PROSPECTIVE LONGITUDINAL STUDY ON VEGETABLE INTAKE AND STOMACH CANCER

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Vegetables are rich in vitamins and micronutrients and able to prevent against many types of cancer. This study prospectively analyzes the association of vegetables intake and stomach cancer in the period of 2008-2018. This is a prospective longitudinal research study to investigate the past one year of vegetable consumption habits of 50.097 individuals. The data collection tool is the validated semi-quantitative food frequency questionnaire. By 2018, 80 patients had passed away from stomach cancer, and there were 46,605 healthy individuals without any type of cancer. Data were analyzed for Hazard Ratio and 95% confidence interval (HR - 95% CI) using the Cox-Proportional Hazard Model method. After adjustment for age, sex, and smoking habit, there was no statistically significant relationship between stomach cancer and the habit of consuming water morning glory, broccoli, katuk, tomato, bok choy, asian radish, cabbage, winter melon, edible luffa, mung bean sprouts, sour bamboo shoots, laverbread, kohlrabi, cauliflower. Noticeably, eating carrots reduces the risk of stomach cancer with statistical significance (eating more compared with eating less) HR (95% CI): 0.52 (0.29 - 0.94), p for trend = 0.03. The significant association was remained after adjusted for additional multi-variable factors. Among 15 popular vegetables, the findings suggest that carrots have a potential protective effect in reducing the risk of stomach cancer.

Keywords: Stomach cancer, vegetable intake, longitudinal study

I. INTRODUCTION

In 2018, Vietnam had 17,527 stomach cancer patients, representing 11% of the country's total cancer patients.[1] Stomach cancer is the third most common cancer after liver and lung cancer. Stomach cancer is one of the significant public health concerns around the world due to its increasing frequency, limited treatments, and difficult prognosis.[2] Nearly half of stomach cancers in the world occur in East Asia.[3] Although many studies have shown *Helicobacter pylori (H. pylori)* infection to be the leading cause of stomach cancer, researchers still believe that the risk of stomach cancer is also linked to environmental factors, including diet.[4–6] Fruits and vegetables are rich sources of vitamins and minerals, such as vitamin C, vitamin A, vitamin E, carotenoids, folate ... that are believed to work to prevent the formation of nitrosamines, regulates DNA methylation, creates detoxifying enzymes, and promotes apoptosis.[7] With antioxidant properties, these vitamins can remove reactive radicals formed in the stomach lining, reducing stem-mediated DNA damage.[8]

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Furthermore, vitamin C may inhibit the growth of stomach cancer cells and alter cell cycle events caused by *H. pylori.*[9] However, there are no clear conclusions about the association between diet and stomach cancer from previous epidemiological studies. Several cohort studies and the majority of case-control studies have suggested that a diet rich in fruits and vegetables is inversely associated with the risk of stomach cancer. In contrast, other studies also found no evidence of an association.[10–13,13–16] Therefore, the purpose of this prospective longitudinal is to examine the relationship between the consumption of vegetables and the mortality of stomach cancer

II. SUBJECTS AND METHODS

1. Study design and participants

A prospective longitudinal study was performed for the period 2008-2018 in the general communities of the Hanoi City and some closed provinces. The baseline exposure survey to collect data regarding demographic information, lifestyles, diet, cooking methods, health history and other information from all participants was completed in 2008. Then a follow-up of all participants for the outcome of stomach cancer mortality and other health event from 2008 to 2018 was conducted. The last follow-up was by December 2018.

The 50,097 individuals of 12,746 households at the time of the survey in 2008 belonged to nine communes of Phung Hung, Da Trach and Dong Tien (Khoai Chau District-Hung Yen), Bac Hong, Viet Hung, Dong Hoi, Lien Ninh, and Thuong Cat (Hanoi City) and Tu Da (Phu Ninh-Phu Tho). These communes were selected because the commune health station has been working well in mortality registration from 2005 to date and the local government has been allowed to conduct the present prospective longitudinal study with written documents. Each of these nine commune health stations has a Medical Doctor working full-time and that is convenient for both a baseline exposure survey and follow-up for many years later with a reasonable quality of data collection.

Sample size estimation for a prospective longitudinal study on cancer

The present prospective longitudinal study on stomach cancer will make a comparison with an internal control group. Stomach cancer mortality rates are to be compared between two groups, with two dose levels. Suppose that the two groups are of equal size and age structure, and that we observe O_1 events in one group and O_2 in the other. Relative risk (R) or Hazard Ratio are based on the binominal parameter of a trial in which O_1 successes have occurred from $O_1 + O_2$ observations.

Where $O_+ = (O_1 + O_2)$. The required sample size is then given by the following formula[17]:

$$O_+ = [(R+1)Z_\alpha + 2Z_{1-\beta}\sqrt{R}]^2 / (R-1)^2$$

From this formula, sample size requirements in cohort studies when the exposed group is to be compared with a control group of k times the size (in this study, k = 1). The estimated number in the table are those expected in the control group is to be 20 (Rounded for 19.8) with the desired relative risk is 2.0 (or 0.5), significance is 5% and the power of the study is 80%. Then the expected events in the exposed group will be 20 x 2 = 40, giving 20 + 40 = 60 cases of stomach cancer are required in the present study. The actual reported cases were 80; therefore, sample size of the present study is greater the minimal required events and it is reasonable.

2. Baseline exposure assessment

We conducted the first baseline exposure assessment in 2008 using the validated

demographic and lifestyle and semi-quantitative food frequency questionnaires (DLQ and SQFFQ).[18] The cross-sectional survey for all households, door-to-door home visit, of nine communes was done in the study. The total number of households of these nine communes in 2008 was 17.853; the participated rate of surveyed households was 71% (12.746 households).

The validated DLQ and SQFFQ included 134 questions of all family member's demographic data; consumption of vegetable, fruits, meats and poultry, rice and noodles, fishes, spices and salt, cooking methods of meats and fishes, household hygienic condition of drinking water, toilet, refrigerator; individual data of education, health history, tobacco smoking habits, alcohol drinking, tea and other beverages, and air pollution at workplaces. The frequency of intake of foods required five levels of seldom or never intake, number of intake time per year or per month or per week or per day; the estimated amount (gram) of each time of consumption.

The interviewers, third year medical students of the Hanoi Medical University, were trained and collected data by face-to-face interview at the participant's households. Data collection was conducted for seven consecutively days of a week by door-to-door home visit with an assistance by the staffs of commune health station. When the household member was absent, the second or third visit was done to recruit study participants as much as possible.

3. The outcomes

The follow-up was started from the date of completed the first baseline exposure assessment in 2008 until 2018. The last follow-up was in December 2018: All household members of nine participating communes participated in the baseline exposure assessment in 2008 were sensor for health and resident status. By 2018, 80 patients have died from stomach cancer and 46,685 healthy individuals without any type of cancer were eligible for the final data analysis, after excluding for 3.412 persons have moved out of the study populations, Figure 1. Mortality due to all causes including stomach cancer has been yearly registered in all nine participated communes. Verbal Autopsy was conducted for each death case to determine the underlying causes of death, especially deaths due to cancer. Stomach cancer, ICD-19: C16, was the outcome of the present study.

4. Data analysis

The individual's person-year of follow-up were estimated from the baseline investigation date in 2008 to the date of a gastric cancer diagnosis or the date of last follow-up in December 2018.

Based on five levels of seldom or never intake, number of intake time per year or per month or per week or per day, each item of vegetable is divided into three levels (Tertile) of the frequency of consumption per year (low, medium, high), with the low group being the reference group. These categories were based on the estimated mean and/or median of the frequency of vegetable intake per year. Hazard Ratio and 95% confidence interval (HR 95% CI) are calculated using the Cox-Proportional Hazard Model method using the STATA 10. The HR 95% CI was adjusted for i) sex, age, and smoking for all food items and ii) sex, age, smoking, and other factors of education, history of stomach ulcer, family history of cancer, current and former alcohol drinking, salty food preferable, and spicy foods for the selected food item having the result in (i) with statistical significant. All p-values were two-slides and the cut of 0.05 (alpha) was considered as a statistically significant difference.

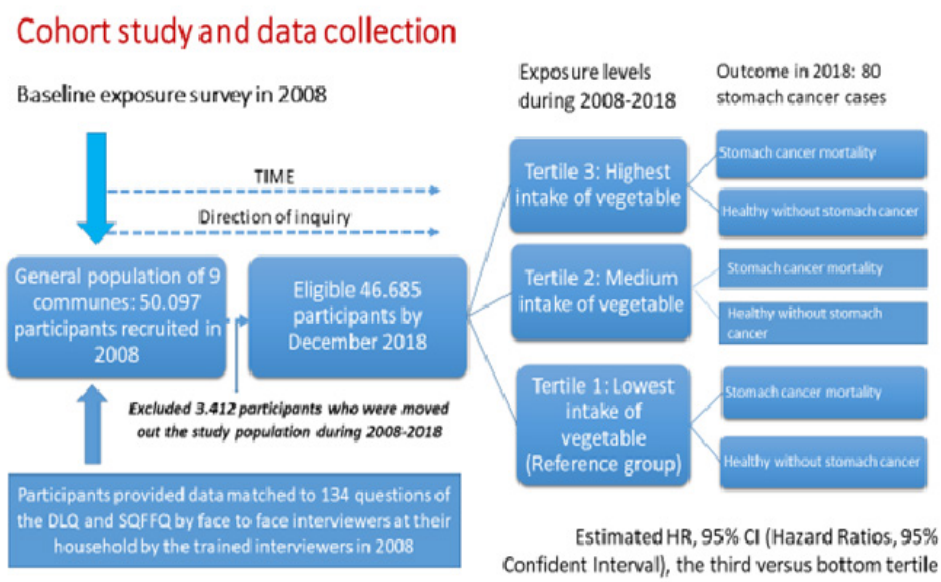

Figure 1. Study diagram of a prospective longitudinal study design

5. Ethical approval

Participants in the interview will be clearly explained about the research purpose, and they entirely voluntarily agree to participate in the study. Subjects have the right to withdraw from the study when they do not want to continue participating in the study. The information of research subjects is kept confidential, only used for research explained. Research results provide initial disease prevention with stomach cacer for the people and the patient's family members.

III. RESULTS

Table 1. Vegetable and food intake by year

Vegetable items and category	Frequency of intake per year (Tertile)		Number of participants
	Mean	Median	
Water morning glory			
Low	107	104	19,319
Medium	221	208	12,015
High	399	365	15,351
Total			46.,85
Broccoli			
Low	19	0	19,085

Vegetable items and category	Frequency of intake per year (Tertile)		Number of participan
	Mean	Median	
Broccoli			
Medium	97	104	12,123
High	242	182	15,477
Total			46,685
Katuk			
Low	25	24	18,116
Medium	103	104	16,090
High	245	182	12,479
Total			46,685
Tomato			
Low	10	12	18,670
Medium	50	52	14,756
High	187	130	13,259
Total			46,685
Bok choy			
Low	0	0	27,595
Medium	13	12	3,561
High	100	78	15,529
Total			46,685
Asian radish			
Low	0	0	28,710
Medium	10	12	5,411
High	67	52	12,564
Total			46,685
Cabbage			
Low	24	18	23,208
Medium	96	104	11,043
High	209	156	12,434
Total			46,685
Winter melon			
Low	0	0	15,885

Vegetable items and category	Frequency of intake per year (Tertile)		Number of participants
	Mean	Median	
Winter melon			
Medium	29	24	21,023
High	133	104	9,777
Total			46,85
Edible luffa			
Low	9	0	16,054
Medium	77	78	20,089
High	223	156	10,542
Total			46,685
Mung bean sprout			
Low	0	0	19,736
Medium	16	12	12,710
High	85	52	14,239
Total			46,685
Sour bamboo shoots			
Low	0	0	30,701
Medium	1	1	392
High	29	18	15,592
Total			46,685
Laverbread			
Low	0	0	45,847
High	43	12	838
Total			46,685
Kohlrabi			
Low	27	24	18,636
Medium	96	104	12,627
High	218	156	15,422
Total			46,685
Cauliflower			
Low	0	0	23,559
Medium	11	12	7,831

Vegetable items and category	Frequency of intake per year (Tertile)		Number of participants
	Mean	Median	
Cauliflower			
High	75	52	15,295
Total			46,685
Carrot			
Low	0	0	27,099
Medium	9	12	7,335
High	75	52	12,251
Total			46,685

Foods including asian radish, winter melon, mung bean sprouts, sour bamboo shoots, laverbread, cauliflower, and carrots are all in the medium or high group, the group with low-frequency (Mean and/or median) of consumption per year is between 0 and less than 10). The water morning glory, broccoli, katuk, tomatoes, cabbage, edible luffa, and kohlrabi are in a high-frequency of consumption group (over 200 times). However, in terms of the number of uses, water morning glory has the highest number of uses (over 600 times per year), followed by broccoli, katuk, tomatoes, cabbage, edible luffa, and winter melon with consumption is in the range (100-300 times per year). The remaining foods are used less than 100 times per year, of which laverbread has the lowest consumption with only about 10 times per year.

Table 2. Hazard ratio and 95% confidence interval and p for trend by food items

Food and vegatable	Healthy	Cancer	Adjusted HR (95% CI) #	P for trend
Water morning glory				
Low	19288	31	1.00 (reference)	0,39
Medium	12000	15	0.88 (0.47 - 1.62)	
High	15317	34	1.24 (0.76 - 2.03)	
Broccoli				
Low	19058	27	1.00 (reference)	0,71
Medium	12107	16	0.89 (0.48 - 1.66)	
High	15440	37	1.09 (0.65 - 1.84)	
Katuk				
Low	18086	30	1.00 (reference)	0,24
Medium	16062	28	1.50 (0.89 - 2.52)	
High	12457	22	1.35 (0.77 - 2.34)	

Food and vegatable	Healthy	Cancer	Adjusted HR (95% CI) #	P for trend
Tomato				
Low	18636	34	1.00 (reference)	0,48
Medium	14,731	25	0.93 (0.56 - 1.57)	
High	13,238	21	0.82 (0.47 - 1,42)	
Bok choy				
Low	27,549	46	1.00 (reference)	0.81
Medium	3,557	4	0.74 (0.27 - 2.06)	
High	15,499	30	1.07 (0.67 - 1.70)	
Asian radish				
Low	28,658	52	1.00 (reference)	0.30
Medium	5,404	7	0.61 (0.28 - 1.35)	
High	12,543	21	0.79 (0.47 - 1.32)	
Cabbage				
Low	23,166	42	1.00 (reference)	0.11
Medium	11,029	14	0.92 (0.50 - 1.68)	
High	12,410	24	1.60 (0.96 - 2.66)	
Winter melon				
Low	15,859	26	1.00 (reference)	0.21
Medium	20,991	32	0.85 (0.51 - 1.43)	
High	9,755	22	1.54 (0.87 - 2.71)	
Edible luffa				
Low	16,026	28	1.00 (reference)	0.26
Medium	20,059	30	1.16 (0.69 - 1.94)	
High	10,520	22	1.38 (0.79 - 2.41)	
Mung bean sprout				
Low	19,701	35	1.00 (reference)	0.82
Medium	12,691	19	0.86 (0.49 - 1.50)	
High	14,213	26	1.08 (0.65 - 1.80)	
Sour bamboo shoots				
Low	30,639	62	1.00 (reference)	0.14
Medium	390	2	1.74 (0.42 - 7.14)	
High	15,576	16	0.65 (0.37 - 1.13)	

Food and vegatable	Healthy	Cancer	Adjusted HR (95% CI) #	P for trend
Laverbread				
Low	45,769	78	1.00 (reference)	-
High	836	2	1.53 (0.37 - 6.21)	
Kohlrabi				
Low	18,601	35	1.00 (reference)	0.64
Medium	12,613	14	0.68 (0.37 - 1.26)	
High	15,391	31	1.14 (0.70 - 1.85)	
Cauliflower				
Low	23,512	47	1.00 (reference)	0.92
Medium	7,822	9	0.71 (0.35 - 1.44)	
High	15,271	24	1.01 (0.62 - 1.65)	
Carrot				
Low	27,046	53	1.00 (reference)	0.03 $
Medium	7,322	13	0.83 (0.45 - 1.52)	
High	12,237	14	0.52 (0.29 - 0.94)	

HR 95%CI: Hazard Ratio and 95% confidence interval. #: Adjusted for sex, age, and smoking. $: # and additional adjusted for education, history of stomach ulcer, family history of cancer, current and former alcohol drinking, salty food preferable, and spicy foods, the third versus bottom tertile, HR (95%CI): 0.30 (0.10, 0.85), p for trend = 0.02

The hazard ratio, when comparing medium, high versus low levels of each vegetable type, shows a tendency to affect differently, but not statistical significant. Water morning glory, broccoli, bok choy, cabbage, winter melon, mung bean sprouts, and kohlrabi will reduce the risk of stomach cancer if consumption intake in group median. However, if consumption intake in a group high, the risk of stomach cancer becomes high. The results of hazard risk analysis katuk, tomatoes, asian radish, and edible luffa showed that there was a similar tendency of influence between the medium and high consumption group when compared to the low consumption group in each vegetable. However, the analysis results did not show that this difference is statistically significant.

Particularly for carrot food, the results of the analysis of the hazard risk showed a reduction in the risk of stomach cancer when comparing high consumption intake with low consumption intake, and the difference was statistically significant with HR (95% CI), adjusted for sex, age, and smoking: 0.52 (0.29 - 0.94). In addition, trend analysis also showed statistical significance with a p for trend = 0.03. After additional adjusted for education, history of stomach ulcer, family history of cancer, current and former alcohol drinking, salty food preferable, and spicy foods, the third versus bottom tertile, HR (95%CI): 0.30 (0.10, 0.85), p for trend = 0.02

IV. DISCUSSION

Total 50,097 individuals were surveyed the first time in 2008 on dietary habits in during the last year using the Semi-quantitative Food Frequency Questionnaire (SQFFQ). These individuals continued to be monitored for health in the following years. In 2018, 80 individuals were dead due to stomach cancer and 46.605 healthy individuals (without any type of cancer). Analysis of the frequency of consumption of foods, including 15 vegetables classified into three levels of a low, medium, and high consumption intake, showed that vegetable consumption has a risk impact on stomach cancer. The results of data analysis of the study using the Cox-Proportional Hazard Model analysis have shown that individuals with high carrot consumption reduce the risk of stomach cancer with a hazard ratio of confidence interval 95% is HR (95% CI): 0.52 (0.29 - 0.94). The difference between the levels of consumption intake affecting the risk of stomach cancer is statistically significant. Comparing this result with the results from the studies of Shimazu et al. 2014 shows similarities.[6] This is appropriate when carrots are quite popular foods in the diets of other countries around the world, in which a carrot can provide the human body 25 calories, 6 grams of carbohydrates, 3 grams. Sugar and 1 gram of protein. At the same time, carrots are an excellent source of vitamin A, providing 210% of the average adult's needs for the day; It also provides 6% of vitamin C needs, 2% of calcium needs, and 2% of iron needs per serving. Carrots also contain fiber, vitamin K, potassium, folate, manganese, phosphorus, magnesium, vitamin E and zinc that have been shown to contribute to cancer risk.[9,12,19]

Results from previous studies have also found a link between the consumption of foods and the risk of stomach cancer.[20–24] The analysis data of this study showed similar results. Still, they could not conclude due to the non-statistical significance, which could be explained by data collected during personal interviews of the study, in the retrospective interview of the consumption of foods that resulted in actual deviations from the individual responses. In addition, the number of individuals with stomach cancer in all 9 communes in 10 years was only 80 individuals, the rate of which was a massive difference compared to healthy individuals in the community, so the ability to detect significant differences. Statistics, when analyzing, is difficult.

The study has certainly limitation due to not available information of histopathological confirmation of each stomach cancer case and study participant status of *H. pylori* infection, the established risk factor induced stomach cancer.[25] During ten years of following up, there was unable to repeat dietary survey for every 4-year as applied in the U.S. Nurses Health Study.[26]

V. CONCLUSION

There was no statistically significant association between stomach cancer and the consumption of spinach, broccoli, spinach, tomatoes, bok choy, turnip, cabbage, zucchini, melon, green bean sprouts, Sour bamboo shoots, dried seaweed, kohlrabi, and cauliflower. However, statistically significant results after an analysis showed that eating carrots reduced the risk of stomach cancer (eating more versus eating less) with HR (95% CI) of 0.52 (0, 29 - 0.94) with p for trend = 0.03.

In 15 popular vegetables, after adjusted for multiple variable factors, the findings suggest that carrots can be considered a potential candidate to have a protective effect on the body in reducing the risk of stomach cancer. This result

warrant future studies on the mechanism of the association.

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Conflict of interest:

There are no conflicts to disclose

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