Title :

Helicobacter pylori is the cause of human gastric cancer.

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Running title:

Helicobacter pylori and gastric cancer.

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(Received: 03.12.2017; Accepted: 03.12.2017; Published: 03.12.2017;)

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Abstract

Objective: Many times a positive relationship between Helicobacter pylori infection and gastric cancer has been reported, yet findings are inconsistent.

Methods: A literature search in PubMed was performed to re-evaluate the relationship between Helicobacter pylori (HP) and carcinoma of human stomach. Case control studies with a least 500 participants were consider for a review and meta-analysis. The meta-/re-analysis was conducted using conditio-sine qua non relationship and the causal relationship k. Significance was indicated by a p-value of less than 0.05.

Result: All studies analyzed provide impressive evidence of a cause effect relationship between H. pylori and gastric cancer (GC). Two very great studies were able to make the proof that H. pylori is a necessary condition of human gastric cancer. In other words, without H. pylori infection no human gastric cancer.

Conclusion: Our findings indicate that Helicobacter pylori (H. pylori) is the cause of gastric carcinoma.

Keywords: Helicobacter pylori, gastric cancer, cause effect relationship, causality

Introduction

The history of Helicobacter pylori dates back more than 60,000 years (Moodley et al., 2012) ago. Several studies indicate that modern humans were already infected by H. pylori before their migrations out of Africa. Finally, in 1875, the German scientists (Kidd et al., 1998; Blasser, 2005) Bottcher (Bottcher, 1875) along with his French collaborator Letulle (1853-1929) found spiral-shaped bacteria (Letulle, 1888) in human stomach without being able to culture them while their result became forgotten. Finally, Robin Warren and Barry Marshall, re-discovered (Warren et al., 1983) of H. pylori (initially termed Campylobacter pyloridis, then C pylori, and, subsequently, H. pylori). Warren and Marshall were awarded the Nobel Prize in Physiology or Medicine in 2005 for the discovery of H. pylori and its role in peptic ulcer disease and gastritis. Initially, several investigations conducted in the 1980s and early 1990s (Correa et al., 1990; Forman et al., 1990; Eurostat, 1993) about the relationship between H. pylori and gastric cancer provided some non-convincing evidence for a link between H. pylori and gastric cancer. In point of fact, based on the compelling results of 3 large cohorts with nested case-controls (Forman et al., 1991; Parsonnet et al., 1991; Nomura et al., 1991) the World Health Organization's International Agency for Research on Cancer classified in 1994 H. pylori as a definite (group 1) carcinogen. Meanwhile infection with Helicobacter pylori (H. pylori) is regarded as the strongest recognized risk factor for gastric carcinoma. In particular, a meta-analysis of 42 studies demonstrated a close relationship between H. pylori infection the risk of developing gastric cancer (Eslick et al., 1999). Additionally, one publication (Barukčić (2017b)) based on the re-analysis of the data of Uemura et al. (2001) was able to provide evidence that Helicobacter pylori (H. pylori) is the cause of gastric cancer. In point of fact, more than half of the world's population is infected with H. pylori (Suerbaum et al., 2002) while the majority of individuals infected with this bacterium do not demonstrate any severe pathology throughout their lives and are more or less completely asymptomatic. Still, gastric cancer is the fifth most commonly diagnosed and third most deadly cancer (Torre et al., 2016) worldwide. However, even if the prevalence of gastric cancer is declining due to

the use of antibiotic and improved sanitation gastric cancer is still a challenging global health issue. Simple and effective gastric cancer prevention strategies (Pan et al., 2016) are possible and necessary.

Materials and methods

Search strategy

For the questions addressed in this paper, was searched Pubmed for case-control studies conducted in any country and published in English independently of the method used to detect H. pylori. Studies with 500 or more participants were considered for a further review and a re-/meta-analysis.

Statistical analysis

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

Conditio sine qua non

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

$$\mathrm{p}\left(\mathrm{H\ pylori} \leftarrow \mathrm{Human\ gastric\ cancer}\right)$$

was used to proof the hypothesis: *without* Helicobacter pylori infection *no* human gastric cancer.

Scholium.

Historically, the notion *sufficient* condition is known since thousands of years. Many authors testified original contributions of the notion material implication only for *Diodorus Cronus*. Still, Philo the Logician (~ 300 BC), a member of a group of early Hellenistic philosophers (the Dialectical school), is the main forerunner of the notion material implication and has made some groundbreaking

contributions (Astorga 2015) to the basics of this relationship. As it turns out, it is very hard to think of the "conditio per quam" relationship without considering the historical background of this concept. Remarkable as it is, Philo's concept of the material implications came very close (Bochenski 1961) to that of modern concept material implication. In propositional logic, a conditional is generally symbolized as "$p \rightarrow q$" or in spoken language "**if** p **then** q". Both q and p are statements, with q the consequent and p the antecedent. Many times, the logical relation between the consequent and the antecedent is called a material implication. In general, a conditional "if p then q" is false only if p is true and q is false otherwise, in the three other possible combinations, the conditional is always true. In other words, to say that p is a sufficient condition for q is to say that the presence of p guarantees the presence of q. In other words, it is impossible to have p without q. If p is present, then q must also be present. To show that p is not sufficient for q, we come up with cases where p is present but q is not. It is well-known that the notion of a necessary condition can be used in defining what a sufficient condition is (and vice versa). In general, p is a necessary condition for q if it is impossible to have q without p. In fact, the absence of p guarantees the absence of q.

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

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

The central limit theorem

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

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

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

where p_{Calc} is the proportion of successes in a Bernoulli trial process with N trials yielding X successes and N-X failures and z is the 1 – (Alpha/2) quantile of a standard normal distribution corresponding to the significance level alpha. For example, for a 95% confidence level alpha = 0.05 and z is z = 1.96. A very common technique for calculating binomial confidence intervals was published by Clopper-Pearson (Clopper et al., 1934). Agresti-Coull proposed another different method (Agresti et al., 1998) for calculating binomial *confidence intervals*. A faster and an alternative way to determine the lower and upper "exact" confidence interval is justified by the F distribution (Leemis et al., 1996).

Scholium.

The sample proportion p_{Calc} can be different from the population proportion π. Thus far, one goal of the test statistic Z is to summarize the sample information. Suppose the sample size is n=3570. Let the population proportion be π=0,975. The sample proportions is p=0,96442577. The test statistic with continuity correction is calculated as

$$Z = \frac{\left(p_{Calc}\right)-\left(\frac{1}{2\times n}\right)-\pi}{\left(\sqrt[2]{\frac{\pi\times\left(1-\pi\right)}{n}}\right)}$$

$$= \frac{\left(0{,}96442577\right)-\left(\frac{1}{2\times 3570}\right)-0{,}975}{\left(\sqrt[2]{\frac{0{,}975\times\left(1-0{,}975\right)}{3570}}\right)}$$

$$= 1{,}640155447$$

Using Microsoft Excel ®, the p value [one sided right tailed] can be calculated as

$$\text{p value [One sided right tailed]} = 1 - \text{NORM.S.DIST}(1{,}640155447;\text{TRUE})$$

$$= 0{,}05048642510029820000$$

Usually, when the sample size is small, t statistics is used. The complete table of critical values of Z for upper, lower and two-tailed tests can be found in the table of Z values. There are about 0,0504864251002982 chances of selecting samples with a sample proportion greater than or equal to π=0,975. Since we use a=0.05 we accept the null hypothesis. This means that the data support our claim that there is not a significant difference between the sample proportion p_{Calc}=0,96442577 and population proportion π=0,975. This means accept the null-hypothesis.

Rule of three

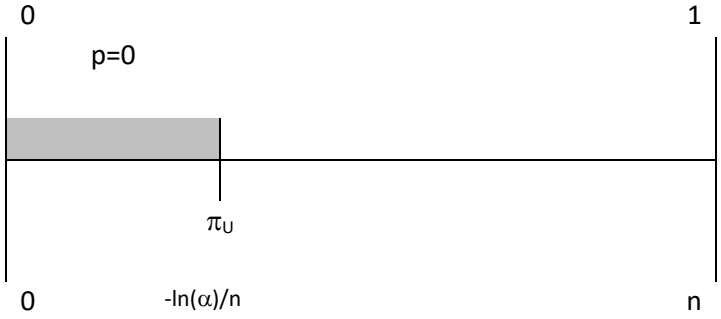
Furthermore, an approximate and conservative (one sided) confidence interval was developed by Louis (Louis 1981) and Jovanovic (Jovanovic et al., 1997) known as *the rule of three*. Briefly sketched, the rule of three can be derived from the binomial model. Let π_U denote the upper limit of the exact one-sided 100 × (1 - α)% confidence interval for the unknown proportion π when in N independent trials *no events occur* (Jovanovic et al., 1997) . Then π_U is the value such that

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

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

Table 1. The one-sided approximate upper 100 × (1 - α)%

confidence bound where **no successes** are observed

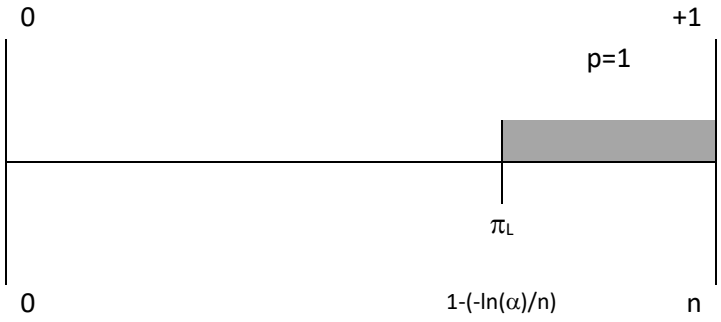


Under conditions where *a certain event did not occur* (Louis 1981) in a sample with *n subjects* (i. e. p=0) the interval from 0 to (-ln(α)/n) is called a 100 × (1 - α)% confidence interval for the binomial parameter for the rate of occurrences in the population.

Another special case of the binomial distribution is based on *a sample of size n* where *only successes* are observed. Accordingly, the lower limit of a one-sided 100 × (1 - α)% confidence interval for a binomial probability π_L, the rate of occurrences in the population, based on *a sample of size n* where *only successes* are observed is given approximately by [(1-(-ln(α)/n)) $\leq \pi \leq$ +1] or (assuming α=0,05)

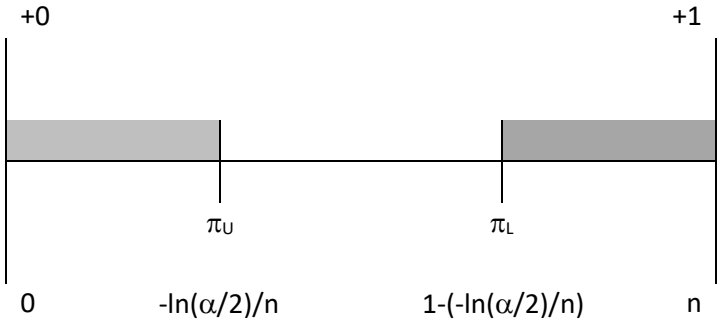
$$\pi_L = 1 - \left(\frac{-\ln(\alpha)}{n} \right) \approx 1 - \left(\frac{3}{n} \right)$$

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



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

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



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

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

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

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

The mathematical formula of the causal relationship k

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

Scholium.

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

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

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

The chi square distribution

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

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

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

Fisher's exact test

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

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

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

Table 6. The hypergeometric distribution and Helicobacter pylori and gastric cancer.

		Gastric cancer		
		YES	NO	SUM
Helicobacter pylori positive	YES	x		U
	NO			N-U
	SUM	W	N-W	N

Study design of Shuto et al. (2017) (Japan)

Shuto et al. (2017) conducted a study with N = 3321 subjects. Altogether (1891/3321) = 56.9% showed serum Helicobacter pylori (Hp)-IgG antibody (HpAb) of 3.0 U/mL or more. A total of 10 patients had gastric cancer (GC) (10/3321) while all gastric cancer patients had serum Hp-IgG antibody (HpAb) of 3.0 U/mL or more. The following 2x2 table (Table 7) may illustrate the data as obtained by Shuto et al.

Table 7. Helicobacter pylori and gastric cancer due to Shuto et al. (2017)

		Gastric cancer		
		YES	NO	TOTAL
H. pylori positive (HpAb ≥ 3 U/mL)	YES	10	1881	1891
	NO	**0**	1430	1430
	TOTAL	10	3311	3321

Study design of Fernández de Larrea-Baz et al. (2017) (Spain)

Fernández de Larrea-Baz et al. (2017) conducted a study with N = 2566 subjects. Altogether 2070 or 2353 controls were Helicobacter pylori positive. A total of (202/213) gastric cancer patients were Helicobacter pylori positive. In particualr, (11/213) gastric cancer patients were Helicobacter pylori negative. The following 2x2 table (Table 8) may illustrate the data as obtained by Fernández de Larrea-Baz et al. (2017)

Table 8. Helicobacter pylori and gastric cancer due to Fernández de Larrea-Baz et al. (2017)

		Gastric cancer		
		YES	NO	TOTAL
H. pylori positive	YES	202	2070	2272
	NO	**11**	283	294
	TOTAL	213	2353	2566

Study design of Huerta et. al. (2017) (Spain)

Huerta et. al. (2017) conducted a study with N = 2277 subjects. Altogether (2016/2277) were Helicobacter pylori positive. A total of (239/257) gastric cancer patients were Helicobacter pylori positive. Finally, (18/257) gastric cancer patients were Helicobacter pylori negative. The following 2x2 table (Table 9) may illustrate the data as obtained by Huerta et. al. (2017) (2017).

Table 9. Helicobacter pylori and gastric cancer due to Huerta et. al. (2017)

		Gastric cancer		
		YES	NO	TOTAL
H. pylori positive	YES	239	1777	2016
	NO	18	243	261
	TOTAL	257	2020	2277

Scholium.

Diagnostic efficacy of a test for Helicobacter pylori infection depends on the sensitivity and specificity of test used which is not all the time equal to 100 %. H. pylori infection status determined serologically by detecting H. pylori-specific IgG or IgA antibodies using a commercial serology H. pylori kit is based on the cutoff values as given by manufacturer. A participant is categorized as either H. pylori seropositive or as H. pylori seronegative depending of a certain cut off value of the kit used. Unfortunately, it is difficult to obtain accurate cutoff value to diagnose Helicobacter pylori (Hp) infection with the consequence that many cases with present/past Helicobacter pylori (Hp) infection may be found below the used cutoff value, suggesting that a participant is Helicobacter pylori (Hp) although the same participant is Helicobacter pylori (Hp) positive. In addition, many gastric cancers may be overlooked which provides to inconsistencies across the studies.

Study design of Shi et al., (2017) (China)

Shi et al., (2017) conducted a study with N = 1650 subjects. Altogether (846/1650) were Helicobacter pylori positive. A total of (597/851) gastric cancer patients were Helicobacter pylori positive. Finally, (254/851) gastric cancer patients were Helicobacter pylori negative. The following 2x2 table (Table 10) may illustrate the data as obtained by Shi et al. (2017).

Table 10. Helicobacter pylori and gastric cancer due to Shi et al., (2017)

		Gastric cancer		
		YES	NO	TOTAL
H. pylori positive	YES	597	249	846
	NO	254	550	804
	TOTAL	851	799	1650

Study design of Sarker et. al. (2017) (Bangladesh)

Sarker et. al. (2017) conducted a study with N = 634 subjects. Altogether (450/634) were Helicobacter pylori positive. A total of (99/114) gastric cancer patients were Helicobacter pylori positive. In particular, (15/114) gastric cancer patients were Helicobacter pylori negative. The following 2x2 table (Table 11) may illustrate the data as obtained by Sarker et. al. (2017).

Table 11. Helicobacter pylori and gastric cancer due to Sarker et. al. (2017)

		Gastric cancer		
		YES	NO	TOTAL
H. pylori positive	YES	99	351	450
	NO	**15**	169	184
	TOTAL	114	520	634

Study design of Binh et al., (2017) (Vietnam)

Binh et al., (2017) conducted a study with N = 552 subjects. Altogether (327/552) were Helicobacter pylori positive. A total of (224/282) gastric cancer patients were Helicobacter pylori positive. In particular, (58/282) gastric cancer patients were Helicobacter pylori negative. The following 2x2 table (Table 12) may illustrate the data as obtained by Binh et al., (2017).

Table 12. Helicobacter pylori and gastric cancer due to Binh et al., (2017)

		Gastric cancer		
		YES	NO	TOTAL
H. pylori positive	YES	224	103	327
	NO	58	167	225
	TOTAL	282	270	552

Study design of Cai et. al., (2016) (East Asia)

Cai et. al., (2016) conducted a study with N = 3570 subjects. Altogether (3080/3570) were Helicobacter pylori positive. A total of (1481/1608) gastric cancer patients were Helicobacter pylori positive. In particular, (127/1608) gastric cancer patients were Helicobacter pylori negative. The following 2x2 table (Table 13) may illustrate the data as obtained by .

Table 13. Helicobacter pylori and gastric cancer due to Cai et. al., (2016)

		Gastric cancer		
		YES	NO	TOTAL
H. pylori positive	YES	1481	1599	3080
	NO	127	363	490
	TOTAL	1608	1962	3570

Study design of Uemura et al., (2001) (Japan)

Uemura et al., (2001) studied 1526 Japanese patients. In point of fact, 1246 had H. pylori infection and 280 did not. In the following, gastric cancers developed in 36 of the H. pylori infected patients but in none of the H. pylori uninfected patients. The following 2x2 table (Table 14) may illustrate the data as obtained by Uemura et al., (2001).

Table 14. Helicobacter pylori and gastric cancer due to Uemura et al., (2001)

		Gastric cancer		
		YES	NO	TOTAL
H. pylori positive	YES	36	1210	1246
	NO	**0**	280	280
	TOTAL	36	1490	1526

Combination of the studies of Shuto et al.(2017) (Japan) and Uemura et al., (2001) (Japan)

Shuto et al.(2017) and Uemura et al., (2001) studied together N = 4847 subjects. Altogether (3137/4847) were Helicobacter pylori positive. A total of (40/40) gastric cancer patients were Helicobacter pylori positive. In particular, (0/40) gastric cancer patients were Helicobacter pylori negative. The following 2x2 table (Table 15) may illustrate the data as obtained by Shuto et al.(2017) and Uemura et al., (2001).

Table 15. Helicobacter pylori and gastric cancer due to Shuto et al.(2017) and Uemura et al., (2001)

		Gastric cancer		
		YES	NO	TOTAL
H. pylori positive	YES	46	3091	3137
	NO	**0**	1710	1710
	TOTAL	46	4801	4847

Results

The study of Shuto et al. (2017)

***Without** Helicobacter pylori infection of human stomach **no** human gastric cancer.*

Helicobacter pylori infection of human stomach is a necessary condition (a conditio sine qua non) of human gastric cancer due to the study of Shuto et al. (2017)

Claims.

Null hypothesis (H_0):

Without Helicobacter pylori infection of human stomach **no** human gastric cancer.

H_0: $\pi_L \leqq \pi$

Alternative hypothesis (H_A)

Without Helicobacter pylori infection of human stomach there is human gastric cancer.

H_A: $\pi_L > \pi$

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

Proof.

The data as obtained by Shuto et al. (2017) about the relationship between Helicobacter pylori infection and human gastric cancer in patients and healthy control subjects are viewed in the 2 × 2 table (Table 7). In general, the proportion of successes of *the conditio sine qua non relationship*, denoted by the term p_{Calc}(Helicobacter pylori infection ← human gastric cancer) is calculated as (Barukčić, 1998; Barukčić, 1997; Barukčić, 2005; Barukčić, 2006a; Barukčić, 2006b; Barukčić, 2011a; 2011b; Barukčić, 2012; Barukčić, 2016a; Barukčić et al., 2016b; Barukčić, 2016c; Barukčić, 2017a; Barukčić, 2017b; Barukčić, 2017c)

$$p_{Calc}\left(\text{Helicobacter pyolori [HP]} \rightarrow \text{Gastric cancer [GC]}\right) = \frac{\left(10+1881+1430\right)}{3321} = \frac{3321}{3321} = 1,0$$

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

$$\pi_L = 1 - \frac{3}{3321} = +0{,}999097943$$

The proportion of successes of the necessary condition, the conditio sine qua non relationship, is calculated as p_{Calc}(Helicobacter pylori infection $\leftarrow$ human gastric cancer) = 1,0. In fact, the one sided 100*(1-α) % confidence bound is calculated as π_L = 0,9680,999097943 and is thus far less than the proportion of successes of the sample. The data as published by Shuto et al. (2017) do support our null hypothesis. Consequently, we accept the null hypothesis and reject the alternative hypothesis. In other words, **without** a Helicobacter pylori infection **no** human gastric cancer.

Helicobacter pylori is a necessary condition (a conditio sine qua non) of human gastric cancer.

Q. e. d.

Significant cause-effect relationship between Helicobacter pylori infection and human gastric cancer due to study of Shuto et al. (2017)

Claims.

Null hypothesis (H_0): (no causal relationship)

There is not a significant causal relationship between Helicobacter pylori infection and gastric cancer.

H_0: k = 0.

Alternative hypothesis (H_A): (causal relationship)

There is a significant causal relationship between Helicobacter pylori infection and gastric cancer.

H_A: $k \neq 0$.

Conditions.

Alpha level = 5%.

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

Proof.

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

$$\mathrm{k}\left(\text{Helicobacter pyolori [HP]} \rightarrow \text{Gastric cancer [GC]}\right) = \frac{\left(\left(3321\times 10\right)-\left(1891\times 10\right)\right)}{\sqrt[2]{\left(1891\times 1430\right)\times\left(10\times 3311\right)}} = +0{,}04779062$$

The value of the test statistic k = +0,04779062 is equivalent to a calculated chi-square value of

$$\chi^2_{\text{Calculated}} = 3321\times\left(\frac{\left(\left(3321\times 10\right)-\left(1891\times 10\right)\right)}{\sqrt[2]{\left(1891\times 1430\right)\times\left(10\times 3311\right)}}\right)\times\left(\frac{\left(\left(3321\times 10\right)-\left(1891\times 10\right)\right)}{\sqrt[2]{\left(1891\times 1430\right)\times\left(10\times 3311\right)}}\right)$$

$$\chi^2_{\text{Calculated}} = 3321\times\left(0{,}04779062\right)\times\left(0{,}04779062\right)$$

$$\chi^2_{\text{Calculated}} = 7{,}584975869$$

The calculated chi-square statistic, uncorrected for continuity, is 7,584975869 and equivalent to a p value of 0,005885675171176320. The calculated chi-square statistic does exceed the critical chi-square value of 3.841458821 (Table 5). Consequently, we reject the null hypothesis and accept the alternative hypothesis. According to the data as obtained by Shuto et al. (2017) there is a significant causal relationship between a Helicobacter pylori infection and human gastric cancer (k = +0,04779062, p value = 0,005885675171176320).

Q. e. d.

The study of Uemura et al. (2001)

***Without** Helicobacter pylori infection of human stomach **no** human gastric cancer.*

Helicobacter pylori infection of human stomach is a necessary condition (a conditio sine qua non) of human gastric cancer due to the study of Uemura et al. (2001)

Claims.

Null hypothesis (H_0):

Without Helicobacter pylori infection of human stomach **no** human gastric cancer.

H_0: $\pi_L \leqq \pi$

Alternative hypothesis (H_A)

Without Helicobacter pylori infection of human stomach there is human gastric cancer.

H_A: $\pi_L > \pi$

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

Proof.

The data as obtained by Uemura et al. (2001) about the relationship between Helicobacter pylori infection and human gastric cancer in patients and healthy control subjects are viewed in the 2 × 2 table (Table 14). In general, the proportion of successes of *the conditio sine qua non relationship*, denoted by the term p_{Calc}(Helicobacter pylori infection ← human gastric cancer) is calculated as (Barukčić, 1998; Barukčić, 1997; Barukčić, 2005; Barukčić, 2006a; Barukčić, 2006b; Barukčić, 2011a; 2011b; Barukčić, 2012; Barukčić, 2016a; Barukčić et al., 2016b; Barukčić, 2016c; Barukčić, 2017a; Barukčić, 2017b; Barukčić, 2017c)

$$p_{Calc}\left(\text{Helicobacter pyolori [HP]} \rightarrow \text{Gastric cancer [GC]}\right) = \frac{\left(36+1210+280\right)}{1526} = \frac{1526}{1526} = 1,0$$

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

$$\pi_L = 1 - \frac{3}{1526} = +0{,}998036873$$

The proportion of successes of the necessary condition, the conditio sine qua non relationship, is calculated as p_{Calc}(Helicobacter pylori infection $\leftarrow$ human gastric cancer) = +1,0. In fact, the one sided 100*(1-α) % confidence bound is calculated as π_L = 0,998036873 and is thus far less than the proportion of successes of the sample. The data as published by Uemura et al. (2001) do support our null hypothesis. Consequently, we accept the null hypothesis and reject the alternative hypothesis. In other words, **without** a Helicobacter pylori infection **no** human gastric cancer.

Helicobacter pylori is a necessary condition (a conditio sine qua non) of human gastric cancer.

Q. e. d.

Significant cause-effect relationship between Helicobacter pylori infection and human gastric cancer due to study of Uemura et al. (2001)

Claims.

Null hypothesis (H_0): (no causal relationship)

There is not a significant causal relationship between Helicobacter pylori infection and gastric cancer.

H_0: k = 0.

Alternative hypothesis (H_A): (causal relationship)

There is a significant causal relationship between Helicobacter pylori infection and gastric cancer.

H_A: $k \neq 0$.

Conditions.

Alpha level = 5%.

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

Proof.

The data for this hypothesis test are obtained by Uemura et al. (2001) and illustrated in the 2 × 2 table (Table 14). The causal relationship k(Helicobacter pylori infection, human gastric cancer) is calculated as (Barukčić, 1998; Barukčić, 1997; Barukčić, 2005; Barukčić, 2006a; Barukčić, 2006b; Barukčić, 2011a; 2011b; Barukčić, 2012; Barukčić, 2016a; Barukčić et al., 2016b; Barukčić, 2016c; Barukčić, 2017a; Barukčić, 2017b; Barukčić, 2017c)

$$k\left(\text{Helicobacter pyolori [HP]} \rightarrow \text{Gastric cancer [GC]}\right) = \frac{\left((1526\times 36)-(1246\times 36)\right)}{\sqrt[2]{(1246\times 280)\times(36\times 1490)}} = +0{,}073684834$$

The value of the test statistic k = +0,073684834 is equivalent to a calculated chi-square value of

$$\chi^2_{\text{Calculated}} = 1526\times\left(\frac{\left((1526\times 36)-(1246\times 36)\right)}{\sqrt[2]{(1246\times 280)\times(36\times 1490)}}\right)\times\left(\frac{\left((1526\times 36)-(1246\times 36)\right)}{\sqrt[2]{(1246\times 280)\times(36\times 1490)}}\right)$$

$$\chi^2_{\text{Calculated}} = 1526\times(0{,}0039966244)\times(0{,}0039966244)$$

$$\chi^2_{\text{Calculated}} = 8{,}285348013$$

The calculated chi-square statistic, uncorrected for continuity, is 8,285348013 and equivalent to a p value of 0,0039966244260480. The calculated chi-square statistic does exceed the critical chi-square value of 3.841458821 (Table 5). Consequently, we reject the null hypothesis and accept the alternative hypothesis. According to the data as obtained by Uemura et al. (2001) there is a significant causal relationship between a Helicobacter pylori infection and human gastric cancer (k = +0,073684834 , p value= 0,0039966244260480).

Q. e. d.

The combination of the study of Shuto et al. (2017) and the study of Uemura et al. (2001)

***Without** Helicobacter pylori infection of human stomach **no** human gastric cancer.*

Helicobacter pylori infection of human stomach is a necessary condition (a conditio sine qua non) of human gastric cancer due to the study of Shuto et al. (2017) and the study of Uemura et al. (2001)

Claims.

Null hypothesis (H_0):

Without Helicobacter pylori infection of human stomach **no** human gastric cancer.

H_0: $\pi_L \leqq \pi$

Alternative hypothesis (H_A)

Without Helicobacter pylori infection of human stomach there is human gastric cancer.

H_A: $\pi_L > \pi$

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

Proof.

The data as obtained by Shuto et al. (2017) and the study of Uemura et al. (2001) about the relationship between Helicobacter pylori infection and human gastric cancer in patients and healthy control subjects are viewed in the 2 × 2 table (Table 15). In general, the proportion of successes of *the conditio sine qua non relationship*, denoted by the term p_{Calc}(Helicobacter pylori infection ← human gastric cancer) is calculated as (Barukčić, 1998; Barukčić, 1997; Barukčić, 2005; Barukčić, 2006a; Barukčić, 2006b; Barukčić, 2011a; 2011b; Barukčić, 2012; Barukčić, 2016a; Barukčić et al., 2016b; Barukčić, 2016c; Barukčić, 2017a; Barukčić, 2017b; Barukčić, 2017c)

$$p_{Calc}\left(\text{Helicobacter pyolori [HP]} \rightarrow \text{Gastric cancer [GC]}\right) = \frac{\left(46+3091+1710\right)}{4847} = \frac{4847}{4847} = 1,0$$

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

$$\pi_L = 1 - \frac{3}{4847} = +0{,}999381941$$

The proportion of successes of the necessary condition, the conditio sine qua non relationship, is calculated as p_{Calc}(Helicobacter pylori infection $\leftarrow$ human gastric cancer) = 1,0. In fact, the one sided 100*(1-α) % confidence bound is calculated as π_L = 0,999381941 and is thus far less than the proportion of successes of the sample. The combined data as published by the study of Shuto et al. (2017) and the study of Uemura et al. (2001) do support our null hypothesis. Consequently, we accept the null hypothesis and reject the alternative hypothesis. In other words, **without** a Helicobacter pylori infection **no** human gastric cancer.

Helicobacter pylori is a necessary condition (a conditio sine qua non) of human gastric cancer.

Q. e. d.

Highly significant cause-effect relationship between Helicobacter pylori infection and human gastric cancer due to study of Shuto et al. (2017) and the study of Uemura et al. (2001)

Claims.

Null hypothesis (H_0): (no causal relationship)

There is not a highly significant causal relationship between Helicobacter pylori infection and gastric cancer. H_0: k = 0.

Alternative hypothesis (H_A): (causal relationship)

There is a highly significant causal relationship between Helicobacter pylori infection and gastric cancer. H_A: $k \neq 0$.

Conditions.

Alpha level = 5%.

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

Proof.

The data for this hypothesis test are obtained by Shuto et al. (2017) and the study of Uemura et al. (2001) and illustrated in the 2 × 2 table (Table 15). The causal relationship k(Helicobacter pylori infection, human gastric cancer) is calculated as (Barukčić, 1998; Barukčić, 1997; Barukčić, 2005; Barukčić, 2006a; Barukčić, 2006b; Barukčić, 2011a; 2011b; Barukčić, 2012; Barukčić, 2016a; Barukčić et al., 2016b; Barukčić, 2016c; Barukčić, 2017a; Barukčić, 2017b; Barukčić, 2017c)

$$k\left(\text{Helicobacter pyolori [HP]} \rightarrow \text{Gastric cancer [GC]}\right) = \frac{\left(\left(4847\times 46\right)-\left(3137\times 46\right)\right)}{\sqrt[2]{\left(3137\times 1710\right)\times\left(46\times 4810\right)}} = +0{,}072269302$$

The value of the test statistic k = +0,072269302 is equivalent to a calculated chi-square value of

$$\chi^2_{\text{Calculated}} = 4847\times\left(\frac{\left(\left(4847\times 46\right)-\left(3137\times 46\right)\right)}{\sqrt[2]{\left(3137\times 1710\right)\times\left(46\times 4810\right)}}\right)\times\left(\frac{\left(\left(4847\times 46\right)-\left(3137\times 46\right)\right)}{\sqrt[2]{\left(3137\times 1710\right)\times\left(46\times 4810\right)}}\right)$$

$$\chi^2_{\text{Calculated}} = 4847\times\left(0{,}072269302\right)\times\left(0{,}072269302\right)$$

$$\chi^2_{\text{Calculated}} = 25{,}31516353$$

The calculated chi-square statistic, uncorrected for continuity, is 25,31516353 and equivalent to a p value of 0,0000004868662405133550. The calculated chi-square statistic does exceed the critical chi-square value of 3.841458821 (Table 5). Consequently, we reject the null hypothesis and accept the alternative hypothesis. According to the combined data as obtained by the study of Shuto et al. (2017) and the study of Uemura et al. (2001) there is a highly significant causal relationship between a Helicobacter pylori infection and human gastric cancer. (k = +0,072269302 , p value = 0,0000004868662405133550).

Q. e. d.

Significant cause-effect relationship between Helicobacter pylori infection and human gastric cancer due to study of Fernández de Larrea-Baz et al. (2017)

Claims.

Null hypothesis (H_0): (no causal relationship)

There is not a significant causal relationship between Helicobacter pylori infection and gastric cancer.

H_0: k = 0.

Alternative hypothesis (H_A): (causal relationship)

There is a significant causal relationship between Helicobacter pylori infection and gastric cancer.

H_A: $k \neq 0$.

Conditions.

Alpha level = 5%.

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

Proof.

The data for this hypothesis test are obtained by Fernández de Larrea-Baz et al. (2017) and illustrated in the 2 × 2 table (Table 8). The causal relationship k(Helicobacter pylori infection, human gastric cancer) is calculated as (Barukčić, 1998; Barukčić, 1997; Barukčić, 2005; Barukčić, 2006a; Barukčić, 2006b; Barukčić, 2011a; 2011b; Barukčić, 2012; Barukčić, 2016a; Barukčić et al., 2016b; Barukčić, 2016c; Barukčić, 2017a; Barukčić, 2017b; Barukčić, 2017c)

$$k\left(\text{Helicobacter pyolori [HP]} \rightarrow \text{Gastric cancer [GC]}\right) = \frac{\left((2566\times)202-(2272\times 213)\right)}{\sqrt[2]{(2272\times 294)\times(213\times 2353)}} = +0{,}059446918$$

The value of the test statistic k = +0,059446918 is equivalent to a calculated chi-square value of

$$\chi^2_{\text{Calculated}} = 2566\times\left(\frac{\left((2566\times)202-(2272\times 213)\right)}{\sqrt[2]{(2272\times 294)\times(213\times 2353)}}\right)\times\left(\frac{\left((2566\times)202-(2272\times 213)\right)}{\sqrt[2]{(2272\times 294)\times(213\times 2353)}}\right)$$

$$\chi^2_{\text{Calculated}} = 2566\times(0{,}059446918)\times(0{,}059446918)$$

$$\chi^2_{\text{Calculated}} = 9{,}068080034$$

The calculated chi-square statistic, uncorrected for continuity, is 9,068080034 and equivalent to a p value of 0,002601100338053330. The calculated chi-square statistic does exceed the critical chi-square value of 3.841458821 (Table 5). Consequently, we reject the null hypothesis and accept the alternative hypothesis. According to the data as obtained by Fernández de Larrea-Baz et al. (2017) there is a highly significant causal relationship between a Helicobacter pylori infection and human gastric cancer (k = +0,059446918 , p value = 0,002601100338053330).

Q. e. d.

Significant cause-effect relationship between Helicobacter pylori infection and human gastric cancer due to study of Huerta et al. (2017)

Claims.

Null hypothesis (H_0): (no causal relationship)

There is not a significant causal relationship between Helicobacter pylori infection and gastric cancer.

H_0: k = 0.

Alternative hypothesis (H_A): (causal relationship)

There is a significant causal relationship between Helicobacter pylori infection and gastric cancer.

H_A: $k \neq 0$.

Conditions.

Alpha level = 5%.

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

Proof.

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

$$k\left(\text{Helicobacter pyolori [HP]} \rightarrow \text{Gastric cancer [GC]}\right) = \frac{\left((2277 \times 239) - (2016 \times 257)\right)}{\sqrt[2]{(2016 \times 261) \times (257 \times 2020)}} = +0{,}049920964$$

The value of the test statistic k = +0,049920964 is equivalent to a calculated chi-square value of

$$\chi^2_{\text{Calculated}} = 2277 \times \left(\frac{\left((2277 \times 239) - (2016 \times 257)\right)}{\sqrt[2]{(2016 \times 261) \times (257 \times 2020)}} \right) \times \left(\frac{\left((2277 \times 239) - (2016 \times 257)\right)}{\sqrt[2]{(2016 \times 261) \times (257 \times 2020)}} \right)$$

$$\chi^2_{\text{Calculated}} = 2277 \times (0{,}049920964) \times (0{,}049920964)$$

$$\chi^2_{\text{Calculated}} = 5{,}674517665$$

The calculated chi-square statistic, uncorrected for continuity, is 5,674517665 and equivalent to a p value of 0,01721307163424570. The calculated chi-square statistic does exceed the critical chi-square value of 3.841458821 (Table 5). Consequently, we reject the null hypothesis and accept the alternative hypothesis. According to the data as obtained by Huerta et al. (2017) there is a highly significant causal relationship between a Helicobacter pylori infection and human gastric cancer (k = +0,049920964, p value = 0,01721307163424570).

Q. e. d.

Highly significant cause-effect relationship between Helicobacter pylori infection and human gastric cancer due to study of Shi et al. (2017)

Claims.

Null hypothesis (H_0): (no causal relationship)

There is not a highly significant causal relationship between Helicobacter pylori infection and gastric cancer. H_0: k = 0.

Alternative hypothesis (H_A): (causal relationship)

There is a highly significant causal relationship between Helicobacter pylori infection and gastric cancer. H_A: $k \neq 0$.

Conditions.

Alpha level = 5%.

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

Proof.

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

$$k\left(\text{Helicobacter pyolori [HP]} \rightarrow \text{Gastric cancer [GC]}\right) = \frac{\left((1650\times 597)-(846\times 851)\right)}{\sqrt[2]{(846\times 804)\times(851\times 799)}} = +0{,}389820707$$

The value of the test statistic k = +0,389820707 is equivalent to a calculated chi-square value of

$$\chi^2_{\text{Calculated}} = 1650\times\left(\frac{\left((1650\times 597)-(846\times 851)\right)}{\sqrt[2]{(846\times 804)\times(851\times 799)}}\right)\times\left(\frac{\left((1650\times 597)-(846\times 851)\right)}{\sqrt[2]{(846\times 804)\times(851\times 799)}}\right)$$

$$\chi^2_{\text{Calculated}} = 1650\times(0{,}389820707)\times(0{,}389820707)$$

$$\chi^2_{\text{Calculated}} = 250{,}7343032$$

The calculated chi-square statistic, uncorrected for continuity, is 250,7343032 and equivalent to a p value of less than 0,00000000000000000000000000001. The calculated chi-square statistic does exceed the critical chi-square value of 3.841458821 (Table 5). Consequently, we reject the null hypothesis and accept the alternative hypothesis. According to the data as obtained by Shi et al. (2017) there is a highly significant causal relationship between a Helicobacter pylori infection and human gastric cancer (k = +0,389820707 , p value < 0,00000000000000000000000000001).

Q. e. d.

Highly significant cause-effect relationship between Helicobacter pylori infection and human gastric cancer due to study of Sarker et. al. (2017)

Claims.

Null hypothesis (H_0): (no causal relationship)

There is not a highly significant causal relationship between Helicobacter pylori infection and gastric cancer. H_0: k = 0.

Alternative hypothesis (H_A): (causal relationship)

There is a highly significant causal relationship between Helicobacter pylori infection and gastric cancer. H_A: $k \neq 0$.

Conditions.

Alpha level = 5%.

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

Proof.

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

$$k\left(\text{Helicobacter pyolori [HP]} \rightarrow \text{Gastric cancer [GC]}\right) = \frac{\left((634\times 99)-(450\times 114)\right)}{\sqrt[2]{(450\times 184)\times(114\times 520)}} = +0{,}163660047$$

The value of the test statistic k = +0,163660047 is equivalent to a calculated chi-square value of

$$\chi^2_{\text{Calculated}} = 634\times\left(\frac{\left((634\times 99)-(450\times 114)\right)}{\sqrt[2]{(450\times 184)\times(114\times 520)}}\right)\times\left(\frac{\left((634\times 99)-(450\times 114)\right)}{\sqrt[2]{(450\times 184)\times(114\times 520)}}\right)$$

$$\chi^2_{\text{Calculated}} = 634\times(0{,}163660047)\times(0{,}163660047)$$

$$\chi^2_{\text{Calculated}} = 16{,}98144336$$

The calculated chi-square statistic, uncorrected for continuity, is 16,98144336 and equivalent to a p value of 0,00003774694582629020. The calculated chi-square statistic does exceed the critical chi-square value of 3.841458821 (Table 5). Consequently, we reject the null hypothesis and accept the alternative hypothesis. According to the data as obtained by Sarker et. al. (2017) there is a highly significant causal relationship between a Helicobacter pylori infection and human gastric cancer (k=+0,163660047 , p value = 0,00003774694582629020).

Q. e. d.

Highly significant cause-effect relationship between Helicobacter pylori infection and human gastric cancer due to study of Binh et al. (2017)

Claims.

Null hypothesis (H_0): (no causal relationship)

There is not a highly significant causal relationship between Helicobacter pylori infection and gastric cancer. H_0: k = 0.

Alternative hypothesis (H_A): (causal relationship)

There is a highly significant causal relationship between Helicobacter pylori infection and gastric cancer. H_A: $k \neq 0$.

Conditions.

Alpha level = 5%.

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

Proof.

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

$$k\left(\text{Helicobacter pyolori [HP]} \rightarrow \text{Gastric cancer [GC]}\right) = \frac{\left(\left(552\times 224\right)-\left(327\times 282\right)\right)}{\sqrt[2]{\left(327\times 225\right)\times\left(282\times 270\right)}} = +0{,}419979486$$

The value of the test statistic k = +0,419979486 is equivalent to a calculated chi-square value of

$$\chi^2_{\text{Calculated}} = 552\times\left(\frac{\left(\left(552\times 224\right)-\left(327\times 282\right)\right)}{\sqrt[2]{\left(327\times 225\right)\times\left(282\times 270\right)}}\right)\times\left(\frac{\left(\left(552\times 224\right)-\left(327\times 282\right)\right)}{\sqrt[2]{\left(327\times 225\right)\times\left(282\times 270\right)}}\right)$$

$$\chi^2_{\text{Calculated}} = 552\times\left(0{,}419979486\right)\times\left(0{,}419979486\right)$$

$$\chi^2_{\text{Calculated}} = 97{,}36328808$$

The calculated chi-square statistic, uncorrected for continuity, is 97,36328808 and equivalent to a p value of 0,000000000000000000000057706088. The calculated chi-square statistic does exceed the critical chi-square value of 3.841458821 (Table 5). Consequently, we reject the null hypothesis and accept the alternative hypothesis. According to the data as obtained by Binh et al. (2017) there is a highly significant causal relationship between a Helicobacter pylori infection and human gastric cancer (k=+0,419979486 , p value = 0,000000000000000000000057706088).

Q. e. d.

Highly significant cause-effect relationship between Helicobacter pylori infection and human gastric cancer due to study of Cai et. al. (2016)

Claims.

Null hypothesis (H_0): (no causal relationship)

There is not a highly significant causal relationship between Helicobacter pylori infection and gastric cancer. H_0: k = 0.

Alternative hypothesis (H_A): (causal relationship)

There is a highly significant causal relationship between Helicobacter pylori infection and gastric cancer. H_A: $k \neq 0$.

Conditions.

Alpha level = 5%.

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

Proof.

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

$$k\left(\text{Helicobacter pyolori [HP]} \rightarrow \text{Gastric cancer [GC]}\right) = \frac{\left(\left(3570\times 1481\right)-\left(3080\times 1608\right)\right)}{\sqrt[2]{\left(3080\times 490\right)\times\left(1608\times 1962\right)}} = +0{,}153309529$$

The value of the test statistic k = +0,153309529 is equivalent to a calculated chi-square value of

$$\chi^2_{\text{Calculated}} = \times\left(\frac{\left(\left(3570\times 1481\right)-\left(3080\times 1608\right)\right)}{\sqrt[2]{\left(3080\times 490\right)\times\left(1608\times 1962\right)}}\right)\times\left(\frac{\left(\left(3570\times 1481\right)-\left(3080\times 1608\right)\right)}{\sqrt[2]{\left(3080\times 490\right)\times\left(1608\times 1962\right)}}\right)$$

$$\chi^2_{\text{Calculated}} = \times\left(0{,}153309529\right)\times\left(0{,}153309529\right)$$

$$\chi^2_{\text{Calculated}} = 83{,}90860737$$

The calculated chi-square statistic, uncorrected for continuity, is 83,90860737 and equivalent to a p value of 0,000000000000000000051818430938. The calculated chi-square statistic does exceed the critical chi-square value of 3.841458821 (Table 5). Consequently, we reject the null hypothesis and accept the alternative hypothesis. According to the data as obtained by Cai et. al. (2016) there is a highly significant causal relationship between a Helicobacter pylori infection and human gastric cancer (k = +0,153309529 , p value = 0,000000000000000000051818430938).

Q. e. d.

Discussion

Global cancer incidence and mortality rates are still threating the population worldwide. Detecting the cause or a cause of a cancer enable us to develop intervention strategies at low cost and quickly. Several studies investigated whether the risk of gastric cancer increases with Epstein-Barr virus (EBV) infection. A recent systematic review of Bae et al. (2016) came to the conclusion that EBV infection increases the risk of gastric cancer. Still, the heterogeneity among the studies analyzed was very high. The discovery of EBV DNA in gastric cancer tissues (Burke et al., (1990)) justifies at least the question about the mechanism through which such a relationship between EBV and gastric cancer is being established. In other words, what was first, the chicken or the egg? Epstein-Barr virus (EBV), currently categorized as a group-1 carcinogen, is a virus which infects more than 90% of the population worldwide (Cohen (2000)). After the primary infection of the human host, Epstein-Barr virus (EBV) persists for life in memory B cells (Decker et al. (1996); Babcock et al. (1998); Babcock et al. (1999)) in the peripheral blood in its human host. Theoretically, it is possible to find memory cells in cancer tissues too. Memory cells are of central importance in the trial of human immune system to overcome a Helicobacter pylori infection or gastric cancer et cetera. Thus far, a possible significant cause effect relationship between EBV and gastric cancer does not imply that EBV is a cause of gastric cancer. The question is, what is the cause, what is the effect? In contrast to Bae et al. (2016) it is necessary to think about the validity of the null-hypothesis: *without* gastric cancer *no* EBV DNA in gastric cancer tissues. While searching for EBV DNA in gastric cancer tissues it is necessary to be very precisely. In this context it is important to note that the *in situ hybridization* (ISH) is able to differentiate between an infection in other cells and viral infections in tumor cells and is regarded as superior to *polymerase chain reaction* (PCR).

Depending to some extent on the commercial serology kits used to diagnose Helicobacter pylori (Hp) infection and the associated cutoff value of the kit, view studies failed to provide clear evidence that a Helicobacter pylori infection is a necessary condition of human gastric cancer. An overview of the results achieved is shown in Table 16.

Table 16. Overview of the results achieved.

Study	Country	Year	N	**p SINE**	p Critical	Signif.	**Causal relationship**	p-value	significant
Shuto et al.	Japan	2017	3321	**1**	0,999097943	**YES**	0,04779062	0,0058856752	YES
Fernández de Larrea-Baz et al.	Spain	2017	2566	0,99571317	0,998832528	NO	0,059446918	0,0026000000	YES
Huerta et. al.	Spain	2017	2277	0,99209486	0,998684351	NO	0,049920964	0,0172130000	YES
Shi et al.	China	2017	1650	0,84606061	0,998184405	NO	0,389820707	**0,00000000000...1**	YES
Sarker et. al.	Bangladesh	2017	634	0,97634069	0,99527487	NO	0,163660047	**0,0000377469**	YES
Binh et al.	Vietnam	2017	552	0,89492754	0,994572949	NO	0,419979486	**5,7706088E - 23**	YES
Cai et. al.	USA	2016	3570	0,96442577	0,999160859	NO	0,153309529	**5,1818430938E - 20**	YES
Uemura et al.	Japan	2001	1526	**1**	0,998036873	**YES**	0,073684834	0,0039966244	YES
Shuto et al. and Uemura et al.	Japan	2017/2001	4847	**1**	0,999381941	**YES**	0,072269302	**0,00000048686624051336**	YES

Still, the very impressive studies of Shuto et al. (2017) [Japan] and Uemura et al., (2001) [Japan] and the combination of the data of both studies with a sample size of n=4847 were able to provide strict evidence, that a Helicobacter pylori infection is a necessary condition of human gastric cancer. In other words, **without a Helicobacter pylori infection no human gastric cancer**. The studies included about n=20943 participants. All studies analysed were able to provide evidence of a cause effect relationship between Helicobacter pylori and gastric cancer. The studies of Shi et al. (2017), Sarker et. al. (2017), Binh et al. (2017), Cai et. al. (2016) provided evidence of a statistically **highly significant cause and effect relationship between Helicobacter pylori and gastric cancer.** Firstly. Without a Helicobacter pylori infection no gastric cancer. Secondly. There is a cause effect relationship between Helicobacter pylori and gastric cancer. Thus far, we are in a position to deduce that Helicobacter pylori is not only a cause but the cause gastric cancer. Finally, the cause of human gastric cancer is identified.

An eradication Helicobacter pylori (H. pylori) is a possible strategy in cancer prevention and might be an effective measure to prevent the development of gastric cancer (GC). Meanwhile some systematic reviews and meta-analysis explored the role of H. pylori eradication in preventing GC, with the consequence that H. pylori eradication is associated with a significantly lower risk of GC (Doorakkers et al., 2016; Rokkas et al., 2017). Still, to manage a H. pylori infection, it is suitable to consider regional differences. Despite the global public health threat by gastric cancer and Helicobacter pylori, progress on developing vaccines against Helicobacter pylori has still not met with the necessary success. A low cost, highly effective and globally available vaccine against Helicobacter pylori has the potential to spare millions of lives.

Conclusion

Helicobacter pylori is the cause of human gastric cancer.

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