INTERACTION OF HELICOBACTER PYLORI INFECTION WITH TOBACCO SMOKING IN THE DEVELOPMENT OF STOMACH CANCER IN VIETNAMESE MEN

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This study aims to examine the joint effect of H. pylori infection and tobacco smoking on the development of stomach cancer among Vietnamese men. A total of 80 stomach cancer cases and 146 controls were recruited in a case - control study conducted in a general hospital. Information on sociodemographic, anthropometric characteristics, tobacco smoking, and the dietary pattern was obtained based on a semi - quantitative food frequency and demographic lifestyle questionnaire; venous anti - H. pylori IgG antibodies were tested by ELISA. Unconditional logistic regression analysis with adjustment for potential confounding was performed to estimate the association between target exposures and stomach cancer, Results: An increase of antibody level was related to an elevated odds of stomach cancer (The fifth versus bottom quintile, OR = 3.07; 95%CI: 1.16, 8.12; p for trend = 0.032). Compared to participants who are negative with both H. pylori infection and tobacco smoking (either cigarette or waterpipe tobacco), individuals exposed to both these factors showed significantly greater odds of stomach cancer (OR = 3.58. (95%CI: 1.32, 9.76, p = 0.013). The similar combined impact of H. pylori infection and tobacco smoking were found in individuals who smoked a cigarette (excluded exclusive waterpipe tobacco smokers, ORs = 3.17; 95%CI: 1.13, 8.94, p = 0.029) or waterpipe tobacco (excluded exclusive cigarette smokers; OR = 3.96, 95%CI: 1.28, 12.26, p = 0.017). The present study suggests an interaction between H. pylori infection and tobacco smoking, even waterpipe tobacco, to induce stomach cancer.

Keywords: Stomach cancer, Helicobacter pylori, tobacco smoking, interaction.

I. INTRODUCTION

Stomach cancer incidence and mortality rates have been showing a steady decline in recent decades, however, it is still an important public health problem globally.[1-3] Although stomach cancer is a multifactorial disease, chronic infection with *H. pylori* has been considered as the primary cause.[4] Results from epidemiological studies and animal models indicated that eradication of *H. pylori* infection brought effective prevention for stomach cancer, especially among persons without severe atrophy or intestinal metaplasia.[5] However, the IARC Working Group reported that evidence from randomized intervention studies regarding the effect of *H. pylori* - eradication on stomach cancer risk was not sufficient.[4] Therefore, the impact of other environmental and behavioral factors, alone or in the association with *H. pylori* infection, on the development of stomach cancer must be taken into account. Among behavioral factors, tobacco smoking has been

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Received date: 12/09/2020
Accepted date: 15/12/2020

determined as the most important risk factor for stomach cancer.[6] Tobacco smoking was a causal factor when numerous studies reported consistent results regarding its role in the development of stomach cancer.[6-10] Tobacco smoking can directly contribute to stomach cancer development through the causing as well as increasing the risk of precursor lesions consist of chronic atrophic gastritis, intestinal metaplasia, and dysplasia.[10] On the other hand, the indirect promotion of smoking to stomach cancer development has been explored by several studies, which showed a significantly elevated frequency of *H. pylori* infection among smokers.[11- 13]

However, results from analyses on the interaction between tobacco smoking and *H. pylori* in promoting stomach cancer remain inconclusive. IARC Working Group reported that *H. pylori* are "little or no relevance" to confound the association between smoking and stomach cancer;[10] and a recent pooled analysis for prospective studies in China, Japan, and Korea also did not support a relationship between tobacco smoking and *H. pylori* seropositive.[7] In contrast, several studies suggested a combination of tobacco smoking and *H. pylori* infection on increasing stomach cancer risk that impressed a strongly elevated cancer risk for subjects who were exposed to both smoking and *H. pylori* infection compared to that among those who negative with both factors.[14 - 16] The present study aims to investigate the separate and joint effect of these both well - known risk factors for stomach cancer in a male Vietnamese population, where have been concerned with the highest stomach cancer incidence in Southeast Asia.[17] Viet Nam has been impressed as a country with a high prevalence of either tobacco smoking (45.3% of men were current smokers)[18] or *H. pylori* infection (56.1% - 74.6% in the general population).[19 - 22]

II. SUBJECTS AND METHODS

1. Study participants

This is a case - control study conducted in a general hospital located in the Northern Viet Nam. Detailed information on study participants and methods as described elsewhere.[23] The new cases of stomach cancer determined by histopathology were weekly selected from the list of new patients admitted to the hospital. For each case, e have to search from the list of new patients admitted to the same hospital to identify two eligible controls, matching for sex and age +/- 5 - year-old. Both cases and controls were voluntarily agreed to participate in the study and signed consent form. In summary, 80 cases were Vietnamese male patients who were newly diagnosis with stomach cancer by histopathology and underwent cancer surgeries at the study site between January and December 2018 (Figure 1). Controls were male patients without a history of cancer (at any sites) who planned to be treated by surgeries in the same department and study period as the cases. Controls were excluded if they had they were dieters or who had a severe health condition or who had other morbidities affecting their dietary patterns. Data obtained for 80 eligible cases and 146 controls were used for this analysis.

2. Sample size

We used the calculated tables of design considerations for unmatched case - control studies published by the International Agency for Research on Cancer. In principle, the calculated tables were based on the following formula for the unmatched case - control studies:

$$n = (Z_{\alpha}\sqrt{2\overline{pq}} + Z_{1-\beta}\sqrt{p_1q_1 + p_2q_2})^2 / (p_1 - p_2)^2$$

3. Assumptions:

Significance is 0.05; the power of the study is about 0.95, exposure to *H. pylori* infection or tobacco smoking is about 40% in the control group (p1); an odds ratio is desired about 3.0; the ratio of the case to control is 0.5. Therefore, the minimal required number of cases and controls are 60 and 120, respectively. To increase the power of the study and increased abilities to adjust for possible multiple variable factors, we collected 80 cases and 146 controls for the present study.

4. Exposure Variables

Variables included smoking status (cigarette and/or waterpipe smoking; the average number of tobacco smoking per day, age at started smoking, age at stopped smoking for the ever smokers), and *H. pylori* infection determined by IgG ELISA analysis.

5. Covariates

Covariates included age, sex, and education, high and weight to calculate body mass index (BMI), frequency of vegetable consumption including water spinach, mustard greens, sauropus, Malabar nightshade, and cabbage.

6. Data collection

A semi - quantitative food frequency and demographic lifestyle questionnaire were used to interview all participants on the day immediately before their surgery to obtain information on sociodemographic characteristics, anthropometric characteristics (height, weight), cancer history of both patients and their family members, tobacco smoking, and dietary habit. Also, medical records were obtained to collect information on the histopathological diagnosis of stomach cancer.

To analyze antibodies to *H. pylori* infection, 3 ml aliquots of overnight fasting blood was to be collected from both cases and controls. The anti - *H. pylori* serum IgG titers were tested by enzyme - linked immunosorbent assay (ELISA) based on the sandwich principle using *H. pylori* IgG ELISA kit (RE56381) from IBL International (Hamburg, Germany). The experiences investigators of the Microbiology and Infectious Disease, College of Veterinary Medicine, Vietnam National University of Agriculture performed laboratory work for all plasma samples. According to the manufacturer's instructions, *H. pylori* serostatus was classified into three groups based on Cut - Off Index (COI) including negative (COI < 0.8), equivocal (0.8 - 1.2), and positive (COI > 1.2). Also, we additionally categorized the quantitative results of anti - *H. pylori* IgG concentration into five quintiles based on the distribution of the Cut - off Index (COI) in the controls to examine the relationship between the increasing trend of antibody level and stomach cancer

Regarding tobacco smoking, participants were categorized into two groups as "ever" and "never" smoking. Never smokers were those who never smoked completely neither one cigarette nor waterpipe tobacco (WPT) in their lifetime. For ever - smokers, the information on types of tobacco products including cigarettes, WPT, or both types was obtained. The description of waterpipe smoking equipment commonly used in Viet Nam was introduced elsewhere.[24] In Viet Nam. WPT tobacco is prepared from the leaves (made from a plant called Nicotiana rustica) which are shredded and sundried or sometimes dried in large bamboo - burning kilns. The smoking method of Vietnamese WPT is similar to that of the Arabian WPT whereby smoke passes through water before being inhaled. A WPT smoking session is about five minutes.[25, 26]

Information on the frequency of five common vegetables consumed in Northern

Viet Nam including water spinach, mustard greens, sauropus, Malabar nightshade, and cabbage within the last 12 months was obtained based on a semi - qualitative food frequency questionnaire.[23]

7. Statistical analysis

Unconditional logistic regression analysis was used to estimate the odds ratio and 95% confidence interval (OR, 95% CI) for the association between target exposures (*H. pylori* infection and tobacco smoking) and stomach cancer. The association between *H. pylori* infection and stomach cancer was adjusted for potentially confounding factors like age group, tobacco smoking, BMI, frequency of vegetable consumption. To investigate the combined effect of *H. pylori* infection and tobacco smoking on stomach cancer, patients with equivocal results of anti - *H. pylori* test was categorized as a negative group, leaving two groups of *H. pylori* serostatus as negative and positive. Then, all participants were classified into four groups comprised *H. pylori* - negative and never smoking; *H. pylori* - positive and never smoking; *H. pylori* - negative and ever smoking; and *H. pylori* - positive and ever smoking. Regarding the sub - group analysis for types of tobacco products, smokers, who consumed either a cigarette or WTP, were divided into subgroups as “cigarette lifetime smokers” and “Waterpipe lifetime smokers”. Thereby, all smokers who exclusive smoke WPT were excluded in the group of “cigarette lifetime smokers”; and all exclusive cigarette smokers were excluded in the “Waterpipe lifetime smokers” group. The joint effects of tobacco smoking and *H. pylori* infection on stomach cancer were adjusted for age, BMI, frequency of vegetable consumption. All data analysis was performed using Stata version 15.0 (Stata Corp, College Station, Texas). All p - values were two - slides and the cut of 0.05 (alpha) was considered as a statistically significant difference.

8. Ethics consideration

We obtained written informed consent from all participants. The protocol for the present study was obtained from the Hanoi Medical University IRB and the University of Health and Welfare IRB, Japan.

III. RESULTS

Characteristics of 226 men participants consisted of 80 stomach cancer patients and 146 non - cancer patients were displayed in Table 1**.** The highest stomach cancer incidence was observed at aged 60 - 69 years (35%), followed by 50 - 59 years (30%), and 70 years and older (17.5%). However, there were 17.5% of cancer patients were below 50 years old, in which 12.5% aged 40 - 49 years. The majority of participants were categorized as ever smokers (79.20%, either a cigarette or WTP), in which, cases were likely to smoke than controls (88.75% versus 73.97%). In terms of vegetable consumption, five vegetables, which were commonly consumed by participants, were evaluated comprised of water spinach (95.58%), mustard greens (95.58%), sauropus (96.02%), Malabar nightshade (94.69%), and cabbage (94.25%) (data not shown).

Table 1. Participant characteristics

Variables	Stomach cancer		Non - cancer		Total	
	n	%	n	%	n	%
Age group (ages)						
20 - 29	1	1.25	4	2.74	5	2.21

Variables	Stomach cancer		Non - cancer		Total	
	n	%	n	%	n	%
30 - 39	3	3.75	12	8.22	15	6.64
40 - 49	10	12.50	31	21.32	41	18.14
50 - 59	24	30.00	53	36.3	77	34.07
60 - 69	28	35.00	31	21.23	59	26.11
≥ 70	14	17.50	15	10.27	29	12.83
Total	80	100	146	100	226	100
Education (year)						
< 6	15	18.75	18	12.33	33	14.60
6 - 9	36	45.00	64	43.84	100	44.25
10 - 12	15	18.75	46	31.51	61	26.99
> 12	13	16.25	17	11.64	30	13.27
Unknown	1	1.25	1	0.68	2	0.88
Total	80	100	146	100	226	100
BMI (kg/m2)[a]						
18.5 to < 23	42	52.50	73	50.00	115	50.88
23 to < 25	9	11.25	30	20.55	39	17.26
≥ 25	5	6.25	18	12.33	23	10.18
< 18.5	24	30.00	22	15.07	46	20.35
Unknown	0	0	3	2.05	3	1.13
Total	80	100	146	100	226	100
Lifetime tobacco smoking						
Never	9	11.25	38	26.03	47	20.80
Ever	71	88.75	108	73.97	179	79.20
Total	80	100	146	100	226	100

[a]BMI, Body Mass Index (BMI = weight (kg) / height ((m)²)

Regarding *H. pylori* serostatus, following the manufacture's procedure, the percentage of positive, equivocal, and negative results of *H. pylori* infection were 42.48%, 18.58%; and 38.94%; respectively.

Table 2. H. pylori infection characteristics

Variables	Total N%	Mean ± SD [a]	Min - max [a]
H. pylori infection status [b]			
Negative (COI < 0.8)	88 (38.94)	0.49 ± 0.17	0.13 - 0.79
Equivocal (COI 0.8 - 1.2)	42 (18.58)	1.01 ± 0.12	0.81 - 1.20
Positive (COI > 1.2)	96 (42.48)	2.47 ± 0.96	1.21 - 5.01
Total	226 (100)		

Variables	Total N%	Mean ± SD [a]	Min - max [a]
Anti - H. pylori IgG concentration quintiles [c]			
1st	50 (22.12)	0.37 ± 0.11	0.13 - 0.52
2nd	47 (20.80)	0.69 ± 0.11	0.55 - 0.90
3rd	45 (19.91)	1.12 ± 0.14	0.91 - 1.43
4th	43 (19.03)	1.91 ± 0.28	1.51 - 2.36
5th	41 (18.14)	3.41 ± 0.69	2.41 - 5.01
Total	226 (100)		

[a] Mean ± SD, Mean ± Standard deviation; Min - Max, Minimum – Maximum; b. Classification according to the manufacturer's instructions; c. Classification according to anti - H. pylori IgG concentration of the Cut - off Index (COI) quantitative; There are normally distributed

Another classification, based on anti - *H. pylori* antibody concentration, was also used to divide participants into quintiles of antibody level. Thereby, the percentage of the first to the fifth quintile and corresponding means were 22,12% (0.37 ± 0.11); 20.80% (0.69 ± 0.11); 19.91% (1.12 ± 0.14); 19.03% (1.91 ± 0.28); and 18.14% (3.41 ± 0.69), respectively. Compared to the negative group, the equivocal and the positive groups showed greater odds of stomach cancer with ORs of 1.59 (95%CI: 0.69, 3.69) and 1.85 (95%CI: 0.96, 3.57), respectively, even though no statistical significance was found (p for trend = 0.070).

Table 3. Crude and adjusted Odds ratios and 95% CIs of H. pylori infection and stomach cancer

Variables	Case		Control		Crude OR (95% CI)	P_ trend	Adjusted OR (95% CI)[b]	P_ trend
	n	%	n	%				
H. pylori serostatus [c]								
Negative (COI < 0.8)	25	31.25	63	43.15	1.00 (reference)	0.062	1.00 (reference)	0.070
Equivocal (COI 0.8 - 1.2)	15	18.75	27	18.49	1.40 (0.64, 3.06)		1.59 (0.69, 3.69)	
Positive (COI > 1.2)	40	50.00	56	38.36	1.80 (0.97, 3.33)		1.85 (0.96, 3.57)	
Total	80	100	146	100				
Anti - H. pylori IgG concentration quintiles [d]								
1st	11	13.75	39	26.71	1.00 (reference)	0.033	1.00 (reference)	0.032

Variables	Case		Control		Crude OR (95% CI)	P_ trend	Adjusted OR (95% CI)[b]	P_ trend
	n	%	n	%				
2nd	17	21.25	30	20.55	2.01 (0.82, 4.92)		2.02 (0.78, 5.28)	
3rd	17	21.25	28	19.18	2.15 (0.87, 5.30)		2.33 (0.90, 6.04)	
4th	17	21.25	26	17.81	2.32 (0.94, 5.74)		2.26 (0.86, 5.93)	
5th	18	22.5	23	15.75	2.77 (1.12, 6.89)		3.07 (1.16, 8.12)	
Total	80	100	146	100				

a OR (95% CI): odds ratio 95% confidence interval; b Adjusted for age groups (20 - 49, 50 - 59, 60 - 69, ≥70 ages), education levels (primary school, secondary school, high school or higher), BMI (< 18.5, 18.5 to < 23, 23 to < 25, ≥ 25 kg/m2), tobacco smoking (ever/never smokers), consumption of five common types of vegetables (water spinach, mustard greens, sauropus, Malabar nightshade, cabbage); c Classification according to the manufacturer's instructions; d Classification according to anti - H. pylori IgG concentration of the Cut - off Index (COI) quantitative.

Meanwhile, a positive association between stomach cancer and *H. pylori* antibody concentration was indicated when the increasing trend of antibody level was related to an elevated odds of stomach cancer with OR of 3.07 (95%CI: 1.16, 8.12), p for trend = 0.032 (Fifth versus bottom quintile).

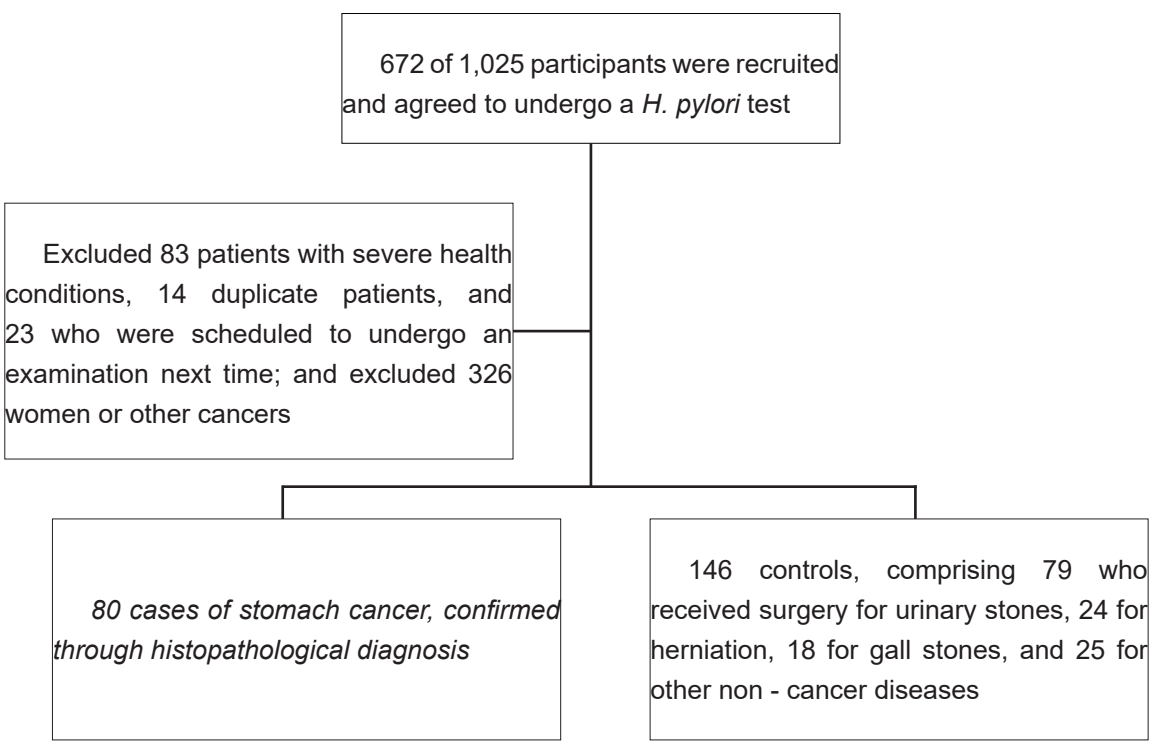

Figure 1. Flow chart of study participants recruited in 2017 - 2018 for the present study

Analysis of the interaction between *H. pylori* and tobacco smoking was shown in Table 4. There was 35.84% (47.50% of cases and 29.35% of controls) of participants exposed to both tobacco smoking and stomach cancer. Compared to the *H. pylori* - negative never - smoker (neither cigarette nor WTP), *H. pylori* - negative ever smokers (either cigarette or WTP) showed a higher, but not statistically significant, odds of stomach cancer (OR = 1.91, 95%CI: 0.71, 5.16, p = 0.201) while ever smokers positive with H. pylori - positive showed the greatest odds (OR = 3.58. 95%CI: 1.32, 9.76, p = 0.013). Similar results also were found in patients who smoke cigarette (excluded WTP; OR = 3.17; 95%CI: 1.13, 8.94, p = 0.029) or WTP (excluded cigarette; OR = 3.96; 95%CI: 1.28, 12.26, p = 0.017).

Table 4. Combined effects of tobacco smoking and H. pylori infection on the risk for stomach cancer

Variables	Case (n = 80)		Control (n = 146)		Crude OR (95% CI)	p	Adjusted OR(95% CI)[b]	p
	n	%	n	%				
All lifetime smokers								
H. pylori (-) & never - smoking [a]	7	8.75	25	17.12	1.00 (reference)		1.00 (reference)	
H. pylori (+) & never - smoking	2	2.5	13	8.9	0.55 (0.10, 3.03)	0.492	0.50 (0.08, 2.91)	0.437
H. pylori (-) & ever - smoking [a]	33	41.25	65	44.52	1.81 (0.71, 4.63)	0.213	1.91 (0.71, 5.16)	0.201
H. pylori (+) & ever - smoking	38	47.50	43	29.45	3.16 (1.23, 8.12)	0.017	3.58 (1.32, 9.76)	0.013
Total	80	100	146	100				
Cigarette lifetime smokers								
H. pylori (-) & never - cigarette smoking [a]	7	11.67	25	20.49	1.00 (reference)		1.00 (reference)	
H. pylori (+) & never - cigarette smoking	2	3.33	13	10.66	0.55 (0.10, 3.03)	0.492	0.46 (0.08, 2.73)	0.391
H. pylori (-) & ever - cigarette smoking [a]	23	38.33	49	40.16	1.68 (0.63, 4.44)	0.298	1.84 (0.65, 5.21)	0.252
H. pylori (+) & ever - cigarette smoking	28	46.67	35	28.69	2.86 (1.08, 7.57)	0.035	3.17 (1.13, 8.94)	0.029
Total	60	100	122	100				
Water pipe lifetime smokers								
H. pylori (-) & never - waterpipe smoking [a]	7	14	25	28.09	1.00 (reference)		1.00 (reference)	

Variables	Case (n = 80)		Control (n = 146)		Crude OR (95% CI)	p	Adjusted OR(95% CI)[b]	p
	n	%	n	%				
H. pylori (+) & never - water pipe smoking	2	4	13	14.61	0.55 (0.10, 3.03)	0.492	0.54 (0.09, 1.19)	0.496
H. pylori (-) & ever - waterpipe smoking [a]	21	42	32	35.96	2.34 (0.86, 6.39)	0.096	2.05 (0.70, 5.99)	0.187
H. pylori (+) & ever - waterpipe smoking	20	40	19	21.35	3.76 (1.32, 10.71)	0.013	3.96 (1.28, 12.26)	0.017
Total	50	100	89	100				

[a] H. pylori (-) included negative and equivocal results of H. pylori serostatus; b Adjusted for groups (20 - 49, 50 - 59, 60 - 69, ≥70 ages), education levels (primary school, secondary school, high school or higher), BMI (< 18.5, 18.5 to < 23, 23 to < 25, ≥ 25 kg/m2), consumption of five common types of vegetables (water spinach, mustard greens, sauropus, Malabar nightshade, cabbage).

IV. DISCUSSION

Our findings supported the positive association between *H. pylori* infection and stomach cancer by categorizing the quantitative results of anti - *H. pylori* IgG concentration into five quintiles. Also, the results have supported the hypothesis of the interaction between chronic bacterial infection with *H. pylori* and tobacco smoking in the development of stomach cancer. Thereby, the combination of *H. pylori* infection and tobacco smoking, either cigarette or waterpipe, was a synergistic association that increased the odds of stomach cancer.

Regarding the association between *H. pylori* infection and stomach cancer, we were unable to find a significant association between stomach cancer and *H. pylori* status (negative, equivocal, and positive); however, our findings reconfirmed the role of *H. pylori* infection on the risk of stomach cancer through the elevated trend of odds across five quintiles of antibody titer. According to IARC, chronic infection with *H. pylori* is carcinogenic to humans (Group 1) which causes non - cardia gastric carcinoma.[4,27] Besides, previous studies explored the positive association between *H. pylori* titer and stomach cancer where a higher *H. pylori* antibody titer as a predictor for a greater stomach cancer incidence.[28-30] However, the evaluation of stomach cancer risk based on *H. pylori* IgG antibody alone may lead to an underestimation of the risk. Plummer et al.[31] suggested that the extensive atrophy in advance stomach cancer cases may cause the decline of anti - *H. pylori* antibody tilter that impaired the level of antibody to below the COI for a positive diagnosis. Moreover, stomach cancer patients may be misclassified as negative *H. pylori* even they had an infection due to the loss of bacteria in the stomach.[32] Therefore, a combination of serum pepsinogen and *H. pylori* antibody has been suggested to be a useful tool to predict stomach cancer risk.[33]

For the joined effect of tobacco smoking and *H. pylori* infection on stomach cancer, the present study found a significant increase in the odds of stomach cancer in positive - *H. pylori* ever - smoker when compared with that in negative - *H. pylori* never - smoker (Table 4). Although tobacco smoking and *H. pylori* infection were independent risk factors,[4,10] the present finding

was in line with previous studies to indicate that individuals who were exposed to both tobacco smoking and *H. pylori* infection showed the greatest odds of stomach cancer.[14-16,34,35] The mechanisms of the interaction between *H. pylori* infection and tobacco smoking has been discussed previously but no conclusive result was reported. Tobacco smoking can promote the impact of *H. pylori* infection on the development of stomach cancer in several ways such as increasing the susceptibility and incidence of *H. pylori* infection;[11-13,36,37] or/and increasing the rate of failure of *H. pylori* eradication.[38] Besides, prior studies suggested an increased inflammatory reaction to *H. pylori* infection among smokers due to the effects of smoking on the immune system.[39] On the other hand, several studies indicated the concentration of some vitamins, which showed the protective effect on stomach cancer development including vitamin A, vitamin C, vitamin E was significantly lower in smokers compared to that in non - smokers.[40-44] Moreover, the effectiveness of these vitamins against stomach cancer was reported to be reduced by *H. pylori* infection.[45-47] Therefore, the combination of tobacco smoking and *H. pylori* is likely to deeply raise the risk of stomach cancer among individuals with the presence of both factors. Shikata et al. showed that the combination of these two risk factors was a synergistic association that elevated their contribution to stomach cancer risk up to 87%.[15]

In Viet Nam, the present findings were consistent with prior studies to show a high prevalence of both *H. pylori* infection (more than 50%[20,21,48,49] as well as tobacco smoking (45.3% of men were current smokers)[18] among study participants. However, up to date, there is a lack of evidence on the association between these two factors, either separately or in combination, and stomach cancer has been reported for the Vietnamese population. Binh T. T et al.[49] explored the association between H. pylori infection and stomach cancer while Lai H. T et al.[24] indicate a positive correlation between WPT and stomach cancer.

To our knowledge, our investigation is the very first study that analyzes the association between *H. pylori* infection and its joint effect with tobacco smoking on stomach cancer among the Vietnamese population. We found that 35.84% of participants were exposed to both risk factors as well as suggested a joint impact of *H. pylori* infection and tobacco smoking (either cigarette or WPT) on the development of stomach cancer. Thereby, the present study pointed out an important group with a high priority for targeting efforts of prevention and screening to detect stomach cancer.

The present study has several limitations. First, the information on the tumor location was not analyzed that limited the investigation for the association between target exposures (*H. pylori* infection and tobacco smoking) and the sub - sites of stomach cancer. Numerous studies, but not all, reported no difference in the impact of tobacco smoking by stomach cancer location while others observed a greater relative risk of cardia stomach cancer among smokers compared to that of non - cardia.[6,50] Also, IARC concluded sufficient evidence for the association between *H. pylori* infection and non - cardiac stomach cancer, but insufficient for cardiac.[4] Second, the evaluation for the association of the sub - groups of tobacco product consumption and stomach cancer was not done in this analysis due to the small sample size. The previous investigation among the Vietnamese population showed that a stronger association between smoking was found among exclusive WPT smokers compared to current WPT (including individuals

who exclusive smoke WPT or who smoke both WPT and cigarette).[24] Third, anti - *H. pylori* IgG test could not determine the current active infection, or it was due to previous infections.

In conclusion, our findings confirm the positive association between *H. pylori* infection and stomach cancer and suggest a combination of this bacterial infection and tobacco smoking, either a cigarette or water pipe, to induce stomach cancer in participated Vietnamese men.

Acknowledgments

The Grant Agreement No.: 18/FIRST/1a/HMU, Under the Project: "Fostering Innovation through Research, Science and Technology".

Conflict of interest: there are no conflict to be disclosed.

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