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Helicobacter Pylori is the Cause of Gastric Cancer

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Abstract

Objective: This study presents a systematic meta-analysis of the relationship between Helicobacter pylori (HP) infection and gastric cancer (GC).

Materials and Methods: Twelve articles including 21589 subjects were selected (1237 cases and 20352 controls). These data were analyzed using the mathematical formula of the conditio sine qua non relationship and the causal relationship formula.

Results: The data re-analyzed support the Null hypothesis *without* a Helicobacter pylori infection *no* human gastric cancer. The causal relationship between HP and GC is highly significant.

Conclusion: Helicobacter pylori is the cause of human gastric cancer.

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

1. Introduction

Gastric cancer mortality and incidence decreased substantially over the last decades in most countries worldwide. Still, gastric cancer (GC) is among the most common causes of cancer death globally (Ferro et al., 2014) and the second leading cause of cancer-related mortality worldwide. Early modern humans migrated (Correa & Piazuelo, 2012) out of Africa along with the bacterium Helicobacter pylori, its own oldest and closest companion, approximately 60,000 years ago. Meanwhile, H. pylori infection affects about 50% of the global (Tobacco Smoke and Involuntary Smoking. 2004) population. German scientists (Blaser, 2005) identified spiral-shaped bacteria in the human stomach in 1875. Bizzozero (Bizzozero, 1893) an Italian pathologist, described similarly shaped bacteria in the stomach of dogs in 1893. H. pylori is a spiral-shaped, gram-negative microaerophilic bacterium which has been re-discovered (Buzás, 2004) by Barry J. Marshall and J. Robert Warren (Warren & Marshall, 1983) in 1983. The first description of gastric ulceration (Buckley & O'Morain, 1998) was reported in 1586 by an Italian physician (Donati, 1586). For a long time, the therapy of gastric ulceration was dominated by the 1910 dictum *'no acid, no ulcer'* (Schwarz, 1910) of the Croatian physician Karl Schwarz. In particular, several studies (Forman et al., 1991; Nomura et al., 1991; Parsonnet et al., 1991; Estevens et al., 1993) reported a higher risk of the development of gastric cancer in subjects with positive serologic tests for H. pylori. Finally, the World Health Organization and the International Agency for Research on Cancer (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. 1994) classified H pylori as a class 1 carcinogen in 1994. The rates of Helicobacter pylori infection in patients with gastric cancer vary greatly among studies. Thus far, most but not all studies, systematic reviews and meta-analysis confirmed (Lin et al., 1995) that H. pylori is associated with gastric cancer. However, due to conflicting reports (Moss, 2017) in the literature regarding the relationship between H. pylori and human gastric cancer Helicobacter pylori is still not accepted as the cause of gastric cancer (Barukčić, 2005; Barukčić, 2006; Barukčić, 2006; Barukčić, 2009; Barukčić, 2017; Ando et al., 2006).

2. Material and Methods

The rates of Helicobacter pylori infection vary greatly among studies. These variations are attributable to differences in the methods of detecting H. pylori (enzyme-linked immunosorbent assay (ELISA), western blot et cetera) which are associated with different false negative results or with the definition of cut of values and other factors.

2.1 Search Strategy

For the questions addressed in this paper, Pubmed was searched for appropriate studies conducted in any country which investigated the relationship between Helicobacter pylori and gastric cancer.

The search in Pubmed was performed while using medical key words like “Helicobacter pylori” and “gastric cancer” and “antibody” and “review” et cetera. The articles found where saved as a *.txt file while using Pubmed support (Menu: Send to, Choose Radio Button: File, Choose Format: Abstract (text). Click buttom “create file”). The created *.txt file was converted into a *.pdf file. The abstracts where studied within the *.pdf file.

Those articles were considered for a review which provided access to data without any data access barrier; no data access restrictions were accepted. Additionally, references from relevant publications and review articles were checked. Studies were included if the same allowed to compare the prevalence of Helicobacter pylori in patients with gastric cancer with the prevalence in healthy controls.

Studies were excluded if insufficient data were provided to calculate the measures of relationship or if there were data access barriers.

2.2 The Data of the Studies Analyzed

The data of the studies analyzed are presented by the table 1 (**Table 1**). In point of fact, bias due to the differences in the methods used to detect HP and a systemic and substantial under-detection of Helicobacter pylori infection and underestimation of its effect on gastric cancer is at the end not excluded.

Table 1. The data of the studies considered for a meta-analysis

Study Id	Year	Country	N	Case Pos	**Case Tot**	Contol pos	**Control Tot**
Forman et al. (Forman et al., 1991)	1991	UK	145	20	**29**	54	**116**
Parsonnet et al. (Nomura et al., 1991)	1991	USA	295	92	**109**	111	**186**
Nomura et al. (Parsonnet et al., 1991)	1991	USA	218	103	**109**	83	**109**
Uemura et al. (Uemura et al., 2001)	2001	Japan	1526	36	**36**	1210	**1490**
Miki (Miki 2011)	2011	Japan	5290	59	**63**	4151	**5227**
González et al. (González et al., 2012)	2012	Spain	476	72	**88**	188	**388**
Keck et al. (Keck et al., 2014)	2014	USA	468	112	**122**	285	**346**
Yoshida et al. (Yoshida et al., 2014)	2014	Japan	4655	81	**87**	3576	**4568**
Sarker et al. (Sarker et al., 2017)	2017	Bangladesh	634	99	**114**	351	**520**
Huerta et al. (Huerta et al., 2017)	2017	Spain	2277	239	**257**	1777	**2020**
Fernández de Larrea-Baz et al. (Fernández et al., 2017)	2017	Spain	2284	202	**213**	1822	**2071**
Shuto et al. (Shuto et al., 2017)	2017	Japan	3321	10	**10**	1881	**3311**
		Total	**21589**	1125	1237	15489	20352

Table 2. The sample space of a contingency table

		Conditioned B_t (Crohn’s disease)		
		Yes = +1	*Not = +0*	*Total*
Condition A_t (HP PCR DNA)	Yes =+1	$\mathbf{a}_t$	$\mathbf{b}_t$	A_t
	Not = +0	$\mathbf{c}_t$	$\mathbf{d}_t$	$\underline{\mathbf{A}}_\mathbf{t}$
	Total	B_t	$\underline{\boldsymbol{B}}_\boldsymbol{t}$	N_t

2.3 Statistical Analysis

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

2.3.1 The 2x2 Table

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

In general it is $(a+b) = A_t$, $(c+d) = \underline{A}_t$, $(a+c) = B_t$, $(b+d) = \underline{B}_t$ and $a_t+b_t+c_t+d_t=N_t$. Equally, it is $B_t+\underline{B}_t = A_t + \underline{A}_t = N_t$. In this context, it is $p(a_t)=p(A_t \cap B_t)$, $p(A_t) = p(a_t)+p(b_t)$ or in other words $p(A_t)= p(A_t \cap B_t)+p(A_t \cap \underline{B}_t)$ while $p(A_t)$ is not defined as $p(a_t)$. In the same context, it should be considered that $p(B_t) = p(a_t)+p(c_t) = p(A_t \cap B_t) +p(c_t)$ and

equally that $p(\underline{B_t}) = 1- p(B_t) =p(b_t)+p(d_t)$. In point of fact, the joint probability of A_t and B_t is denoted by $p(A_t \cap B_t)$. It is $p(a_t)+p(c_t)+p(b_t)+p(d_t) = 1$. These relationships are viewed by the table (**Table 3**) as follows.

Table 3. The probabilities of a contingency table

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

2.3.2 Independence

In the case of independence of A_t and B_t it is

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

2.3.3 Necessary Condition (Conditio Sine Qua Non)

The formula of the necessary condition (conditio sine qua non) (Barukčić, 2005; Barukčić, 2006; Barukčić, 2006; Barukčić, 2009; Barukčić, 2017), (Barukčić, 1989; Barukčić, 1997) relationship was derived as

$$p\left(A_t \leftarrow B_t\right) \equiv p\left(A_t \cap B_t\right) + \left(1 - p\left(B_t\right)\right) \equiv \frac{a_t + b_t + d_t}{N} \equiv +1 \tag{2}$$

and used to proof the hypothesis: *without* A_t (i.e. condition, "risk factor") *no* B_t (i. e. conditioned, outcome).

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

Under conditions where the chi-square (Pearson, 1900) goodness of fit test cannot be used it is possible to use an approximate and conservative (one sided) confidence interval as discussed by Rumke (Rumke, 1975), Louis (Louis, 1981), Hanley et al. (Hanley & Lippman-Hand, 1983) and Jovanovic (Jovanovic & Levy, 1997) known as the rule of three. According to the definition of the conditio sine qua non relationship it is

$$p\left(A_t \cap B_t\right) + \left(1 - p\left(B_t\right)\right) \equiv +1 \tag{3}$$

or

$$p\left(A_t \cap B_t\right) + 1 - p\left(B_t\right) \equiv +1 \tag{4}$$

or

$$p\left(A_t \cap B_t\right) - p\left(B_t\right) \equiv 0 \tag{5}$$

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

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

or

$$N \times p\left(A_t \cap B_t\right) - N \times p\left(B_t\right) = 0 \tag{7}$$

The square operation yields

$$\left(N \times p\left(A_t \cap B_t\right) - N \times p\left(B_t\right)\right) \times \left(N \times p\left(A_t \cap B_t\right) - N \times p\left(B_t\right)\right) = 0 \times 0 \tag{8}$$

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

$$\frac{\left(N \times p\left(A_t \cap B_t\right) - N \times p\left(B_t\right)\right)^2}{N \times p\left(B_t\right)} = 0 \tag{9}$$

which is equivalent with

$$\frac{\left(a_t-\left(B_t\right)\right)^2}{\left(B_t\right)}=\frac{\left(a_t-\left(a_t+c_t\right)\right)^2}{\left(B_t\right)}=\frac{\left(c_t\right)^2}{\left(B_t\right)}=0 \tag{10}$$

Adding 0 yields

$$\frac{\left(c_t\right)^2}{\left(B_t\right)}+0=0+0 \tag{11}$$

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

$$\chi^2\left(\mathrm{SINE}\right)\equiv\frac{\left(c_t-\left(\frac{1}{2}\right)\right)^2}{\left(B_t\right)}+0=0 \tag{12}$$

This definition of the X^2 distribution of a *conditio sine qua non* distribution (degrees of freedom = 2-1=1) is more precise than already published (Barukčić, 2018; Barukčić, 2018; Barukčić, 2018) formulas. The use of the continuity correction should follow the rules of statistics as established and valid today. In this context, it is not necessary to improve the definition of the X^2 distribution of a *conditio per quam* distribution as already published (Barukčić, 2018; Barukčić, 2018; Barukčić, 2018).

2.3.5 The Mathematical Formula of the Causal Relationship k

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

$$k\left({}_R U_t, {}_0W_t\right)\equiv\frac{\left(p\left({}_R U_t\times {}_0W_t\right)-\left(p\left({}_R U_t\right)\times p\left({}_0W_t\right)\right)\right)}{\sqrt[2]{\left(p\left({}_R U_t\right)\times p\left({}_R\underline{U}_t\right)\right)\times\left(p\left({}_0W\right)\times p\left({}_0\underline{W}_t\right)\right)}} \tag{13}$$

where ${}_RU_t$ denotes the cause and ${}_0W_t$ denotes the effect while the chi-square distribution (Pearson, 1900) can be applied to determine the significance of causal relationship k. Correlation is not causation, causation is not correlation. The relationship between correlation and causation is discussed already in many publications (Pearson, 1900). This does not necessarily imply that repeating itself over and over again may contribute anything new to further scientific progress.

Table 4. 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

2.3.6 The Chi Square Distribution

Evaluating hypotheses in the light of empirical facts is not an easy task. In particular, mathematics and statistics provide us with specific methods to relate facts and hypotheses under certain conditions. And there is so much more. Interested readers may bear in mind that an entirely different approach and one very important aspect of statistics is the conceptual analysis of causal relations too. A general discussion of the justification of inferences or procedures which extrapolate from data to predictions and general facts may be found in secondary literature. In this context, the chi-squared distribution (Pearson, 1900), a widely known distribution in hypothesis testing, in inferential statistics or in construction of confidence intervals, is of use. It can be insightful to consider the following critical values of the chi square distribution as visualized by **Table 4**.

3. Results

3.1 Helicobacter Pylori Infection is the Cause of Human Gastric Cancer

Claims.

Null hypothesis:

A Helicobacter pylori infection is a necessary condition (a conditio sine qua non) of human gastric cancer. In other words, the sample distribution of the study analyzed agrees with the hypothetical (theoretical) distribution of a necessary condition.

Table 5. *Without* Helicobacter pylori infection *no* gastric cancer

Study Id	Year	Country	N	a_t	b_t	c_t	d_t	p(SINE)	X^2(Sine)	k	p val (k)
González et al. []	2012	Spain	476	72	188	16	200	0.9663	2.7301136	0.260153233	1.38E-08
Parsonnet et al. []	1991	USA	295	92	111	17	75	0.9423	2.4977064	0.257623841	9.65E-06
Sarker et al. []	2017	Bangladesh	634	99	351	15	169	0.9763	1.8442982	0.163660047	3.77E-05
Nomura et al. []	1991	USA	218	103	83	6	26	0.9724	0.2775229	0.259237924	0.0001294
Yoshida et al. []	2014	Japan	4655	81	3576	6	992	0.99871	0.3477011	0.048902986	0.0008483
Fernánd. de L.-B. et al. []	2017	Spain	2284	202	1822	11	249	0.9951	0.5176056	0.062797121	0.0026896
Uemura et al. []	2001	Japan	1526	36	1210	0	280	1	0.0069444	0.073684834	0.0039966
Miki	2011	Japan	5290	59	4151	4	1076	0.9992	0.194444	0.038312294	0.0053273
Shuto et al. []	2017	Japan	3321	10	1881	0	1430	1	0.025	0.04779062	0.0058856
Keck et al. []	2014	USA	468	112	285	10	61	0.9786	0.739754	0.115440677	0.0125120
Huerta et al. []	2017	Spain	2277	239	1777	18	243	0.9920	1.191634	0.049920964	0.0172130
Forman et al. []	1991	UK	145	20	54	9	62	0.9379	2.491379	0.179348735	0.0308001
		Total	**21589**	1125	15489	112	4863	0.99481	12.86	X^2 (Calculated k)=	143.776593
						Alpha =	0.05			Alpha =	0.05
					Degrees of freedom (D. f.) =		12			D. f. =	12
					X^2 (Critical SINE) =		21.0261			X^2 (Critical k)=	21.0260698
					X^2 (Calculated SINE)=		12.8641			X^2 (Calculated k)=	143.776593
										p value (k)=	1.03E-24

Alternative hypothesis:

A Helicobacter pylori infection is not a necessary condition (a conditio sine qua non) of human gastric cancer. In other words, the sample distribution of the study analyzed does not agree with the hypothetical (theoretical) distribution of a necessary condition.

The significance level (Alpha) below which the null hypothesis will be rejected is alpha=0,05.

Proof.

The results of the re-analyses of the data reviewed by this article (**Table 1**) which investigated the relationship between Helicobacter pylori and gastric cancer are viewed by the table (**Table 5**). Altogether, 12 studies were meta-analyzed while the level of significance was alpha = 0,05. In toto, 12 from 12 studies provide significant evidence of a conditio sine qua non relationship between Helicobacter pylori and gastric cancer. The sample size was N = 21589 while the conditio sine qua non probability/relative frequency of the studies analyzed was (21589- 112)/ 21589= 0.99481. In other words, the data analyzed support the hypothesis *without* a Helicobacter pylori infection *no* human gastric cancer. In the same respect, 12/12 studies analyzed provided evidence of a significant or highly

significant cause effect relationship between Helicobacter pylori and human gastric cancer. In point of fact, since without a Helicobacter pylori infection human gastric cancer will not develop we authorized to draw the following conclusion. Helicobacter pylori is the cause of human gastric cancer (k ~ +0,081607078, p-value = 1,03E-24). **Q. e. d.**

4. Discussion

Since the re-discovery of Helicobacter pylori the possibility of a relationship with gastric cancer has been tested but still not supposedly proven. Numerous different studies of various designs from many countries around the world and several meta-analyses (Huang et al., 1998; Rokkas, Rokka & Portincasa, 2017) have been published looking at the relationship between H pylori infection and gastric cancer. Over the years, studies have produced conflicting results. Gastric cancer remains a major scientific, medical and public health challenge. The exact mechanisms by which H pylori might cause gastric cancer is still under investigation and remains to be discovered. H. pylori infection varies among regions but besides of all there is emerging evidence that H. pylori is able to raise the risk of gastric cancer. Thus far, the findings of this study are consistent with those of several previous studies and meta-analysis. The prevalence of IgG antibodies to H pylori in blood samples of cases and controls is one way to proof the relationship between gastric cancer and helicobacter pylori. The presence of H pylori antibodies does not guarantee the presence of H. pylori inside the stomach and is a potential sources of human, systematic and random error and bias and can cause the results of a research study to be incorrect. The set of study or experimental data is seldom perfect and complete which may threat the validity of the study. In general, researchers even if aware of the bias as associated with study design and the data the amount of studies which are reporting the same result is difficult to be ignored. Without a Helicobacter pylori infection no human gastric cancer (N=21589, p(SINE)=0.99481, X^2(Calculated SINE)=12,86 < X^2 (Critical SINE) = 21,0261, p value (k)= 1,03E-24). This study is of help to further reduce the burden of this disease and invites us all to accept the following inescapable conclusion.

5. Conclusion

Without a Helicobacter pylori infection no gastric cancer. Helicobacter pylori is the cause of gastric cancer.

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