

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 are 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 reanalysed. **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 significant evidence that a *Helicobacter pylori* infection is the cause of human gastric cancer. **Conclusions:** Without a *Helicobacter pylori* infection of human stomach no development of human gastric cancer. *Helicobacter pylori* is the cause of human gastric cancer ($k = +0.07368483$, $p\text{-value} = 0.00399664$).

Keywords

Human Gastric Cancer, *Helicobacter pylori*, Causal Relationship

1. Introduction

Despite of the overall decline of gastric cancer in 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 than 15% [4]. *Helicobacter pylori*, the most common bacterial infection worldwide [5], is a microbial species able to colonize gastric epithelium, can induce a persistent local inflammatory response, and 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, was 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 were 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 was 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 between *Helicobacter pylori* and human gastric cancer.

		Human gastric cancer		
		Yes	No	
<i>Helicobacter pylori</i> infection	Yes	36	1210	1246
	No	0	280	280
		36	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

$$p(\textit{Helicobacter pylori} \leftarrow \text{Human gastric cancer}) \quad (1)$$

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

2.2.2. The Rule of Three

In general, describing properties of data (*descriptive statistics*) or drawing conclusions about a population of interest based on a sample drawn from that population (*inferential statistics*) is of key importance in empirical scientific research. Many times, the relation between empirical data and hypotheses is based on a set of measurements of individuals (a sample, a subset of a population) from a certain population (a set of objects which are of interest in a statistical study). The distinction between as ample together with its statistics and a population together with its parameters is of fundamental importance, since every scientific research rests on it. A sample either selected at random or at least representative is used to make inferences about a population from which the same sample was drawn. Generally, the quality of the data is only as good as the sample that produced it. From the sample data various statistics can be calculated. And yet, it is worth noting that despite a long history of progress in statistics, an estimate can be distorted or biased and depends not only on the size of a sample. One such statistics is the key idea of the construction of the *i.e.* 95% confidence interval. These confidence intervals itself are constructed entirely from the sample data. 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

$$P_{\text{Crit}} = P_{\text{Calc}} \pm \left(z_{\text{Alpha}/2} \times \left(\sqrt{\frac{1}{N} \times P_{\text{Calc}} \times (1 - P_{\text{Calc}})} \right) \right) \quad (2)$$

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 $1 - (\text{Alpha}/2)$ quantile of a

standard normal distribution corresponding to the significance level α . For example, for a 95% confidence level $\alpha = 0.05$ and z is $z = 1.96$. The Agresti-Coull [10] interval is also another method for calculating binomial confidence intervals. But it is worth noting that another very common technique for calculating binomial confidence intervals was published by Clopper-Pearson [11] too. A faster and an alternative way to determine the lower and upper “exact” confidence interval for p_{Calc} is justified by the F distribution [12]. In this study, we will use *the rule of three* [13] to calculate the confidence interval for p_{Calc} . Briefly sketched, the rule of three can be derived [14] from the binomial model. The rule of three defines that $3/N$ is an upper 95% confidence bound for a binomial probability p_{Calc} when in N independent trials no events occur [15]. Under conditions where a certain event did not occur [16] in a sample with N subjects (*i.e.* $p_{\text{Calc}} = 0$) 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 three the same interval is calculated for a sample sizes of 30 - 50 or more as

$$p_{\text{Crit}} = \left(\frac{3}{N} \right) \quad (3)$$

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

$$p_{\text{Crit}} = 1 - \left(\frac{3}{N} \right) \quad (4)$$

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 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.

2.2.4. 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**.

2.2.5. 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

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

	p-value	One sided X ²	Two sided X ²
	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
The chi square distribution	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

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 [19]. 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 testis 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

$$p(x) = \frac{\binom{U}{x} \times \binom{N-U}{n-x}}{\binom{N}{n}} \quad (5)$$

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 [20], [21] is another exact test which is useful for the analysis of contingency tables.

3. Results

3.1. Without a *Helicobacter pylori* Infection of Human Stomach No Development of Human Gastric Cancer

Claims.

Null hypothesis:

A *Helicobacter pylori* infection is a *conditio sine qua non* of human gastric cancer ($p_{\text{Calc}} \geq p_{\text{Crit}}$).

Alternative hypothesis:

A *Helicobacter pylori* infection is not a *conditio sine qua non* of human gastric cancer ($p_{\text{Calc}} < p_{\text{Crit}}$).

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

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

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

$$p_{\text{Crit}} = 1 - \frac{3}{1526} = 0.998034076$$

The critical value is $p_{\text{Crit}} = 0.998034076$ and is thus far less than the proportion of successes calculated as $p(\text{Helicobacter pylori infection} \leftarrow \text{human gastric cancer}) = 1$. 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 of Human Stomach 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

$$k(\text{Helicobacter pylori infection, Human gastric cancer}) = \frac{((1526 \times 36) - (36 \times 1246))}{\sqrt[2]{(1246 \times 280) \times (36 \times 1490)}} = +0.07368483$$

The value of the test statistic $k = +0.07368483$ is equivalent to a calculated [9] chi-square value of

$$\begin{aligned} \chi_{\text{Calculated}}^2 &= 1526 \times \frac{((1526 \times 36) - (36 \times 1246))}{\sqrt[2]{(1246 \times 280) \times (36 \times 1490)}} \times \frac{((1526 \times 36) - (36 \times 1246))}{\sqrt[2]{(1246 \times 280) \times (36 \times 1490)}} \\ \chi_{\text{Calculated}}^2 &= 0.07368483 \times 0.07368483 \times 1526 \\ \chi_{\text{Calculated}}^2 &= 8.28534801 \end{aligned}$$

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 [22] [23] demonstrated a close relationship between *H. pylori* infection and human gastric cancer. Still, the etiology of human gastric cancer is unknown even if human gastric cancer is rare among individuals without a *H. pylori* infection. I conducted a reanalysis 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 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 reanalysis of the data of Uemura *et al.* is the result that there is a highly significant 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 of human stomach is the cause of human gastric cancer ($k = +0.07368483$, $p\text{-value} = 0.00399664$).

5. Conclusion

On the basis of this systematic reanalysis 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 of human gastric cancer.

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