Original Article
The protective role of Vit C and Vit C-containing foods in head and neck cancer

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Abstract: Objective: Vitamin C (Vit C) protects the immune system and reduces allergic reactions. However, the significance of Vit C in cancers, such as head and neck cancer (HNC), remains unknown. Herein, we aimed to evaluate the beneficial effect of Vit C supplements and Vit C-containing foods in HNC. Methods: Five hundred twenty six HNC patients and 647 healthy subjects were enrolled in our study. A case-control method was used to investigate the association between dietary Vit C and HNC risk. T test was applied for the continuous variables and chi-square test was applied for the categorical variables during the testing. Results: Lower levels of Vit C consumption were found among subjects with HNC compared with control subjects. When adjusted for factors including HNC family history, job, smoking status and practice of regular exercise, a negative correlation between Vit C consumption and risk of HNC was found among the two groups with the highest level ($\geq$ 121.5 mg/d) and lowest level (< 79.5 mg/d) of Vit C intake (OR, 0.57; 95% CI, 0.42-0.96, P < 0.01). Moreover, a protective effect against HNC risk was found in the multivariate analysis of Vit C-containing foods, including cabbage, lettuce, mandarins, strawberries, persimmons, bananas, orange juice, watermelon and apples. Conclusions: These findings indicate that a low level of Vit C consumption is associated with a high risk of HNC, suggesting that Vit C and Vit C-containing foods display potential protective effects against HNC.

Keywords: Dietary, vitamin C, cabbage, head and neck cancer, strawberries

Introduction

Head and neck cancer (HNC) is one of the most commonly occurring cancers [1]. A negative association has been found between fruit and vegetable intake and HNC risk, as vitamins in fruits and vegetables could exhibit anti-oxidative properties [2]. In addition, vitamins maintain the normal DNA repair progress and are important for normal cell differentiation [3]. Recently, doubts were raised concerning the protective effect of vegetables and fruit against cancer risk [4, 5]. Therefore, a thorough research of the association between vegetables/fruits and cancer risk is needed.

Vegetables and fruit are rich in vitamins, minerals, fiber, and phytochemicals that are well-known for their anti-carcinogenic nature. These nutrients have anti-proliferation and anti-oxidation properties and could activate the immune system, methylation and DNA synthesis [6]. In particular the relationship between Vit C and upper aero-digestive tract cancer (UADTC) has been studied and a negative correlation was found by the most of studies [7]. However, the evidence is still limited with regards to HNC.

As a well-known antioxidant found in vegetables and fruits, Vit C could be the key in understanding the anti-carcinogenesis mechanism [8]. In fact, Vit C protects DNA from oxidative damage, which is a major cause of carcinogenesis [9]. In addition, many meta-analyses and observational studies have found that Vit C possesses an anti-HNC effect [1, 10], although several other observational studies reached different conclusions [11, 12]. The protective effect of Vit C against HNC has been controversial up until now.

In this study, we aimed to investigate the beneficial effect of Vit C supplements and Vit C-containing foods in HNC. A case-control

Table 1. Clinical characteristics of the study subjects

Characteristic	HNC group (n = 526)	Control group (n = 647)	P value
Gender n (%)			
Male	304 (57.8)	341 (52.7)	0.47
Female	222 (42.2)	306 (47.3)	
Age (yr), mean ± SD	55.3 ± 10.4	56.1 ±11.5	0.22
BMI (kg/m²) n (%)			
< 23	207 (39.4)	273 (42.2)	0.92
23-25	172 (32.7)	195 (30.1)	
≥ 25	147 (27.9)	179 (27.7)	
Family history of HNC n (%)			
Yes	137 (26.0)	75 (11.6)	< 0.01
No	389 (74.0)	572 (88.4)	
Marital status n (%)			
Married	489 (93.0)	586 (90.6)	0.59
Other	37(7.0)	61 (9.4)	
Job n (%)			
In the labor force	173 (32.9)	128 (19.8)	0.03
Not in the labor force	353 (67.1)	519 (80.2)	
Alcohol consumption n (%)			
Non-drinker	117 (22.2)	195 (30.1)	0.43
Ex-drinker	86 (16.3)	98 (15.1)	
Current drinker	323 (61.4)	354 (54.7)	
Smoking status n (%)			
Non-smoker	204 (38.8)	313 (48.4)	< 0.01
Ex-smoker	135 (25.7)	242 (37.4)	
Current-smoker	187 (35.6)	92 (14.2)	
Regular exercise n (%)			
No	352 (66.9)	269 (41.6)	< 0.01
Yes	174 (33.1)	378 (58.4)	

HNC: head and neck cancer; BMI: body mass index. T test was applied for the continuous variables and chi-square test was applied for the categorical variables during significant testing.

method was used to investigate the association between dietary Vit C and HNC risk.

Subjects

A total of 526 HNC patients and 647 healthy subjects were recruited. All subjects were referred to Shanghai Pudong New District Zhoupu Hospital between Mar 2012 and Nov 2015. The HNC cases were selected if they had a diagnosis of invasive tumor of larynx, hypopharynx, oropharynx, oral cavity, pharynx or oral cavity not otherwise specified, or unspecified HNC. Control subjects were selected from patients who underwent a health check-up in the Cancer Prevention and Detection Center of

the same hospital. Patients were excluded if they had a history of carcinoma of the salivary glands, or carcinoma of the nasal cavity, ear, or paranasal sinuses was found. Patients with a history of diabetes, cancer diagnosis in the past 5 years, severe systemic disease, advanced HNC, or mental disease were excluded from the study. This study was approved by the ethics review committee of the Shanghai Pudong New District Zhoupu Hospital. Written informed consent was obtained from each participant prior to the study.

Data collection

Each participant was required to fill in a self-reported questionnaire for their demographic, medical history and lifestyle information. A food frequency questionnaire (FFQ) was applied to collect the dietary consumption information [13]. The FFQ includes nine categories of food intake frequency and three categories of portion size (large/medium/small) of specific food consumed in the past year. The Computer Aided Nutritional Analysis Program v 4.0 was applied to compute the average daily nutrient consumption of each subject, the daily consumption of Vit C (mg/d) was calculated as a sum of Vit C consumption from various foods.

Definition of the exposure variable

A preliminary search of definitions, recommended consumption periods, and measurement units of Vit C across studies was conducted. We compiled a list of foods that were consumed on a daily basis [14]. To evaluate the comparability of the parameters across studies, kernel density estimation was performed on the datasets of Vit C consumption.

Statistics

T test was applied for the continuous variables and chi-square test was applied for the categorical variables during testing. Candidate foods were selected according to their contribution of Vit C. Each kind of food was ranked by its con-

Table 2. Comparison of intakes of Vit C and Vit C-contributing foods

Food (g/d)	HNC group (n = 526)	Control group (n = 647)	P value
Vitamin C (mg/d)	93.2 ± 36.1	112.5 ± 43.7	< 0.01
Energy (Kcal/d)	1943.6 ± 531.7	1736.4 ± 496.3	< 0.01
Spinach	10.4 ± 16.3	11.5 ± 18.6	0.48
Radish kimchi	30.6 ± 24.7	29.6 ± 32.6	0.57
Cabbage	8.9 ± 7.6	15.3 ± 12.7	< 0.001
Potatoes and starches	42.5 ± 27.6	46.8 ± 36.9	0.027
Green pepper	8.9 ± 7.6	9.2 ± 8.5	0.53
Radish	25.4 ± 18.7	23.6 ± 20.5	0.32
Lettuce	6.8 ± 7.6	9.7± 8.6	< 0.001
Onion	16.7 ± 10.8	17.5 ± 11.7	0.41
Mustard leaf kimchi	13.1 ± 22.3	14.5 ± 45.3	0.51
Zucchini	19.3 ± 17.6	20.2 ± 19.5	0.55
Fruits	123.4 ± 86.3	204.7 ± 115.6	< 0.001
Mandarins	17.5 ± 20.6	26.8 ± 23.9	< 0.001
Strawberries	6.3 ± 7.9	10.6 ± 12.3	< 0.001
Persimmons	19.6 ± 26.3	21.1 ± 32.9	0.39
Bananas	12.6 ± 20.5	23.7 ± 26.1	< 0.001
Citrus tea	36.2 ± 47.5	38.1 ± 50.6	0.51
Orange juice	9.4 ± 15.3	22.3 ± 27.9	< 0.001
Watermelon	15.1 ± 19.3	25.4 ±37.8	< 0.001
Apples	28.2 ± 37.1	55.6 ± 49.3	< 0.001

Data are presented as mean ± SD. Vit C: vitamin C; HNC: head and neck cancer.

smoker) and practice of regular exercise (positive, negative). Statistical analyses were performed on SPSS 17.0. Two-tailed *P* value < 0.05 was considered statistically significant for all tests of significance.

Results

Clinical characteristics of the study subjects

Distributions of subjects (647 in the control group and 526 in the HNC group) in terms of general characteristics are presented in **Table 1**. Subjects in the HNC group tend to have a higher rate of HNC family history (P < 0.01), higher employment levels more labor force (P = 0.03), higher tobacco consumption (P < 0.01) and undertake less regular exercise (P < 0.01). No significant difference was found in the other characteristics between the HNC group and the control group.

Intakes of Vit C and Vit C-containing foods

tent of Vit C, and the selected foods represent > 80% of the Vit C vitamin consumption of the general population. A linear residual regression method was used to adjust the consumption of dietary Vit C intake and Vit C-containing foods, according to the total energy consumption. The consumption of Vit C and Vit C-containing foods was subgrouped according to their tertile ranks in the control group. The first tertile group was considered the reference group. Trend tests were performed on the median of each of the Vit C consumption and Vit C-containing food tertile groups.

A logistic regression model was built to assess the association between HNC risk and dietary factors. Adjustments for potential confounders were performed to obtain an unbiased estimate. The 95% confidence interval (CI) and odds ratio (OR) were also computed. The multivariate analysis was adjusted for the following factors: participant's history of first-degree relatives (positive, negative); employment status (in the labor force or not), cigarette-smoking status (current smoker, ex-smoker, and non-

Vit C and Vit C-containing food intakes of the HNC group and the control group are presented in **Table 2**. Increased energy intake (P < 0.01) and a lower level of Vit C consumption (P < 0.01) were found among subjects with HNC compared with control subjects. Less consumption of potatoes and starches (P = 0.027), cabbage (P < 0.01), lettuce (P < 0.01), fruits (P < 0.01), strawberries (P < 0.01), mandarins (P < 0.01), bananas (P < 0.01), watermelon (P < 0.01), orange juice (P < 0.01) and apples (P < 0.01) were found in subjects with HNC as compared with controls. Consumption of Vit C-containing food such as spinach, radish, green pepper, radish, onion, mustard leaf kimchi, zucchini, persimmons and citrus tea showed no significant difference between subjects with HNC and control subjects.

Vit C consumption and the risk of HNC

To explore the connection of Vit C consumption and the risk of HNC, the consumption of Vit C and Vit C-containing foods was subgrouped according to their tertile ranks in the control

Table 3. Odds ratio and 95% confidence interval of HNC by tertiles of dietary vitamin C

Tertile ranks	Range (mg/d)	HNC group (n = 526)	Control group (n = 647)	Model I OR (95% CI)	Model II OR (95% CI)
Tertile 1#	< 79.5	213 (40.5%)	226 (34.9%)	1	1
Tertile 2#	79.5-121.5	194 (36.9%)	207 (32.0%)	0.55 (0.37-0.94)	0.62 (0.48-1.03)
Tertile 3#	≥ 121.5	119 (22.6%)	214 (33.1%)	0.48 (0.32-0.85)	0.57 (0.42-0.96)
P value for trend				< 0.001	< 0.01

HNC: head and neck cancer; OR: odds ratio, CI: confidence interval. Trends were calculated using the median intake for each dietary vitamin C category as a continuous variable. Model I: Unadjusted; Model II: Adjusted by family history of HNC, job, smoking status, regular exercise.

Table 4. The logistic regression analysis of vitamin C contributing food consumption associated with HNC risk

Vitamin C contributing food consumption	Odds ratio (OR)	95% Confidence interval	P value
Total vegetable consumption	0.91	0.67-1.23	0.42
Potatoes and starches	0.76	0.51-1.46	0.03
Total fruit consumption	0.38	0.24-0.62	< 0.001
Spinach	0.73	0.52-1.11	0.21
Radish kimchi	0.91	0.67-1.25	0.43
Cabbage	0.37	0.28-0.59	< 0.001
Potatoes	0.86	0.54-1.23	0.28
Green pepper	0.89	0.61-1.34	0.36
Radish	0.78	0.53-1.17	0.16
Lettuce	0.54	0.41-0.92	< 0.001
Onion	0.97	0.65-1.37	0.64
Mustard leaf kimchi	1.05	0.69-1.42	0.41
Zucchini	0.95	0.71-1.39	0.73
Mandarins	0.5	0.39-0.94	< 0.001
Strawberries	0.48	0.29-0.72	< 0.001
Persimmons	0.43	0.31-0.69	< 0.001
Bananas	0.36	0.22-0.54	< 0.001
Citrus tea	0.93	0.61-1.24	0.37
Orange juice	0.39	0.21-0.63	< 0.001
Watermelon	0.55	0.38-0.86	< 0.001
Apples	0.32	0.21-0.59	< 0.001

Consumption of Vit C-containing food and the risk of HNC

To determine the influence of Vit C-containing food on the risk of HNC, we performed a multivariate analysis. Association between consumption of Vit-C containing food and HNC risk is presented in **Table 4**. We observed that the consumption of potatoes and starches (OR, 0.76; 95% CI, 0.51-1.46), fruits (OR, 0.38; 95% CI, 0.24-0.62), cabbage (OR, 0.37; 95% CI, 0.28-0.59), lettuce (OR, 0.54; 95% CI, 0.41-0.92), mandarins (OR, 0.50; 95% CI, 0.39-0.94), strawberries (OR, 0.48; 95% CI, 0.29-0.72), persimmons (OR, 0.43; 95% CI, 0.31-0.69), bananas (OR, 0.36; 95% CI, 0.22-0.54), orange juice (OR, 0.39; 95% CI, 0.21-0.63), watermelon (OR, 0.55; 95% CI, 0.38-0.86) and apples (OR, 0.32; 95% CI, 0.21-0.59) decreased the risk of HNC, suggesting that the consumption of Vit C-containing food has a protective effect against HNC.

Discussion

group. Trend tests were performed on the median of the Vit C consumption and Vit C-containing foods. The OR and 95% CI for Vit C consumption were presented in **Table 3**. A negative correlation between Vit C consumption and risk of HNC was found among the two groups with the highest dose (≥ 121.5 mg/d) and the lowest dose (< 79.5 mg/d) of Vit C intake in an unadjusted model and an adjusted model (adjusted for confounding factors such as smoking status, HNC family history, job, practice of regular exercise; OR, 0.57; 95% CI, 0.42-0.96, P < 0.01).

Here, we explored the associations between Vit C intake and the risk of HNC. A negative correlation between Vit C consumption and the risk of

HNC was found among the two groups with the highest and lowest levels of Vit C intake. Consumption of Vit C-containing foods, including cabbage, lettuce, mandarins, strawberries, persimmons, bananas, orange juice, watermelon and apples reduced the risk of HNC, which suggests that Vit C-containing food displays a potential protective effect against HNC.

The International Head and Neck Cancer Epidemiology (INHANCE) consortium indicated that Vit C supplementation decreases the risk of HNC [14]. An analysis showed that no clear associations were found between supplementation and risk of HNC [15]. This different result regarding vitamin intake could be caused by the small sample size. Several case-control studies have evaluated vitamin intake and the risk of HNC [16]. Negri et al. showed a negative correlation between Vit C consumption and risk of oral and pharyngeal cancer and a significant protective effect of vitamin E and carotene against oral and pharyngeal cancer. A recent study found a negative correlation between Vit C-containing food consumption and HNC, which reflects a protective effect of Vit C-containing food against these cancers [17]. Our results in this study are consistent with those of previous reports in that a negative correlation between Vit C and the HNC risk was found. Based on the evidence listed above, Vit C seems to be a strong factor in preventing HNC.

However, one study reached a different conclusion regarding the role of Vit C in preventing cancer risk. Two case-control studies with small-size samples, conducted in Italy and Mexico, suggested no effect of Vit C in the prevention of cancer [12]. A health study conducted on both male and female residents of Shanghai found no significant correlation between dietary nutrients (Vit C, Vit A, Vit E, retinol, carotin, folic acid and selenium) and risk of gastric carcinoma [11]. A cohort study for the relationship of fruit and vegetable intake and HNC showed that a higher fruit and vegetable intake had a stronger benefit for oral cavity cancer than for laryngeal cancer [2]. The conflicts of study results could be caused by differences in study design and random errors.

In the analysis of the relationship between Vit C-containing food consumption and HNC risk, our results are consistent with the conclusion of one meta-analysis [1, 17]. A meta-analysis on eight observational studies of Japanese and Korean populations found a negative association between the consumption of fresh vegetables and risk of gastric carcinoma [18]. Similar conclusions were made by other meta-analyses on observational studies, that fruit and vegetables have a protective effect against the risk of gastric carcinoma [19, 20]. In addition, the same conclusion was yielded by prospective case studies and prospective cohort studies [21, 22].

In this research, we found negative correlations between the intake of cabbage, lettuce, mandarins, strawberries, persimmons, bananas, orange juice, watermelon, apples and HNC risk. Our finding is comparable with another cohort study [4], which found a negative correlation between gastric carcinoma and the intake of pulses, vegetables, apples, pears, and raw leaf vegetables.

How vitamin consumption reduces cancer risk is still largely unknown and several theories of anti-cancer mechanisms have been proposed. Some suggest that the anti-inflammatory effect of Vit C, which protects DNA from harmful oxidants, contributes to the prevention of cancer [23]. Some research suggests that, with the help of H_2O_2, Vit C could kill cancer cells owing to its pro-oxidant nature. In addition, Vit C could inhibit the spread of cancer cells through the facilitation of collagen synthesis and inhibition of hyaluronidase, which increases the extracellular matrix. Vit C, along with other antioxidants, could also help to remove the radicals (a major cause of cancer cells) from human body [24, 25].

Owing to funding and time limits, there are some limitations to this study: 1) case selection bias; selection of patients may not be a true representation of the whole population; 2) recall bias. 3) small sample size. Further study should also focus on a more detailed subgrouping of study subjects (e.g. grouping according to the location of the tumor).

To conclude, a negative correlation was found between Vit C consumption and HNC risk. The same trend was also found between total fruit intake, certain vitamin C-contributing foods and HNC risk. These findings indicate that Vit C and Vit C-containing foods display potential protective effects against HNC.

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Disclosure of conflict of interest

None.

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