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Original Article

Assessment of dietary pattern and serum levels of vitamins A, C, and E in patients with head and neck squamous cell carcinoma (HNSCC): A case-control study

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Abstract

Background: The importance of dietary pattern and vitamins in the incidence of cancers has been demonstrated in many studies. As there are cultural differences and various dietary patterns in different countries, the results of other studies are not necessarily applicable to our society. This study aimed to evaluate the role of some vitamins and dietary patterns in developing head and neck cancer.

Methods: Dietary pattern and serum levels of vitamins in 39 patients with head and neck squamous cell carcinoma (HNSCC) were compared to 37 healthy individuals. A native questionnaire was used to obtain the dietary pattern. The existence of a significant relationship between serum levels of vitamins and dietary pattern with the risk of HNSCC was assessed. The independent *t* test, chi-square and exact Fisher's test were employed for statistical analysis.

Results: The mean serum levels of these vitamins in the case group were significantly lower as compared to the control subjects ($P<0.005$). Two dominant eating patterns were identified, and after adjusting for confounding factors such as age, education, physical activity, body mass index (BMI), and place of residence, it was found that people with unhealthy dietary patterns were 6.55 times more likely to develop cancer than people with a healthy diet.

Conclusion: Lower serum levels of vitamins C and E are associated with an increased risk of HNSCC. Unhealthy dietary patterns also increase the risk of developing this cancer.

Keywords: Carcinoma, Squamous cell; Head and neck neoplasms; Vitamins, Dietary supplements

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Introduction

Head and neck cancers are a class of cancers that develop in the nasal cavity, para-nasal sinuses, pharynx, larynx, salivary glands, lips and oral cavity. Most of these cancers, with the exception of salivary gland neoplasms, are squamous cell carcinoma (SCC). Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer worldwide with high mortality and low survival rates.[1]

In a retrospective study from 2005 to 2015 examining body tumors in southern Iran, 1.4% of patients had SCC of the head and neck. The most common affected site was the larynx and the well differentiated type had the highest incidence rate from a histopathological viewpoint.[2] Moreover, the age-standardized incidence rate was 2.2 in men and 1.8 in women according to the latest studies.[3] In addition to smoking and alcohol use, which are the most common risk factors of this cancer, other factors, such as

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demographic factors, HPV infection, and nutrition also play a role. Dietary pattern has a crucial role in developing oral cancer. In fact, a healthy diet and nutritional factors can reduce the risk of cancer by altering tumorigenesis in the body.[4]

Cancer is caused by the interaction of genetic and environmental factors, including diet, smoking, and ionizing radiation, which alters normal DNA in cancerous cells. According to the World Health Organization evaluation, 35%–55% of all types of cancer and about 15% of oropharyngeal cancers can be attributed to nutritional deficiencies or imbalances. Nutrition and cancer are linked through two mechanisms: direct carcinogenesis, which is the direct effect of existing carcinogens in some foods, and indirect carcinogenesis, in which the synthesis of carcinogens in the body is due to altered metabolism resulting from changes in eating habits.[5]

Pervious epidemiological studies have revealed that high intake of vegetables and fruits could reduce the risk of a variety of cancers, including oral cancer, a finding that may be related to the protective effect of vitamins A, C, E, folate flavonoids, and phytosterols. On the other hand, animal fats and salt-cured meat are considered risk factors.

Dietary micronutrients such as vitamins C and E, beta-carotene, and lycopene potentially have protective properties that can neutralize active radicals and prevent cell damage. Vitamins A, E, and C have antioxidant effects; they bind to and dissolve carcinogens in the gastrointestinal tract.[6,7]

There is compelling evidence that changing eating habits can reduce the risk of development of the cancers, including oral cancer, through preventing the formation of carcinogens, reducing their metabolic activation, and increasing their excretion. Susceptibility to cancer varies between individuals due to underlying and intrinsic differences, and hereditary traits. External factors also play a significant role in the developing some cancers in humans.

To date, no comprehensive study has been carried out in Iran to study these factors. On the other hand, the results of other studies worldwide are not necessarily applicable for health planning due to cultural differences and different dietary patterns in societies. Therefore, the aim of the present study was to assess the role of some vitamins as antioxidants and to study dietary patterns by means of a native questionnaire.

Methods

Patients selection

This case-control study was conducted from August 2018 to April 2019 at the ENT clinic of Omid Hospital, Reza Medical Center, and Mashhad Faculty of Dentistry (all located in Mashhad, Iran). Statistical samples consisted of 76 subjects, including 39 with HNSCC as the case group and 37 healthy individuals as the control group.

Controls were subjects with no history of cancer admitted to the same clinics for non-neoplastic conditions or for dental treatments.

Inclusion criteria in the case group were patients between 40 and 75 years of age, who had been recently pathologically diagnosed with HNSCC, and they had not received any treatment. Exclusion criteria in the case group included following a particular diet, taking any vitamin supplement or compound, a history of chronic and severe hepatic or renal or gastrointestinal disorders, diabetes or chronic diseases that influence nutrition, taking medications that affect vitamin and micronutrient levels (including anticonvulsants, hydrocortisone, and tetracycline antibiotic), pregnant and lactating women, and patients with a history of chronic oral lesions. Exclusion criteria in the control group were a history of any type of cancer in any area of the body, in addition to the exclusion criteria for the case group. Group matching was performed, and the control group was similar to the case group regarding to age, gender, and socio-economic status.

Evaluating serum levels of vitamins

After obtaining written informed consent from all subjects, blood samples were collected at 8–10 AM after an overnight fast. In order to measure the serum levels of vitamins, 5 mL of blood was taken from the cubital median vein.

Because retinol decomposes in light, the samples were kept in tubes covered with aluminum foil. The samples were then left at room temperature for 15 minutes to form a clot. The samples were then centrifuged for 5 minutes to separate the serum.

Assessment of the dietary pattern

The questionnaire in this study was a semi-quantitative tool including 160 Iranian foods. The options in the questionnaire were determined based on the usual food consumption in Iran. The questionnaire measured the frequency of eating each food and the amount of food consumed in a month and included 25 sections for different food groups (Supplementary file 1).

The questionnaire was developed and validated by the Nutrition Department of Mashhad University of Medical Sciences. The validation paper has been published elsewhere,[8] the correlation coefficients of the validation study ranged from 0.225 to 0.323 for macronutrients and from 0.128 to 0.476 for micronutrients, which shows acceptable validity.[8]

In completing the questionnaire, healthy participants were asked to fill out the questionnaire about the frequency of routine consumption of each food item (daily, weekly, and monthly) over the past months. The interviewer emphasized that the case subjects should mention their eating habits before developing the cancer. The questionnaires were completed by an educated interviewer in order to increase the accuracy of the answers.

Statistical methods

The collected data were analyzed using the SPSS (ver. 22) software. Frequency tables, graphs, and mean and standard deviation indices were applied to describe the data. The independent *t* test was used to compare quantitative variables in the two groups. Chi-square or exact Fisher's test was also employed to compare qualitative variables between the two groups. The forward conditional logistic regression model was applied to control the intervening variables, and dietary patterns were determined using exploratory factor analysis. The significance level in all tests was 0.05.

Results

Demographic data

A total of 76 participants, 38.2% female and 61.8% male, were included in this study, of whom 37 were in the control group and 39 were in the case group. In the case group, 17 patients had oral SCC, 15 had SCC of the pharynx and/or larynx, 5 had SCC of the lip and/or maxilla and/or para-nasal sinuses, and 2 had SCC extended to the pharynx and larynx and the oral cavity. The average size of the lesions was less than 2 cm in 16 patients, between 2 to 4 cm in 18 patients and more than 4 cm in 5 patients. The demographic information of both groups is presented in Table 1.

According to Table 1, there was a remarkable difference between the case and control groups in terms of educational level, physical activity, place of residence, body mass index (BMI), and age ($P=0.001$, $P=0.02$, $P=0.02$, $P<0.001$, $P=0.039$, respectively).

Nutrition status

In order to determine dietary patterns, the 160 foods were initially divided into 25 groups based on the similarity of their micronutrients. In some cases, foods were classified as a single group due to their specific nutrients (Supplementary file 1).

The food groups were divided using factor analysis into two hypergroups. The first hyper group included fast foods, potatoes, desserts, offal, carbonated beverages, refined grains, red meat, soups, and pickles, and the second included salads, nuts, vegetables, fruits, beans, eggs, and poultry (Table 2).

The statistical analysis showed the mean amount of intake of some food groups, including vegetables, fruits, coffee, sugar, nuts, poultry, egg, salads, and desserts in the control group was remarkably higher as compared to HNSCC patients ($P<0.05$); however, there was not any significant difference between two groups regarding

Table 1. Demographic data of the case and control groups

Variables	Case group (n=39) No. (%)	Control group (n=37) No. (%)	*P* value
Gender*			0.67
Male	25 (64.1)	22 (59.5)	
Female	14 (35.9)	15 (40.5)	
Educational level **			0.001
Illiterate	19 (48.7)	4 (10.8)	
Primary school-high school	14 (35.9)	17 (45.9)	
High school diploma and above	6 (15.4)	16 (43.2)	
Residence*			0.02
Rural	9 (23.1)	2 (5.4)	
Urban	30 (76.9)	35 (94.6)	
Family history of cancer*			0.37
Yes	11 (28.2)	14 (37.8)	
No	28 (71.8)	23 (62.2)	
Tobacco smoking**			0.08
Yes	5 (12.8)	4 (10.8)	
No	22 (56.4)	28 (75.7)	
Former user	12 (30.8)	5 (13.5)	
Hookah smoking**			0.9
Yes	2 (5.1)	3 (8.1)	
No	33 (84.6)	31 (83.8)	
Former user	4 (10.3)	3 (8.1)	
Paan consumption **			0.25
Yes	1 (2.6)	1 (2.7)	
No	33 (84.6)	35 (94.6)	
Former user	5 (12.8)	1 (2.7)	
Alcohol consumption**			0.35
Yes	1 (2.6)	0 (0.0)	
No	37 (94.8)	34 (91.9)	
Former user	1 (2.6)	3 (8.1)	
Occupation **			0.15
Worker	16 (41.0)	8 (22.2)	
Officer	2 (5.1)	7 (19.4)	
Homemaker	13 (33.3)	12 (33.3)	
Unemployed or retired	8 (20.5)	9 (25.0)	
Physical activity*			0.02
Yes	13 (33.3)	22 (59.5)	
No	26 (67.7)	15 (40.5)	
Quantitative variable	**Mean ± SD**	**Mean ± SD**	***P* value**
Age (y)***	58.1 ± 10.2	53.5 ± 8.3	0.039
BMI***	24.1 ± 3.5	27.5 ± 2.7	<0.001

* Chi-square test; ** Fisher's exact test; *** Independent *t* test.

to other food groups ($P>0.05$). Eating vegetables, fruits, coffee, nuts, poultry, eggs, salads, and desserts is often considered as healthy dietary pattern.

The number of people with healthy eating patterns in the case group was lower as compared to the control group ($P=0.002$) (Table 3). This was also true for the number of people with an above-median healthy eating pattern ($P=0.008$). However, this was not the case for the two groups with unhealthy eating patterns as there was no significant difference between those with above- and under-median unhealthy eating patterns $P=0.35$) (Table 3). To assess the relationship between the dietary pattern and the risk of HNSCC and determine a borderline between healthy and unhealthy dietary patterns, the variables including dietary pattern, BMI, age, occupation, physical activity, smoking, and educational level were entered into a forward conditional logistic regression model to adjust the effects of other confounding factors. The results are given for the individuals with healthy and unhealthy dietary patterns in Table 4.

According to Table 4 and after adjusting the effect of confounding factors, an unhealthy diet increases the risk of developing head and neck SCC up to 6.55-fold. Moreover, a median unhealthy diet has no connection with the risk of HNSCC. However, an above-median healthy diet offers 13.97 times more protection against cancer. In other words, a healthier diet offers better protection against cancer.

Table 2. Results of factor analysis of the two dietary patterns in the subjects

Dietary pattern	Food group	Loading Factor
Unhealthy dietary pattern (Western dietary pattern)	Fast Food	0.756
	Potato	0.745
	Deserts	0.726
	Viscera meat (offal)	0.721
	Carbonated beverages	0.696
	Refined grains	0.614
	Red meat	0.574
	Soup	0.496
	Pickles	0.403
Healthy dietary pattern	Salads	0.721
	Nuts	0.686
	Vegetables	0.677
	Fruits	0.667
	Beans	0.600
	Eggs	0.473
	Poultry	0.366

Table 3. Frequency of subjects according to dietary pattern and median of healthy and unhealthy scores

Dietary pattern		Case group	Control group	P value
Healthy dietary pattern		11 (31.4)	24 (68.6)	0.002
Unhealthy dietary pattern		24 (68.6)	11 (31.4)	
Healthy score	≤Median	9 (81.8)	8 (33.3)	0.008
	>Median	2 (18.2)	16 (66.7)	
Unhealthy score	≤Median	15 (62.5)	3 (27.3)	0.35
	>Median	9 (37.5)	8 (72.7)	

Assessment of vitamins

The mean serum levels of all three vitamins in the case group were remarkably lower compared to the control subjects (Table 5).

For the purpose of investigating the relationship between the ingestion of some vitamins and HNSCC, the variables of age, BMI, place of residence, educational level, occupation, physical activity, smoking, and serum levels of vitamins A, C, and E were entered into the forward conditional logistic regression model. The final model is presented in Table 6.

Table 4. Logistic regression of association of dietary pattern with head and neck squamous cell carcinoma

Variables	Regression coefficient	Standard error	P value	OR (CI, 95%)
Dietary pattern				
Unhealthy	1.88	0.713	0.008	6.55 (1.62–26.50)
Healthy	0.0			1.00
BMI	-0.655	0.184	<0.001	0.51 (0.362–0.744)
Age	0.83	0.038	0.027	1.08 (1.01–1.16)
Physical activity				
No	2.44	0.866	0.004	11.56 (2.13–62.58)
Yes	0.0			1.00

* Variables of dietary pattern, BMI, physical activity, age, educational level, and place of residence, occupation, smoking were entered into a forward conditional logistic regression model.

Table 5. Serum levels of vitamins A, C and E in the case and control groups

Vitamin	Case group (Mean ± SD)	Control group (Mean ± SD)	P value*
Vitamin A (mg/L)	44.14 ± 9.9	56.13 ± 4.9	0.001
Vitamin C (mg/L)	3.3 ± 8.9	6.4 ± 9.3	0.005
Vitamin E (mg/L)	8.3 ± 5.3	12.5 ± 2.3	0.001

*All comparisons were done by independent *t*-test.

Table 6. Logistic regression of association of serum vitamins levels with neck squamous cell carcinoma

Variables	Regression coefficient	Standard Error	P value	OR* (CI, 95%)
Vitamin C	-0.150	0.086	0.081	0.86 (0.726–1.019)
Vitamin E	-0.184	0.092	0.047	0.832 (0.694–0.998)
BMI	-0.642	0.189	0.001	0.52 (0.36–0.76)
Age	0.079	0.039	0.043	1.082 (1.003-1.168)
Physical activity				
No	2.432	0.844	0.004	11.38 (2.17–59.51)
Yes	0.0			1.00

* Variables of physical activity, BMI, age, educational level, place of residence, occupation, smoking, and serum vitamins levels were entered into a forward conditional logistic regression model.

According to Table 6, increasing the serum levels of vitamins C and E by one unit reduced the risk of developing cancer by 0.14 and 0.17, respectively. Vitamin A was not listed in the table because it did not have any connection with the risk of cancer in the logistic regression model.

Discussion

In this case-control study, we examined dietary patterns and serum levels of vitamins A, C, and E in the HNSCC patients and compared them with the healthy individuals. The main findings were the existence of a significant correlation between serum levels of vitamins C and E and the risk of head and neck SCC. In other words, increasing the serum levels of these vitamins reduced the risk of developing this cancer whereas the association with vitamin A concentration was not significant. In terms of dietary pattern, the risk of development of HNSCC in people with unhealthy eating habits was 6.55 times higher compared to people with healthy eating habits. Furthermore, regarding the degree of healthiness, an above-median healthy eating habit offered up to 14 times more protection than an under-median healthy habit. In other words, a healthier diet leads to better protection against HNSCC. There was also no significant relationship between the degree of diet healthiness and the risk of this malignancy.

The focus in this study was more on the relationship between the dietary pattern and the risk of head and neck SCC than on the individual foods. This was because a dietary pattern, while taking into account the intake of all foods, considers the relationship between dietary components. Therefore, it better reflects the relation between the nutritional behavior of individuals, which provides a comprehensive picture of food and nutrient intake and risk of the diseases.

Fruits and vegetables, salads, nuts, beans, poultry, and eggs were identified as healthy foods in this study, whereas fast food, potato, desserts, red meat, offal, carbonated beverages, refined grains, soups, stews, and pickles were identified as unhealthy foods.

It has been estimated that high intake of vegetables and fruits (>400 g/d) can prevent at least 20% of all cancers. A 2008 study by Freedman et al in the United States found a strong inverse relationship between the intake of fruits and vegetables and the risk of developing HNSCC. The protective effect of vegetables was more than fruits in that study.[1]

In a cohort study on 265,118 Japanese men, Chyou et al found that high intake of green and yellow vegetables reduced the risk of mouth and throat malignancies.[9]

This beneficial effect of fruits and vegetables is basically due to their micronutrients including carotenoids, vitamins A and C, flavonoids, polyphenols, folic acid, fiber, and other antioxidant components.[10,11] In the present study, these two groups were also identified as healthy foods.

The average intake of beans (legumes) in the control group was higher as compared to the case group in this study, though the difference was not significant. Thus, we suggested beans as healthy food. According to some epidemiological studies the consumption of beans is related to a reduced incidence of a number of chronic diseases, including cancers. The specific isoflavonoids found in beans may play an antitumor role against many cancers, including oral cancer.[12] Kingsley et al reported that in the United States, the use of bean protein inhibited the growth of oral cancer cells in vitro.[13]

Eggs were identified as healthy food in our study. The relationship between the consumption of eggs and the risk of developing cancer in different studies is contradictory because method of using egg varies in the societies. For example, in the cohort study by Chyou et al in Japan, a direct relationship was found between egg consumption and the risk of oral cancer, while the cohort study by Kjaerheim et al in Norway implied otherwise.[9,14] A 2004 study by Toporcov et al also found that eating eggs more than three times a week increased the risk of oral cancer.[15]

In this study the average consumption of whole and refined grains in the control group was higher compared to in the case group, although the difference was not significant. When assessing the dietary pattern, whole grains were removed from the model due to lack of correlation with other food groups, whereas refined grains were identified as unhealthy food.

In the cohort study by Chyou et al, rice consumption was directly related to the risk of upper digestive tract cancers while bread consumption was inversely related to developing these cancers.[9]

Moreover, it was reported in the prospective study by Kjaerheim et al in 1998 in Norway that bread consumption is inversely related to the risk of upper digestive tract cancers.[14] The relationship between the consumption of cereals and the risk of oral SCC depends on the degree of refinement of these products, since whole grains are rich in soluble and insoluble fibers as compared to refined grains. Similar to fruits, whole grains also contain micronutrients such as antioxidant vitamins, polyphenols, and lignans. For this reason, the consumption of whole grains is inversely related to the risk of developing such cancers. In contrast, refined grains are absorbed more than whole grains during congestion. This increases glycemic load and thus increases blood insulin levels, which in turn increases IGF-I, a mutagenic stimulus for tumor cells in vitro.[10]

In their cohort study, Kjaerheim et al found an inverse relationship between consumption of meat and developing upper digestive tract cancers.[14] However, in another study by Bravi et al, there was a direct link between red meat consumption and the risk of oral cancer.

This negative effect is probably due to high amounts of cholesterol in the red meat, which are micronutrients associated with oral and throat cancers. Other reasons include the carcinogenic effect of nitrites and N-nitrous compounds, which are abundant in processed meat. Also, the polycyclic amines and aromatic hydrocarbons that are formed during the cooking process of meat can act as mutagens.[7]

Depending on how meat is cooked, the highest risk of cancer is associated with roasted meat, while the lowest risk is associated with cooked and grilled meat.[16] In the present study, red meat was also identified as an unhealthy food.

Some studies, including the studies performed by Chyou et al, Franceschi et al and Toporcov et al have found a direct relationship between consuming soups and the risk of oral and throat cancer. This could be due to the fact that soups were consumed when they were still hot. In addition, high consumption of soups could be a symptom of poor dental condition.[9,15,17] In addition to the reasons mentioned earlier, in the present study, the reason for identifying soups and stews as unhealthy food could be related to their red meat and fat content (one example is a traditional soup popular in Mashhad, Iran), the use of refined grains and the presence of special spices.

Regarding micronutrients in our study, the mean serum levels of vitamin A in patients were noticeably lower compared to the control subjects. However, in logistic regression analysis no significant relationship was found between the levels of vitamin A and the risk of HNSCC after removing the effect of other confounding factors. The study by Maserejian et al in the USA found an inverse relationship between alpha-carotene levels and the risk of precancerous oral lesions in men. They also found a direct relationship between beta-carotene levels and the risk of precancerous oral lesions in men. However, ingestion of vitamin A (from both food and supplements) was not significantly associated to the risk of developing HNSCC, although the results have sometimes been contradictory.[6]

Such a contradictory role has also been reported by several studies. On the one hand, it has been suggested that vitamin A could play a protective role against oral cancer. This hypothesis is based on studies reporting that vitamin A deficiency is linked to the risk of SCC. This hypothesis is also confirmed by the finding that vitamin A causes leukoplakia to regress. On the other hand, an epidemiological study found no connection between continuous intake of vitamin A and the risk of developing HNSCC.[18]

The mean serum levels of vitamin C in the case group in this study were significantly lower than the control group. According to the logistic regression analysis, an increase in serum levels of vitamin C is associated with a decrease in the risk of developing HNSCC. The study by Maserejian et al in the United States indicated that the intake of vitamin C from foods rather than supplements reduces the risk of precancerous oral lesions in men.[6] Bravi and colleagues' study also found that the intake of vitamin C reduces the risk of oral and pharyngeal cancer.[7] This beneficial role of vitamin C in reducing the risk of cancer may be due to its ability to inhibit oxidative stress and reduce the degradation of tumor suppressor genes.[19]

The mean serum levels of vitamin E in the present study were remarkably lower in the case group compared to the controls. Moreover, an inverse relationship was found between the serum levels of vitamin E and the risk of HNSCC after logistic regression analysis. These results are consistent with other studies,[20-23] and confirm the role of this vitamin. It is therefore recommended to consider taking vitamin E as a protective agent in people with other risk factors such as smoking.

This study had some limitations that need to be considered. Similar to other studies conducted through a questionnaire, food frequency assessments could be affected by recall bias. Biochemical measures are more precise, but the concentrations of serum vitamins only reflect recent food intake.

Briefly, a healthy eating pattern reduces the risk of developing HNSCC and contains more fruits, vegetables, beans, poultry, eggs, salads, and nuts and less refined grains, potato, desserts, pickles, fast food, carbonated beverages, red meat, offal, soups, and stews. Even in people with healthy diets, eating healthier food leads to better protection against cancer.

Conclusion

In this study, there were significant differences regarding risk factors of HNSCC in terms of age, educational level, place of residence, physical activity, and BMI. Also, the mean serum levels of vitamins A, C, and E in the control group was higher as compared to the case group, and an inverse relationship was found through logistic regression analysis between increased serum levels of vitamins C and E and the risk of HNSCC. There was no connection between the serum levels of vitamin A and HNSCC. Furthermore, a healthy eating pattern decreases the risk of developing HNSCC.

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Competing Interests

The authors declare that there is no conflict of interest.

Ethical Approval

The study process was carried out after the approval of the protocol of the study by the Ethics Committee of Mashhad University of Medical Sciences (MUMS) with the ethics code of IR.MUMS.sd.REC.1397.41. The participants were enrolled into the study after signing informed consent form. Besides, on this study, no therapeutic intervention was performed. Additionally, in order to keep personal information of the subjects, each of them was given a code.

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Supplementary Files

Supplemental file 1. Food groups used for factor analysis in determination of dietary patterns

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