Helicobacter pylori – The cause of human gastric cancer

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Abstract

Background: Many studies documented an association between a Helicobacter pylori infection and the development of human gastric cancer. None of these studies were able to identify Helicobacter pylori as a cause or as the cause of human gastric cancer. The basic relation between gastric cancer and Helicobacter pylori still remains uncertain.

Objectives: This systematic review and re-analysis of Naomi Uemura et al. available long-term, prospective study of 1526 Japanese patients is performed so that some new and meaningful inference can be drawn.

Materials and Methods: Data obtained by Naomi Uemura et al. who conducted a long-term, prospective study of 1526 Japanese patients with a mean follow up about 7.8 years and endoscopy at enrolment and in the following between one and three years after enrolment were re-analysed.

Statistical analysis used:

The method of the conditio sine qua non relationship was used to proof the hypothesis without a helicobacter pylori infection no development of human gastric cancer. The mathematical formula of the causal relationship was used to proof the hypothesis, whether there is a cause effect relationship between a helicobacter pylori infection and human gastric cancer. Significance was indicated by a P value of less than 0.05.

Results:

Based on the data published by Uemura et al. we were able to make evidence that without a helicobacter pylori infection no development of human gastric cancer. In other words, a Helicobacter pylori infection is a conditio sine qua non of human gastric cancer. In the same respect, the data of Uemura et al. provide a significant evidence that a helicobacter pylori infection is the cause of human gastric cancer.

Conclusions:

Without a Helicobacter pylori infection no development of human gastric cancer. Helicobacter pylori is the cause (k=+0,07368483, p Value = 0.00399664) of human gastric cancer.

Keywords

Human gastric cancer, Helicobacter pylori, Causal relationship

1. Introduction

Despite of the overall decline of gastric cancer incidence and mortality over the past 70 years [1] gastric cancer is the fourth most common cancer and still one of the leading causes of cancer-related death worldwide[2]-[3]. Each year approximately 700,000 people succumb to this malignancy while the 5-year survival rates in the United States are less then 15%. [4] Helicobacter pylori, the most common bacterial infection worldwide [5], is a microbial species able to colonize gastric epithelium and induce a persistent local inflammatory response, has been discussed for a long time as being associated with human gastric cancer. "There is sufficient evidence in humans for the carcinogenicity of infection with Helicobacter pylori ...Infection with Helicobacter pylori is carcinogenic to humans (Group 1). " [6]. Even if only a small proportion of infected individuals develop malignancy H. pylori significantly increases the risk of developing gastric adenocarcinoma. One of the first large, randomized placebo-controlled trials to examine the relationship between H. pylori eradication and the incidence of gastric cancer were able to provide evidence that the risk of developing cancer in infected individuals without pre-malignant lesions is significantly decreased by eradication of H. pylori. [7] In several, previous (epidemiologic) studies and meta-analysis it has been reported that there is a close relation between a H. pylori infection of human stomach and human gastric cancer. Still, the cause of human gastric cancer is not identified.

2. Material and methods

2.1. Study design

Naomi Uemura et al. [8] conducted a long-term, prospective study of a group of 1526 Japanese patients (869 men and 657 women; mean age, 52 years; range, 20 to 76) who were assessed for H. pylori infection by endoscopy and biopsy, by histologic examination, rapid urease test and serologic testing. Patients with gastric cancer and other severe underlying diseases where previously excluded from the study. Patients in whom the histologic examination or the rapid urease test also known as the CLO test (Campylobacter-like organism test) or serologic evaluation were positive were classified H. pylori positive. Those patients in whom all three were negative were considered H. pylori negative. The group studied underwent endoscopy with biopsy at enrolment and about one and three years later after enrolment (mean follow-up was 7.8 years, range, 1.0 to 10.6). According to the Vienna classification, an invasion of neoplastic epithelium into the lamina propria of the mucosa or beyond was defined as gastric cancer. Altogether, 1246 patients were H. pylori positive while 280 patients were H. pylori negative. Human gastric cancer developed in 36 of 1246 H. pylori positive patients. In contrast to this fact, none of the 280 H. pylori negative developed gastric cancer. The data obtained by Uemura et al. are presented by the 2 by 2-table (**Table 1**).

Table 1. The relationship betwee helicobacter pylori and human gastric cancer.

		Human gastric cancer		
		yes	no	
Helicobacter pylori infection	**yes**	36	1210	1246
	no	0	280	280
		0	1490	1526

2.2. Statistical Analysis

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

2.2.1. Conditio sine qua non

The formula of the condition sine qua non [9] relationship

$$p\left(\text{Helicobacter pylori} \leftarrow \text{Human gastric cancer}\right) \tag{1}$$

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

2.2.2. The rule of three

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 30 and more). The formula, justified by the central limit theorem, is

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

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 $1 - (2/\text{Alpha})$ 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. The Agresti-Coull [10] interval is also another approximate binomial confidence interval for calculating binomial confidence intervals. Another very common method for calculating binomial confidence intervals is the Clopper-Pearson interval [11] too. A faster way to determine the lower and upper "exact" confidence interval for p_{Calc} can be based on the F distribution [12] too. In this study, we will use the rule of threes [13] to calculate the confidence interval for p_{Calc}. Briefly sketched,

the rule of threes can be derived [14] from the binomial model. The rule of three defines that 3/N is an upper 95% confidence bound for binomial probability p_{Calc} when in N independent trials no events occur [15]. Under conditions where a certain event did not occur in a sample with N subjects (i. e. $p_{Calc} = 0$) the interval from 0 to 3/n is called a 95% classical confidence interval for the binomial parameter for the rate of occurrences in the population. According to the rule of the same is calculated for a sample sizes of 30-50 or more as

$$p_{lower} = \left(\frac{3}{N} \right) \tag{3}$$

By symmetry, the one-sided 95 percent confidence interval for only successes (i.e. $p_{Calc}=1$) is

$$p_{lower} = 1 - \left(\frac{3}{N} \right) \tag{4}$$

2.2.3. The mathematical formula of the causal relationship k

The mathematical formula of the causal relationship k [17] and the chi-square distribution [18] were applied to determine the significance of causal relationship between a Helicobacter pylori infection and human gastric cancer. A one-tailed test makes it much more 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. In general, a p value of < 0.05 is considered as significant.

2.2.3. The chi square distribution
The chi-squared distribution [18] is a widely known distribution and used in hypothesis testing, in inferential statistics or in construction of confidence intervals. The critical values of the chi square distribution are visualized by **Table 2**.

Table 2. The critical values of the chi square distribution (degrees of freedom: 1).

	p-Value	One sided X²	Two sided X²
The chi square distribution	0,1000000000	1,642374415	2,705543454
	0,0500000000	**2,705543454**	**3,841458821**
	0,0400000000	3,06490172	4,217884588
	0,0300000000	3,537384596	4,709292247
	0,0200000000	4,217884588	5,411894431
	0,0100000000	5,411894431	6,634896601
	0,0010000000	9,549535706	10,82756617
	0,0001000000	13,83108362	15,13670523
	0,0000100000	18,18929348	19,51142096
	0,0000010000	22,59504266	23,92812698
	0,0000001000	27,03311129	28,37398736
	0,0000000100	31,49455797	32,84125335
	0,0000000010	35,97368894	37,32489311
	0,0000000001	40,46665791	41,82145620

3. Results

3.1. Without a Helicobacter pylori infection no development of human gastric cancer

Claims.

Null hypothesis:

A Helicobacter pylori infection is a conditio sine qua non of human gastric cancer

$(p_0 \geq p_{Crit})$.

Alternative hypothesis:

A Helicobacter pylori infection is not a conditio sine qua non of human gastric cancer

$(p_0 < p_{Crit})$.

Significance level (Alpha) below which the null hypothesis will be rejected: 0.05.

Proof.

The data of a Helicobacter pylori infection in patients and healthy control subjects are viewed in the 2×2 table (**Table 1**). The proportion of successes of a conditio sine qua non relationship p(Helicobacter pylori infection human gastric cancer) is calculated [9] as

$$p\left(\text{Helicobacter pylori inf ection} \leftarrow \text{Human gastric cancer}\right) = \frac{(36 + 1210 + 280)}{1526} = \frac{1526}{1526} = 1$$

The critical value p_{Crit} (significance level alpha = 0.05) is calculated [9] approximately as

$$p_{Crit} = 1 - \frac{3}{1526} = 0{,}998034076$$

The critical value is p_{Crit} = 0,998034076 and is thus far less than the proportion of successes calculated as p(Helicobacter pylori infection ← human gastric cancer) =1. Consequently, we cannot reject the null hypothesis in favor of the alternative hypotheses. The data as published by Uemura et al. do support our Null hypothesis that a Helicobacter pylori infection is a conditio sine qua non of human gastric cancer. In other words, without a Helicobacter pylori infection no development of human gastric cancer.

Q. e. d.

3.2.   There is a highly significant cause effect relationship between a Helicobacter pylori infection and human gastric cancer

Claims.

Null hypothesis: (no causal relationship)

There is no causal relationship between a Helicobacter pylori infection and human gastric cancer (k=0).

Alternative hypothesis: (causal relationship)

There is a causal relationship between a Helicobacter pylori infection and human gastric cancer (k<>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 illustrated in the 2 × 2 table (**Table 1**). The causal relationship k(Helicobacter pylori infection , human gastric cancer) is calculated [9], [17] as

$$k\left(\text{Helicobacter pylori inf}\,ection,\text{Human gastric cancer}\right) = \frac{\left(\left(1526\times36\right)-\left(36\times1246\right)\right)}{\sqrt[2]{\left(1246\times280\right)\times\left(36\times1490\right)}} = +0,07368483$$

The value of the test statistic k=+0,07368483 is equivalent to a calculated [9] chi-square value of

$$\chi^2{}_{\text{Calculated}} = 1526\times\frac{\left(\left(1526\times36\right)-\left(36\times1246\right)\right)}{\sqrt[2]{\left(1246\times280\right)\times\left(36\times1490\right)}}\times\frac{\left(\left(1526\times36\right)-\left(36\times1246\right)\right)}{\sqrt[2]{\left(1246\times280\right)\times\left(36\times1490\right)}}$$

$$\chi^2{}_{\text{Calculated}} = 0,07368483\times0,07368483\times1526$$

$$\chi^2{}_{\text{Calculated}} = 8.28534801$$

The calculated chi-square statistic, uncorrected for continuity, is 8.28534801 and equivalent to a P value of 0.00399664. The calculated chi-square statistic exceeds the critical

chi-square value of 3.841458821 (**Table 2**). Consequently, we reject the null hypothesis and accept the alternative hypotheses.

There is a highly significant causal relationship between a Helicobacter pylori infection and human gastric cancer (k=+0,07368483, p Value = 0.00399664). The result is significant at $p < 0.05$.

Q. e. d.

4. Discussion

Several epidemiologic studies [19], [20] demonstrated a close relationship between H. pylori infection and human gastric cancer. Still, the aetiology of human gastric cancer is unknown even if human gastric cancer is rare among individuals without a H. pylori infection. I conducted a re-analysis of the study of Uemura et al. to re-investigate the relationship between Helicobacter pylori infection and human gastric cancer. The study of Uemura et al. was properly constructed, the danger to underestimate the rate of H. pylori infection in patients with gastric cancer was minimized as much as possible but was not zero. Neither a C13 urea breath test nor a H. pylori antigen antigen stool test was used to identify additionally a H. pylori infection. Sill and in accordance with previous studies, Uemura et al. found   that H. pylori infection is associated with the development of human gastric cancer but failed to detect the true meaning of the H. pylori infection in the pathogenesis of human gastric cancer. Using some of the data published by Uemura et al. I questioned whether Helicobacter pylori is the cause or a cause of human gastric cancer. On the basis of this re-analysis of the data of Uemura et al. it can be summarized that without a helicobacter pylori infection no development of human gastric cancer. The most important finding of this systematic re-analysis of the data of Uemura et al. the result that there is a cause effect relationship between H. pylori and human gastric cancer (p-value 0.00399664). Since without a helicobacter pylori infection human gastric cancer cannot develop we are able to state that a helicobacter pylori infection is not only a cause human gastric cancer. A helicobacter pylori infection is the cause of human gastric cancer (k=+0,07368483, p Value = 0.00399664).

5. Conclusion

On the basis of this systematic re-analysis of the data of Uemura et al., it can be concluded that there is a cause effect relationship between a helicobacter pylori infection and human gastric cancer. Helicobacter pylori is the cause (k=+0,07368483, p Value = 0.00399664) of human gastric cancer.

Acknowledgements

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