

RESEARCH ARTICLE

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Waterpipe Tobacco Smoking and Risk of Stomach Cancer: A Case-Control Study in Vietnamese Men

Cong Long Nguyen^{1,2}, Khanpaseuth Sengngam^{3,4}, Tran Hieu Hoc⁵, Phuoc Hong Le⁶, Lai Thi Minh Hang⁷, Hang Viet Dao⁸, Le Tran Ngoan^{9,10*}

Abstract

Objective: This study investigated the impacts of waterpipe tobacco (WTP) and cigarette smoking on stomach cancer development in Vietnamese men. **Methods:** A total of 80 stomach cancer cases and 146 controls were recruited in a hospital-based case-control study. Data on sociodemographic, anthropometric characteristics, tobacco smoking, and the dietary pattern was obtained based on a semi-quantitative food frequency and demographic lifestyle questionnaire; and venous anti-*Helicobacter pylori* IgG antibodies were tested by ELISA. Unconditional logistic regression analysis with adjustments for potential confounding was performed to estimate the association between target exposures and stomach cancer. **Results:** Compared to the never tobacco smokers, the risk of stomach cancer significantly increased among tobacco smokers (OR 2.95, 95%CI 1.26-6.90, $p=0.013$). Those who early started tobacco smoking before 26 years old had a high risk of SC (OR 3.04, 95%CI 1.29-7.20, p for trend=0.011). For types of tobacco, It was increased risk in exclusively cigarette smokers (OR 2.85, 95%CI 1.19-6.85, $p=0.019$) and in WPT smokers (OR 3.09, 95%CI 1.24-7.68, $p=0.015$). The daily frequency and longer duration of exclusively WTP or cigarette smoking tended to be significantly higher SC risk. **Conclusions:** The findings suggest that tobacco smoking, particularly water pipe tobacco smoking, dramatically and independently increased the risk of stomach cancer.

Keywords: Stomach cancer- waterpipe tobacco smoking- cigarette smoking

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Introduction

From 2015, WHO has noted that more studies on the role of waterpipe tobacco (WTP) and cancer risk were needed and recommended action for regulators against this type of tobacco usage (WHO, 2015). However, few observational studies on this association have been performed to date. Our previous study findings suggested that WTP is significantly induced stomach development. This study has a limitation of not available data of *H. pylori* infection that was carcinogenesis of this cancer site (IARC, 2012). This current study investigated the impacts of WTP and cigarette smoking on stomach cancer development in Vietnamese men.

Materials and Methods

Study design and participants

A case-control study was conducted at Bach Mai hospital, a general hospital in northern Viet Nam, between January 2018 and December 2018. Cases were Vietnamese men who were first diagnosed with stomach cancer by histopathology, and who underwent surgery for cancer treatment. Controls included all Vietnamese male patients without a history of cancer (of any sites) who spent their operation at the same department with cases during the study period. Controls were randomly selected based on the list of patients who were planned to have surgery in the same week with corresponding cases. Exclusion criteria included participants under 18 years, who were under severe health conditions, or who declined to take a blood test for the *Helicobacter pylori* (*H. pylori*) examination.

¹Gastroenterology and Hepatology Center, Bach Mai Hospital, Giai Phong road, Ha Noi, Vietnam. ²Department of Gastroenterology, School of Medicine and Pharmacy, Vietnam National University, Hanoi, Vietnam. ³Department of Occupational Health, Hanoi Medical University, Hanoi, Viet Nam. ⁴National Institute of Public Health, Vientiane, Lao PDR. ⁵Department of Surgery, Hanoi Medical University, Hanoi, Viet Nam. ⁶Faculty of Public Health, University of Medicine and Pharmacy, Ho Chi Minh City, Viet Nam. ⁷National Institute of Occupational and Environmental Health, Hanoi, Viet Nam. ⁸Department of Internal Medicine, Hanoi Medical University, Hanoi, Viet Nam. ⁹Institute of Research and Development, Duy Tan University, Da Nang 550000, Viet Nam. ¹⁰Department of Public Health, School of Medicine, International University of Health and Welfare, Japan.
*For Correspondence: letngoan@hmu.edu.vn

H. pylori infection status was a crucial confounding because it has been well-known as a risk factor for stomach cancer (IARC, 2012), and has considerable influences on the association between tobacco smoking and stomach cancer (Shikata et al., 2008). All participant confirmed their participation by written informed consent. A total of 80 incident stomach cancer cases and 146 eligible controls were recruited in the study.

Data collection

Data collection was done by two methods namely questionnaire surveys and clinical data collection. Thereby, trained interviewers face-to-face interviewed participants one day before patients' surgery based on a structured questionnaire. This questionnaire obtained information on participants' demographic characteristics; family history of cancer; anthropometric characteristics (height, weight), lifestyle-related habits consisting of tobacco smoking and alcohol intake, and dietary habits. In addition, medical records and blood samples were obtained to collect data on the history of interested comorbidities; histopathological diagnosis of stomach cancer; and status of *H. pylori* infection.

For tobacco smoking, participants were asked about all types of tobacco use (including cigarette, waterpipe tobacco (WPT)); the average number of tobacco consumed per day by types and by the age group of 15-20, 21-25, 26-30, 31-40, 41-50, 51-60, 61-70, 71+; the duration of smoking (for the current smoker); and the duration of quit smoking (for current and ex-smokers). Participants were then categorized as "ever" or "never" smokers. An "ever-smoker" was determined if he consumed completely one tobacco product (of any type). Current smokers were defined if they completely consumed one tobacco product (of any type) within the last six months. Participants who were "ever smokers" but not current smokers were classified as ex-smokers. 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 (Lai et al., 2016). 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 (She et al., 2014, WHO 2015).

To analyze antibodies to *H. pylori* infection, 3 ml aliquots of overnight fasting blood were 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). 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).

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 (Phuoc et al., 2020).

Statistical analysis

Data were analyzed by Stata version 10.0 (Stata Corp, College Station, Texas). To compare the different impacts of WTP smoking and cigarette smoking on stomach cancer, participants were classified into subgroups of WTP smoking and cigarette smoking. Thereby, WTP smokers were categorized into three-subgroup current WTP smoking only, former WTP smoking only, current and tobacco WTP smoking. Similarly, cigarette smokers were stratified as current cigarette smoking only, former cigarette smoking only, current and former cigarette smoking. For the daily tobacco smoking frequency, participants were categorized into three groups corresponding to three tertiles of distribution of the frequency in controls. Also, WTP smoking and cigarette smoking duration was divided into tertiles based on the distribution of usage years in controls.

Unconditional logistic regression analysis was used to estimate the odds ratio and 95% confidence interval (OR, 95% CI) for the association between WTP smoking, cigarette smoking, and stomach cancer. The association between favor exposures and stomach cancer was adjusted for the age group in the early analysis and then adjusted for potential confounding factors such as *H. pylori* status, age group, education levels, Body Mass Index (BMI), and frequency of five common types of vegetable consumption. All tests were two-slides, and $p < 0.05$ was considered as a statistically significant difference.

Ethics consideration

Written informed consent was obtained from all participants. The present study was approved by the Hanoi Medical University (IRB No. 3918/HMUIRB) on 25 December 2018 and by the International University of Health and Welfare, Graduate School, Japan on 27 May 2019.

Results

The total number of subjects was 226 recruited in Bach Mai hospital during 2018-2019, in which 80 (35.4%) were stomach cancer and 146 (64.6%) were non-cancer. Stomach cancer cases were in the age group of 60+ years (35.0%), followed by a group of 50-59 years (30.0%), 70+ years (17.5%), and less than 50 years (17.5%). Most of the subjects were at the secondary education level (44.2%, 100/226) and the normal range of BMI (50.9%, 115/226). The rate of subjects smoking tobacco in their lifetime was high in both stomach cancer cases and non-cancer cases (88.75% and 73.97%, respectively). For *H. pylori* serostatus, its positive rate in the stomach cancer group (50.0%) was higher than that in the non-cancer group (38.36%) (Table 1).

Table 2 showed the result on the relationship between tobacco usage and stomach cancer (SC) risk. Tobacco usage including pipe and cigarette was positively

Table 1. Participant Characteristics

Variables	Stomach cancer		Non-cancer	
	n	%	n	%
Age group (ages)				
20-49	14	17.5	47	32.19
50-59	24	30	53	36.3
60-69	28	35	31	21.23
≥70	14	17.5	15	10.27
Total	80	100	146	100
Education (years)				
<6	15	18.75	18	12.33
6-9	36	45	64	43.84
10-12	15	18.75	46	31.51
>12	13	16.25	17	11.64
Unknown	1	1.25	1	0.68
Total	80	100	146	100
BMI (kg/m ²) ^a				
18.5 to <23	42	52.5	73	50
23 to <25	9	11.25	30	20.55
≥25	5	6.25	18	12.33
<18.5	24	30	22	15.07
Unknown	0	0	3	2.05
Total	80	100	146	100
Lifetime tobacco smoking				
Never	9	11.25	38	26.03
Ever	71	88.75	108	73.97
Total	80	100	146	100
<i>H. pylori</i> serostatus ^b				
Negative (COI <0.8)	25	31.25	63	43.15
Equivocal (COI 0.8-1.2)	15	18.75	27	18.49
Positive (COI >1.2)	40	50	56	38.36
Total	80	100	146	100

^aBMI, Body Mass Index (BMI= weight (kg) / height ((m)²);

^bClassification according to the manufacturer's instructions;

^dClassification according to anti-*H. pylori* IgG concentration of the Cut-off Index (COI) quantitative

associated with SC risk (OR=2.95, 95%CI=1.26-6.90, p=0.013)). The early start of smoking was also related

to the higher risk of SC. Those who started smoking before 26 years old had a high risk of SC (OR=3.04, 95%CI=1.29-7.20, p for trend=0.011) in comparison with never smokers.

We further examined the association of WPT smoking with SC risk using exclusively WPT smokers (Table 3). The high SC risk was found in total exclusively WPT smokers (OR 3.09, 95%CI 1.24-7.68, p=0.015), in which current WPT smokers (OR 2.90, 95%CI 1.05-7.97, p=0.039) and former WPT smokers (OR 4.55, 95%CI 1.23-16.85, p=0.023). For the dose-response, those who smoked WPT 8 or more times per day showed a significantly high SC risk (OR 3.12, 95%CI 1.24-7.85, p for trend=0.025). The daily frequency and longer duration of WPT smoking tended to be significantly higher in SC risk.

We also examined the association of cigarette smoking with SC risk using exclusively cigarette smokers in Table 4. SC risk was significantly high in a total of current and former cigarette smoking (OR 2.85, 95%CI 1.19-6.85, p=0.019) and especially in current cigarette smoking (OR 3.26, 95%CI 1.24-8.55, p=0.017). Those who currently smoked cigarettes 20 or more times per day increased significantly SC risk (OR 4.17, 95%CI 1.27-13.70, p for trend=0.012). The higher SC risk was found among those who formerly smoked cigarettes for 38 or more years when compared to never smokers (OR=5.79, 95%CI=1.40-23.92, p for trend=0.018). The daily frequency and longer duration of cigarette smoking tended to be significantly higher SC.

Discussion

This is a hospital-based case-control study to examine the association of tobacco smoking with SC risk among Vietnamese men, which was conducted at Bach Mai hospital in Northern Viet Nam. The present study showed a significantly high SC risk among tobacco smokers, and this association was much stronger among WPT smokers only after excluding cigarette smokers. Furthermore, SC risk tended to be significantly higher with the daily frequency and duration of WPT smoking only.

The strengthening of the present study included the new method of tobacco smoking assessment in advanced detail. Types of WPT and cigarette tobacco smoking

Table 2. Tobacco Usage Including Pipe, Cigarette, and Risk of Stomach Cancer

	Control	Cancer	Total	Age adjusted OR (95% CI)	p	Multivariable OR (95% CI)&	p
Tobacco usage including pipe and cigarette							>1.00
No	38	9	47	>1.00			
Yes	108	71	179	3.21 (1.42, 7.29)	0.005	2.95 (1.26, 6.90)	0.013
Total	146	80	226				
Age at started smoking							
No	38	9	47	>1.00		>1.00	
26+	13	8	21	2.68 (0.82, 8.70)		2.40 (0.71, 8.06)	
<26	95	63	158	3.30 (1.44, 7.56)	0.005*	3.04 (1.29, 7.20)	0.011*
Total	146	80	226				

*p for trend; & 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), consumption of five common types of vegetables (water spinach, mustard greens, saurupus, Malabar nightshade, cabbage); and *H. pylori* infection, OR (95% CI), odds ratio 95% confidence interval.

Table 3. Water Pipe Tobacco Smoking and Risk of Stomach Cancer

Water pipe tobacco	Control	Cancer	Total	Age-adjusted OR (95% CI)	<i>p</i>	Multivariable OR (95% CI)&	<i>p</i>
Current pipe smoking only							
No	38	9	47	>1.00		>1.00	
Yes	38	26	64	3.44 (1.35, 8.75)	0.01	2.90 (1.05, 7.97)	0.039
Total	76	35	111				
Former pipe smoking only							
No	38	9	47	>1.00		>1.00	
Yes	13	15	28	4.22 (1.45, 12.27)	0.008	4.55 (1.23, 16.85)	0.023
Total	51	24	75				
Current and former pipe smoking only							
No	38	9	47	>1.00		>1.00	
Yes	51	41	92	3.61 (1.53, 8.52)	0.003	3.09 (1.24, 7.68)	0.015
Total	89	50	139				
Former pipe smoking number a day (Missing data of 1 participant)							
No	38	9	47	>1.00		>1.00	
20	5	8	13	5.24 (1.33, 20.61)		6.33 (1.18, 33.99)	
44	5	6	11	4.34 (1.04, 18.10)	0.016*	4.75 (0.70, 32.46)	0.044*
Total	48	23	71				
Number of pipe smoking a day among a total of pipe smokers							
No	38	9	47	>1.00		>1.00	
2	32	21	53	3.34 (1.29, 8.61)		3.02 (1.13, 8.11)	
8	45	35	80	3.43 (1.44, 8.18)	0.009*	3.12 (1.24, 7.85)	0.025*
Total	115	65	180				
Former pipe smoking years (Missing data of 1 participant)							
No	38	9	47	>1.00		>1.00	
20	8	8	16	3.51 (1.00, 12.33)		3.02 (0.58, 15.68)	
44	3	6	9	6.65 (1.35, 32.75)	0.009*	10.91 (1.58, 75.11)	0.013*
Total	49	23	72				

**p* for trend; & 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), consumption of five common types of vegetables (water spinach, mustard greens, saupopus, Malabar nightshade, cabbage); and *H. pylori* infection, OR (95% CI), odds ratio 95% confidence interval.

were collected by the age of study participants by eight groups from 15 years old to 71+ years old. This detailed available information allows the examination for overall tobacco smoking (lifetime never and ever smokers), and to examine a dose-respond by the age at starting smoking, duration of tobacco smoking, number of WPT, and cigarette tobacco smoking per day. The database was available the status of *H. pylori* infection, food frequency intake, and demographic data of the study participants. That information was being controlled for possible confounding factors.

Our findings are consistent with the result of several previous studies on WPT smoking and SC risk. In the Iranian cohort study, more than three-fold increased SC risk was reported in hookah smokers. This result was slightly higher than that of our study, which might be because of their target high-risk population namely *H. pylori*-infected subjects (Sadjadi et al., 2014). In the other Vietnamese case-control study, SC risk increased significantly nearly three times in current exclusively WPT smokers when compared to never smokers. It was lower than our results, which might be explained by the lacking of examination on *H. pylori* infection in

their study (Lai et al., 2016) and the method of tobacco smoking assessment was more detailed and better in the present study.

The present study observed a significant association of cigarette smoking with SC risk, exclusively cigarette smokers. Our results were consistent with that of a systematic review among the Japanese population, which showed a significantly elevated risk for cigarette smoking among men in case-control studies (Nishino et al., 2006). The Iranian study also reported a significant increase in SC risk for cigarette smoking (Sadjadi et al., 2014).

The smoke of Arabian WPT contains a large range of carcinogenic and toxic substances such as tar, nicotine, CO, PAH, aldehydes, and heavy metals (Jacob et al., 2011; Eissenberg and Shihadeh, 2009). The levels of them in the smoke of one Hookah session (one-hour exposure) were equal to or higher than those in the smoke of 10 cigarettes (equivalent to 50-min exposure): tar, CO, PAHs, aldehydes, chromium, and lead (Maziak, 2013).

Vietnamese/Chinese WPT may have lower carcinogenic effects than Arabian WPT because of the non-use of charcoal and generally shorter smoking duration (approximately 5 minutes). However, a

Table 4. Cigarette Smoking and Risk of Stomach Cancer

	Control	Cancer	Total	Age adjusted OR (95% CI)	<i>p</i>	Multivariable OR (95% CI)&	<i>p</i>
Current cigarette smoking only							
No	38	9	47	>1.00		>1.00	
Yes	45	31	76	3.51 (1.42, 8.71)	0.007	3.26 (1.24, 8.55)	0.017
Total	83	40	123				
Former cigarette smoking only							
No	38	9	47	1		>1.00	
Yes	39	20	59	2.53 (0.95, 6.76)	0.063	2.75 (0.93, 8.18)	0.069
Total	77	29	106				
Current and former cigarette smoking only							
No	38	9	47	1		1	
Yes	84	51	135	3.01 (1.29, 7.00)	0.01	2.85 (1.19, 6.85)	0.019
Total	122	60	182				
Number of cigarettes a day among current and former smoking only (Missing data of 4 participants)							
No	38	9	47	>1.00		>1.00	
4	28	15	43	2.58 (0.96, 6.95)		2.64 (0.95, 7.35)	
15	50	32	82	3.11 (1.28, 7.55)	0.015*	2.85 (1.14, 7.15)	0.035*
Total	116	56	172				
Former cigarette smoking years (Missing data of 1 participant)							
No	38	9	47	>1.00		>1.00	
19	28	9	37	1.48 (0.48, 4.57)		1.87 (0.54, 6.43)	
38	10	10	20	5.45 (1.57, 18.96)	0.011*	5.79 (1.40, 23.92)	0.018*
Total	76	28	104				
Number of cigarettes smoking a day among current cigarettes smoking only							
No	38	9	47	>1.00		>1.00	
6	33	19	52	2.97 (1.12, 7.83)		2.80 (0.98, 8.02)	
20	12	12	24	4.89 (1.59, 15.01)	0.004*	4.17 (1.27, 13.70)	0.012*
Total	83	40	123				

**p* for trend; & 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), consumption of five common types of vegetables (water spinach, mustard greens, saurpous, Malabar nightshade, cabbage); and *H. pylori* infection, OR (95% CI), odds ratio 95% confidence interval.

significantly high level of CO was also identified in the exhalation of Chinese WPT smokers (She et al., 2014) despite charcoal, a suspected main source of CO and PAHs (Monzer et al., 2008), not being used. It is also true for a cigarette which type of tobacco smoking is not required charcoal, however, CO and PAHs levels are still high among cigarette smokers. Vietnamese/Chinese WPT smoking may have similar carcinogenic effects to Arabian WPT smoking. Further examinations in the content of Vietnamese/Chinese WPT smoke are necessary to estimate the levels of carcinogens in the development of SC.

The present study has certain limitations. First, the information on the tumor location was not collected completely in our study. However, numerous previous studies including case-control and cohort studies reported no difference in the effects of tobacco smoking on SC risk by tumor location (Ladeiras-Lopes et al., 2008; Chow et al., 1999; Sung et al., 2007; Sasazuki et al., 2002). Second, the lack of the information on histological type of SC (intestinal or diffuse type) was not able to examine the effect modification by histological type of tumor. A study on histopathological characteristics of SC patients

in Hanoi Oncology hospital, 2010-2012 showed most Vietnamese SC cases were intestinal type (82.7%) (Anh, 2013). This result suggested that our findings might be mainly from the results of the intestinal type of SC. The study sample size was minimized and only focused on men. Further study in both men and women with a large sample size is highly recommended.

Author Contribution Statement

Conceptualization: KS, THH, LTN. Data curation: CLN. Formal analysis: CLN. Funding acquisition: CLN. Methodology: LTN, KS. Project administration: CLN, KS, THH. Visualization: THH, CLN. Writing - original draft: CLN, LHP, LTMH, DVH. Writing - review and editing: CLN, LHP, LTMH, DVH.

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Available data

The original database will be available upon appropriate request.

Conflict of interest

There are no conflicts to disclose

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