Pures et Appliquées*. 1867;12(2):177-184. doi:http://sites.mathdoc.fr/JMPA/PDF/JMPA_1867_2_12_A11_0.pdf
38. Barukčić I. *Conditio Sine qua Non*. Zenodo; 2022. doi:10.5281/zenodo.5854744
39. Spendel G. *Die Kausalitätsformel Der Bedingungstheorie Für Die Handlungsdelikte: Eine Kritische Untersuchung Der Conditio-Sine-qua-Non-Formel Im Strafrecht*. Univ. Diss.; 1948.
40. Barukčić I. Conditio per quam. *Causation*. 2022;17(3):5-86. doi:10.5281/zenodo.6369831
41. Barukčić I. Mutually exclusive events. *Causation*. 2021;16(11):5-57. doi:10.5281/zenodo.5746415
42. Barukčić I. Cytomegalovirus and lung cancer - a causal relationship? *Causation*. 2023;18(11):5-30. doi:https://doi.org/10.5281/zenodo.7548139
43. Helmert FR. Ueber die Wahrscheinlichkeit der Potenzsummen der Beobachtungsfehler und über einige damit im Zusammenhange stehende Fragen. *Zeitschrift für Mathematik und Physik*. 1876;21(3):102-219.
44. Pearson K. 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*. 1900;50(302):157-175.
45. Yates F. Contingency Tables Involving Small Numbers and the χ 2 Test. *The Journal of the Royal Statistical Society (Supplement)*. 1934;1(2):217. doi:10.2307/2983604
46. Barukčić I. The P Value of likely extreme events. *International Journal of Current Science Research*. 2019;5(11):1841-1861.
47. Cornfield J. A method of estimating comparative rates from clinical data; applications to cancer of the lung, breast, and cervix. *Journal of the National Cancer Institute*. 1951;11(6):1269-1275.
48. Sadowsky DA, Gilliam AG, Cornfield J. The statistical association between smoking and carcinoma of the lung. *J Natl Cancer Inst*. 1953;13(5):1237-1258.
49. Barukčić I. The logical content of the risk ratio. *Causation*. 2021;16(4):5-41. doi:10.5281/zenodo.4679509
50. Yule GU. On the Association of Attributes in Statistics: With Illustrations from the Material of the Childhood Society, &c. *Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences*. 1900;194(252-261):257-319. doi:10.1098/rsta.1900.0019
51. Fisher RA. The Logic of Inductive Inference. *Journal of the Royal Statistical Society*. 1935;98(1):39-82. doi:10.2307/2342435
52. Cox DR. The Regression Analysis of Binary Sequences. *Journal of the Royal Statistical Society Series B (Methodological)*. 1958;20(2):215-242.
53. Yule GU. On the Methods of Measuring Association Between Two Attributes. *Journal of the Royal Statistical Society*. 1912;75(6):579. doi:10.2307/2340126
54. Barukčić I. Index of relationship. *Causation*. 2021;16(8):5-37. doi:10.5281/zenodo.5163179
55. Barukčić I. Index of Unfairness. *Modern Health Science*. 2019;2(1):22-59. doi:10.30560/mhs.v2n1p22
56. Barukčić I. Conditions and study design. *Causation*. 2022;18(1):5-99.

doi:10.5281/zenodo.6816088
57. Barukčić I. *Causal Inference and Study Design*. Zenodo; 2022. doi:10.5281/zenodo.6299686
58. Pearson K. XV. On certain properties of the hypergeometrical series, and on the fitting of such series to observation polygons in the theory of chance. *The London, Edinburgh, and Dublin Philosophical Magazine and Journal of Science*. 1899;47(285):236-246. doi:10.1080/14786449908621253
59. Gonin HT. XIV. The use of factorial moments in the treatment of the hypergeometric distribution and in tests for regression. *The London, Edinburgh, and Dublin Philosophical Magazine and Journal of Science*. 1936;21(139):215-226. doi:10.1080/14786443608561573
60. Pólya G. Über den zentralen Grenzwertsatz der Wahrscheinlichkeitsrechnung und das Momentenproblem: [In English: On the central limit theorem of probability calculation and the problem of moments]. *Mathematische Zeitschrift*. 1920;8(3-4):171-181. doi:10.1007/BF01206525
61. Barukčić I. *Theoriae Causalitatis Principia Mathematica*. First edition. Books on Demand GmbH; 2017.
62. Barukčić I. Unified Field Theory. *Journal of Applied Mathematics and Physics*. 2016;4(8):1379-1438. doi:10.4236/jamp.2016.48147
63. Barukčić I. Index of Independence. *Modern Health Science*. 2019;2(2):1-25. doi:10.30560/mhs.v2n2p1
64. Bergh D. Chi-Squared Test of Fit and Sample Size-A Comparison between a Random Sample Approach and a Chi-Square Value Adjustment Method. *Journal of Applied Measurement*. 2015;16(2):204-217.
65. Bonferroni CE. *Teoria statistica delle classi e calcolo delle probabilità*. Seeber; 1936.
66. Takada K. Epstein-Barr virus and gastric carcinoma. *Mol Pathol*. 2000;53(5):255-261. doi:10.1136/mp.53.5.255
67. Gall JG, Pardue ML. Formation and detection of RNA-DNA hybrid molecules in cytological preparations. *Proceedings of the National Academy of Sciences of the United States of America*. 1969;63(2):378-383. doi:10.1073/pnas.63.2.378
68. Jensen E. Technical review: In situ hybridization. *Anat Rec (Hoboken)*. 2014;297(8):1349-1353. doi:10.1002/ar.22944
69. Watson JD, Crick FH. Molecular structure of nucleic acids; a structure for deoxyribose nucleic acid. *Nature*. 1953;171(4356):737-738. doi:10.1038/171737a0
70. Walker PJ, Siddell SG, Lefkowitz EJ, et al. Changes to virus taxonomy and to the International Code of Virus Classification and Nomenclature ratified by the International Committee on Taxonomy of Viruses (2021). *Arch Virol*. 2021;166(9):2633-2648. doi:10.1007/s00705-021-05156-1
71. Feederle R, Klinke O, Kutikhin A, Poirey R, Tsai MH, Delecluse HJ. Epstein-Barr Virus: From the Detection of Sequence Polymorphisms to the Recognition of Viral Types. *Curr Top Microbiol Immunol*. 2015;390(Pt 1):119-148. doi:10.1007/978-3-319-22822-8_7
72. Babcock GJ, Decker LL, Volk M, Thorley-Lawson DA. EBV persistence in memory B cells in vivo. *Immunity*. 1998;9(3):395-404.
73. Miyashita EM, Yang B, Babcock GJ, Thorley-Lawson DA. Identification of the site of Epstein-Barr virus persistence in vivo as a resting B cell. *J Virol*. 1997;71(7):4882-4891. doi:10.1128/JVI.71.7.4882-4891.1997
74. Amon W, Farrell PJ. Reactivation of Epstein-Barr virus from latency. *Rev Med Virol*. 2005;15(3):149-156. doi:10.1002/rmv.456
75. Cui J, Yan W, Xu S, et al. Anti-Epstein-Barr virus antibodies in Beijing during 2013-2017: What we have found in the different patients. *PLoS One*. 2018;13(3):e0193171. doi:10.1371/journal.pone.0193171
76. Garaud S, Buisseret L, Solinas C, et al. Tumor infiltrating B-cells signal functional humoral immune responses in breast cancer. *JCI Insight*. 2019;5(18):e129641, 129641. doi:10.1172/jci.insight.129641
77. David H. Rudolf Virchow and modern aspects of tumor pathology. *Pathol Res Pract*. 1988;183(3):356-364. doi:10.1016/S0344-0338(88)80138-9
78. Whitford P, Mallon EA, George WD, Campbell AM. Flow cytometric analysis of tumour infiltrating lymphocytes in breast cancer. *Br J Cancer*. 1990;62(6):971-975. doi:10.1038/bjc.1990.419
79. Barukčić I. Gastric Cancer and Epstein-Barr Virus Infection. *Modern Health Science*. 2018;1(2):1-18. doi:10.30560/mhs.v1n2p1
80. Peek RM, Crabtree JE. Helicobacter infection and gastric neoplasia. *J Pathol*. 2006;208(2):233-248. doi:10.1002/path.1868
81. Peek RM, Fiske C, Wilson KT. Role of innate immunity in Helicobacter pylori-induced gastric malignancy. *Physiol Rev*. 2010;90(3):831-858. doi:10.1152/physrev.00039.2009
82. Wong BCY, Lam SK, Wong WM, et al. Helicobacter pylori eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. *JAMA*. 2004;291(2):187-194. doi:10.1001/jama.291.2.187
83. Chiang TH, Chang WJ, Chen SLS, et al.

Mass eradication of Helicobacter pylori to reduce gastric cancer incidence and mortality: a long-term cohort study on Matsu Islands. *Gut*. 2021;70(2):243-250. doi:10.1136/gutjnl-2020-322200

84. Kim J, Wang TC. Helicobacter pylori and Gastric Cancer. *Gastrointest Endosc Clin N Am*. 2021;31(3):451-465. doi:10.1016/j.giec.2021.03.003

85. Henle FGJ. *Von Den Miasmen Und Kontagien Und von Den Miasmatisch-Kontagiösen Krankheiten*. Verlag von August Hirschwald; 1840.

86. Koch HHR. *Untersuchungen Über Die Aetiologie Der Wundinfectionskrankheiten*. Verlag von F. C. W. Vogel; 1878. https://doi.org/10.17192/eb2013.0081