Association between dietary fatty acids pattern and incidence of oral cancer: A case-control study from Southeast China

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Research

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Abstract

Objective

To investigate the relationship between dietary fatty acid pattern and the risk of oral cancer (OC).

Method

In 446 patients with primary oral cancer and 448 controls, we assessed prediagnosis consumption of 159 food items by food frequency questionnaires completed within 1 week of diagnosis. Fatty acid patterns were identified using principal component analysis. Odds ratio (*OR*) and 95% confidence (*CI*) interval was calculated.

Results

General differences of fatty acid intake were observed between case and control, intake of saturated fatty acids such as C14:0, C16:0, C18:0 are higher in case than control group ($p < 0.001$), intake of monounsaturated fatty acid such as C18:1 is higher in case than control group ($p < 0.001$). We identified a fatty acid pattern which was characterized by saturated fatty acids and it explained 33.2% of the overall variability of the 32 fatty acids. The identified fatty acid pattern scores were positively associated with a higher risk of oral cancer [multivariable-adjusted *OR* comparing extreme quintiles, 3.325 (95% *CI*: 2.222, 4.975); $P_{trend} < 0.001$].

Conclusions

General differences of dietary fatty acids were observed between oral cancer patients and controls. A dietary fatty acids pattern, which was mainly composed of saturated fatty acids were positively correlated with the risk of oral cancer.

Introduction

Oral cancers(OC) is one of the most common cancers in head and neck cancers with nearly 40,000 new cases recognized in China in 2015[1]. According to current statistics from the GLOBOCAN 2018, the incidence and mortality of oral cancers in China in 2018 was 2.0/100,000 and 0.97/100,000 respectively [2]. Commonly recognized etiologic factors of oral carcinoma include smoking, drinking, oral hygiene, HPV, betel quid consumption[3–9]. In addition to the above mentioned traditional risk factors, other environmental exposures such as dietary factors were also reported in recent studies[10–12]. Among dietary factors, role of fatty acids in tumorigenesis has got increased interests.

Fatty acids, including saturated fatty acid (SFA), n-3 and n-6 poly unsaturated fatty acid (PUFA), trans fatty acid(TFA), have been reported associated with the risk of varied types of cancer such as prostate cancer[13, 14], pancreatic cancer[15, 16], colorectal cancer[17, 18], lung cancer[19]. However, reports on the association between fatty acid and head and neck tumors, especially oral cancer, are rare.

Most studies have considered individual fatty acids as separate exposures. However, individual fatty acids tend to be correlated with each other, partially due to shared food sources and metabolic pathways. Humans consume foods consisting of a range of meals with complex mixtures of fatty acids that are probably to be interactive or synergistic[20, 21]. Because of the complexity of diet and highly interrelated nature of dietary exposures, analyses of individual fatty acid and foods often ignore the many potential interactions between components of a diet and disease risk [22]. Hence, in addition to examining individual fatty acids, analyzing fatty acids as sets of patterns could capture these complexities and account for these technical issues, while shedding light on the biological interactions between different fatty acids and their relation with disease risk[23, 24].

Therefore, we performed a case-control study to identify potential dietary fatty acid patterns and elucidate their role in the development in oral cancer.

Materials And Methods

Study design and population

From September 2016 and December 2020, a case-control study was conducted in Fujian province, China. As previously described[25], oral cancer patients were recruited from the First Affiliated Hospital of Fujian Medical University. The inclusion criteria of the patients were as follows: (1) Histologically confirmed primary oral cancer; (2) Chinese Han population and residence in Fujian Province; (3) Age above 18 years old. Patients with second primary, recurrent or metastasized cancer, and previous radiotherapy or chemotherapy were excluded. Control participants were recruited from the health examination center of the same hospital during the same period. Those with history of cancer were excluded. Additionally, we excluded: those who have extreme daily caloric intake (> 4200 Kcal or < 700 Kcal for man; > 3500 Kcal or < 500 Kcal for woman). Finally 446 patients and 448 control participants were admitted to the study.

All participants provided a signed informed consent, and the study protocol was approved by the Institutional Review Board of Fujian Medical University (Approval number: 2011053; Approval date: March 10, 2011) and conducted in accordance with the ethical standards described in the Declaration of Helsinki.

Data Collection

A structured questionnaire was used to collect information through face to face interviews conducted by well-trained interviewers. The questionnaire included socio-demographic characteristics, dietary intake, tobacco smoking and alcohol drinking status, oral hygiene, family history of cancer etc.

Body mass index (BMI) was calculated as weight (in kilograms) divided by the square of the height (in meters). Subjects who had smoked at least 100 cigarettes during their lifetime were considered tobacco

smokers. Educational level was coded as low (lower vocational training or primary school), or high (secondary school and above). Alcohol drinker was defined as consumed at least one drink per week and lasting for more than 6 months continuously[26]. A complete description of the oral hygiene score is available in our previous study[7]. Oral hygiene score = teeth brushing + the number of missing teeth + wearing dentures + regular dental visits + recurrent dental ulceration. The range of oral hygiene score was 0–5, and higher score indicated worse oral hygiene.

Information on habitual dietary intake was gathered using a validated semiquantitative Food Frequency Questionnaire (FFQ) at baseline. The dietary data during 1 year prior to the diagnosis for cases or the year prior to interview for controls were selected. The questionnaire contained 8 broad categories (grains; beans and soy products; vegetables; fruits; animal food; algal fungi and nuts; beverages and soup; fried foods and pickled foods) and 17 sub-categories (grains; beans and soy products; dark vegetables; light color vegetables; purple vegetables; fresh beans; fruits; livestock; poultry; fish; processed meat; red meat; eggs; dairy; algal fungi and nuts; fried foods; pickled foods), and the total number of food items is 159. For each food item, participants were asked how often, on average, over the previous year, they had consumed the food, according to a commonly used unit or portion size. The intake of nutrient and dietary fatty acids in food of each item = the intake of food of each item (g/d) × the content of dietary fatty acids and nutrients in the edible part of the food (100g)/100g. The edible food part, and the content of fatty acids and nutrients reference to 2009 "China Food Composition Tables".

Statistical analysis

Intakes of energy and nutrients were log-transformed and then fatty acids intakes were adjusted for energy intake using the residuals method[27]. Quantitative data were presented as median with inter-quartile range, while qualitative variables were presented as frequency (numbers and percentages). Fatty acids patterns were derived using principal component analysis (PCA) based on 32 fatty acids. Principal components were inferred as representing fatty acid patterns. The pattern matrix from PCA was then used to calculate the scores and categorized into tertiles, and the lowest tertiles was used as the reference. The first principal component was submitted for further analyses to provide potential biological implications of this single combination of fatty acids. This removed the need for subjective decisions about how many components to derive, which matrix rotation method to use, and how to account for multiple testing.

Chi-square tests were used to compare the main characteristics between cases and controls. The distribution of dietary fatty acids was analyzed using Wilcoxon rank sum test. Pearson correlation coefficients were calculated, and a hierarchical cluster tree and heatmap were generated to visually assess correlation between fatty acids[28]. Associations between fatty acids pattern score and intakes of 17 food groups, and macronutrients were assessed by spearman correlation analysis. Fatty acids pattern score was evaluated categorically and continuously in the logistic regression model, and ORs and their 95% CIs were calculated. In addition, fatty acids pattern score was evaluated continuously by restricted cubic splines.

All analyses were performed using R software (version 4.0.3), with 2-tailed *p* values < 0.05 considered as statistically significant.

Result

Characteristics of the study population

The baseline characteristics and main lifestyle factors for cases and controls are shown in **Table 1**. Compared with controls, cases were more likely to have a higher proportion of tobacco, alcohol consumption, tumor history and worse oral hygiene. In addition, the distribution of gender, education level, BMI, residence was significantly different between the case and control group ($p<0.05$). General differences of fatty acid intake were observed between case and control, intake of SFA such as C14:0, C16:0, C18:0 are higher in case than control group ($p<0.001$), intake of monounsaturated fatty acids(MUFA) such as C18:1 is higher in case than control group ($p<0.001$). The distribution of dietary fatty acids between the case and control are shown in **Supplement Figure 1**.

Table1 Characteristics of the case(n=446) and control(n=448)

Variable	Case	Control	<i>P</i>
Age			<0.001
<49	94(21.1%)	210(46.9%)	
≥49	352(78.9%)	238(53.1%)	
Gender			0.002
Male	258(57.8%)	213(47.5%)	
Female	188(42.2%)	235(52.2%)	
Education			<0.001
low	77(17.3%)	204(45.5%)	
high	369(82.7%)	244(54.5%)	
Marital status			0.699
Married	408(91.5%)	413(92.2%)	
Unmarried and Others	38(8.5%)	35(7.8%)	
BMI			0.024
<18.5	39(8.7%)	19(4.2%)	
18.5≤	284(63.7%)	297(66.3%)	
≥24	123(27.6%)	132(29.5%)	
Residence			0.008
Country	258(57.8%)	298(66.5%)	
City	188(42.2%)	150(33.5%)	
Occupation			0.231
Farmers and Workers	148(33.2%)	132(29.5%)	
Others	298(66.8%)	316(66.8%)	
Tobacco smoking			0.001
No	259(58.1%)	307(68.5%)	
Yes	187(41.9%)	141(31.5%)	
Alcohol drinking			<0.001
No	294(65.9%)	349(77.9%)	
Yes	152(34.1%)	99(22.1%)	

Tumor history	<0.001	
No	374(83.9%)	413(92.2%)
Yes	72(16.1%)	35(7.8%)
Oral hygiene score	<0.001	
0-2	79(17.7%)	167(37.3%)
3-5	257(57.6%)	248(55.4%)
6-8	110(24.7%)	33(7.4%)

Identification of fatty acid patterns

By applying PCA, we found 4 principal components which could explain 75.7% of the variance of the dietary fatty acid consumption, as the scree plot was shown in **Figure 1**. And we chose the first principal component because it explained 33.2% of the variation of 32 fatty acids. The components is characterized by saturated fatty acid (the “SFA” pattern), which mainly included octanoic acid (C8:0), undecanoic acid (C11:0), lauric acid (C12:0), myristic acid (C14:0), pentacarbonate (C15:0), and (C16:1) in MUFA. Factor loadings of the individual fatty acids in the “SFA” patterns are shown in **Table 2**. Additionally, correlation analysis among individual fatty acids were performed, and heatmap were derived using correlation coefficients among individual fatty acids. A similar pattern was identified in cluster analysis, as fatty acids adjacent in the tree had similar loading values (**Figure 1**).

Table 2 Factor loading of the individual fatty acids in the FA pattern

Type of fatty acid	Name	Loading of the FA pattern *
Saturated fatty acids		
6:0	Caproic	0.334
8:0	Caprylic	0.731
10:0	Capric	0.596
11:0	Undecanoic	0.702
12:0	Lauric	0.783
13:0	Tridecanoic	0.618
14:0	Myristic	0.848
15:0	Pentadecanoic	0.720
16:0	Palmitic	0.787
17:0	Heptadecanoic	0.525
18:0	Stearic	0.792
19:0	Nonadecanoic	0.586
20:0	Arachidic	0.559
22:0	Behenic	0.037
Monounsaturated fatty acids		
14:1	Myristoleic	0.548
15:1	Pentadecenoic	0.575
16:1	Palmitoleic	0.871
17:1	Heptadecenoic	0.449
18:1	Oleic	0.588
20:1	Eicosenoic	0.615
22:1	Erucic	-0.083
Polyunsaturated fatty acids		
16:2	Hexadecadienoic	0.577
18:2	Linoleic	0.210
18:3	Octadecadienoic	0.443
20:2	Eicosadicnoic	0.695

20:3	Eicosatrienoic	0.326
20:4	Arachidonic	0.769
20:5	Eicosapentaenoic	0.387
22:3	Docosatrienoic	0.319
22:4	Docosatetraenoic	0.36
22:5	Docosapentaenoic	0.365
22:6	Docosahexaenoic	0.369

* We analyzed only the principal component 1 with the greatest explanatory degree and listed its factor load. This principal component explained 33.2% of the variation in all 32 fatty acids.

Additionally, we evaluated the correlations between the “SFA” pattern with intakes of nutrients and food groups, results of which was shown in **Supplement Table 2**. The “SFA” pattern was positively associated with intake of protein, total fat, ($r=0.207$, 0.368 respectively, all $p<0.001$), but negatively related to fiber ($r=-0.185$, $P<0.001$). As for food groups, the “SFA” pattern was positively correlated to the intakes of fish, eggs, dairy and red meat ($r=0.372$, 0.320 , 0.283 , 0.282 , respectively, all $p<0.05$), but negatively correlated with grain and vegetables ($r=-0.403$, -0.100 , respectively, all $p<0.05$).

Association of the “SFA” pattern with risk of oral cancer

Table 3 presents the *OR* and 95% *CI* for oral cancer across the tertile categories for the “SFA” pattern. A positive association between the “SFA” pattern and risk of oral cancer was observed. In the crude model, those in the highest tertile of the “SFA” pattern had an increased risk of oral cancer compared with the lowest tertile, with a significant linear trend ($OR=3.054$; 95% *CI*: 2.184–4.265; $P_{trend}<0.004$). In model 1, after adjusting for gender, age, marital status, residence, BMI, occupation and tumor history, the individuals in the highest tertile of the “SFA” pattern tended to have higher odds for oral cancer ($OR=2.874$; 95% *CI*: 1.964–4.205; $P_{trend}<0.001$) compared with those in the lowest tertile. In model 2, this result remained significant after further adjustment for lifestyle factors, including tobacco smoking, alcohol drinking and oral hygiene score ($OR=3.325$; 95% *CI*: 2.222–4.975; $P_{trend}<0.001$). Moreover, this association was similarly observed when we treated the “SFA” pattern score as a continuous variable in the crude model, model 1 and model 2 ($OR=1.697$, 95% *CI*: 1.465–1.965; $OR=1.652$, 95% *CI*: 1.402–1.947; $OR=1.772$, 95% *CI*: 1.490–2.106).

Table 3 The relation between the “SFA” pattern and oral cancer risk

Model	Tertiles of the “SFA” pattern score*			P_{trend}	“SFA” pattern score†
	I	II	III		
case/control(n)	138/196	152/183	144/190		
crude	1.0(reference)	1.431(1.033-1.984)	3.054(2.187-4.265)	□ 0.001	1.697(1.465-1.965)
model1#	1.0(reference)	1.617(1.115-2.344)	2.874(1.964-4.205)	□ 0.001	1.652(1.402-1.947)
model2#	1.0(reference)	1.830(1.241-2.698)	3.325(2.222-4.975)	□ 0.001	1.772(1.490-2.106)

*Three categories were obtained by tertiles of the fatty acid pattern score .Each participant was assigned a fatty acid pattern score.

#Multivariable-adjusted Logistic regression models. Mode I adjusted for demographic characteristics: gender, age, marital status, residence, BMI, tumor, occupation, education.

Model 2 adjusted for demographic characteristics and tobacco smoking, drinking, oral hygiene score.

† Fatty acid pattern score treated as a continuous variable in the crude and two adjusted models

Furthermore, we visualized the association between the “SFA” pattern score and the risk of oral cancer using restricted cubic splines. The risk of oral cancer increased with the increase of “SFA” pattern score. However, the risk of oral cancer was relatively flat until around -0.68 of “SFA” pattern scores and then started to increase rapidly afterwards ($P_{non-linearity}=0.097$) (**Figure 2**).

Stratification analysis between the “SFA” pattern and oral cancer risk

Associations between the “SFA” pattern and oral cancer risk were stratified by demographic characteristics and life style exposure factors, results of which was shown in **Figure 3**. Positive association between oral cancer risk and the “SFA” pattern was observed in all subgroups except for the lower oral hygiene score group. There was no evidence of effect modification by sex, tobacco smoking, alcohol drinking, or oral hygiene score ($P_{heterogeneity}>0.1$). The association varied across age (**Figure 3**; $I^2=87.8\%$, $P_{heterogeneity}=0.004$). The interaction was further tested by multiplying the “SFA” pattern score with age, and a multiplicative interaction was observed ($P_{interaction} < 0.001$).

Discussion

This hospital-based case-control study was conducted in Southeast China to illuminate the association between dietary fatty acids pattern and incidence of oral cancer. In the present study, we observed that the fatty acids intake varied widely between oral cancer patients and healthy controls. A “SFA” pattern

was identified using the principal component analysis, and the “SFA” pattern was positively associated with risk of oral cancer.

Dietary fatty acids, especially for saturated fatty acid has long been reported to be associated with risk of cancers. Kim et al. performed a cross-sectional study, results of which showed that risk of colorectal cancer increased with higher SFA intake in Korean adults[29]. Several epidemiological studies have suggested increased consumption of SFA correlates with increased risk of prostate cancer and may be directly related to risk of biochemical recurrence and cancer progression[30–32]. However, there are also evidence supporting that dietary SFA are not associated with cancer risk or even negatively associated with cancer risk. Cao et al. performed a meta-analysis of prospective cohort studies, results of which showed that highest versus lowest levels of dietary SFA were not associated with the risk of breast cancer[33]. A meta-analysis of prospective cohort studies did not show an association between SFAs intake and colon cancer risk[34]. No associations were observed in the Nurses’ Health Study cohort of dietary SFAs and epithelial ovarian cancer risk[35]. In the European Prospective Investigation into Cancer and Nutrition(EPIC), Aglago et al. found an inverse association between dietary total SFA and colorectal cancer[36]. To the best of our knowledge, reports of the association between dietary SFA and oral cancer are rare. A fatty acid pattern characterized by SFA was identified in our study and was found to be positively associated with oral cancer risk results of which was consist with some previous studies.

The major food sources of SFAs are of animal origin, including meat and dairy products. In fact, the association between dietary fatty acids and cancer risk may depend on types and food sources of fatty acids[37, 38]. When we try to verify the identified “SFA” pattern using the correlation between the “SFA” pattern score with intakes of nutrients and food groups. We found that the intake of red meat and dairy was significantly higher in individuals with higher dietary “SFA” pattern scores. No studies have been conducted on the relationship between dietary saturated fatty acids driven from food sources and oral cancer. A study in Italy suggested that animal-derived foods such as dairy products and red meat could increase the risk of oral cancer[39]. Epidemiological evidence from Greece also indicates that meat products are positively associated with the risk of oral cancer[40]. In addition to the recognized etiologic factors in oral cancer, the relationship between food groups and “SFA” patterns (and the way they interact with “SFA” pattern) could affect the risk of oral cancer in our study. It is unclear whether the association between “SFA” pattern and oral cancer in our study are attributable to its food source or to unmeasured confounding remains unclear for now and warrants investigation.

In further analysis, by stratifying for demographic characteristics and life style exposure factors, we found that age may alter the relationship between the “SFA” pattern and oral cancer risk. Many previous studies have shown that age has an effect on cancer progression[41, 42]. In the present study, the “SFA” pattern were positively associated with oral cancer risk in both age subgroups, but the association was stronger in age groups younger than 49 years. Compared to MUFA and PUFA, SFA are more likely to come from red meat, processed meat and dairy products. Red meat is a primary source of the total amount of SFA, which has been identified as a dietary risk factor closely associated with various cancers [43, 44]. In addition to red meat, excessive intake of dairy products could also contribute to cancer risks [45]. So

different food sources of SFAs may modulate the effect of SFAs on oral cancer risk. In our study, we found that compare with the older age group, the “SFA” pattern was more strongly associated with dairy products in the younger age group (**Supplement** Table 3). The results indicating that younger age groups may consume more saturated fatty acids from dairy products, such as cakes, cheese and ice cream bars, which may be positively associated with risk of oral cancer.

There are several limitations for this study. Firstly, this study was observational. Whereas we adjusted for a range of major oral cancer risk factors, residual confounding from imprecisely measured or unmeasured factors may be present. Secondly, this is a case-control study, since there is a long latency period which means that exposure data must be available for a period of several decades or more in order to identify true overall risks. The dietary fatty acids data was not collected prospectively, so dietary patterns may change over the long latency period, which may result potential bias. Lastly, the sample size of this study is limited and is collected from a single center, prospective study with large scale sample size is needed to verify the current findings.

Conclusion

In conclusion, the dietary fatty acid exposure based study provides support for a possible positive relationship between saturated fatty acids pattern and risk of oral cancer. In addition, potential interactions was found between saturated fatty acids pattern and age in oral cancer risk. Our findings support previous findings that there is suggestive evidence of a link between dietary pattern with head and neck cancer, but go beyond this by highlighting the role of specific fatty acid pattern in oral cancer susceptibility.

Abbreviations

OC: Oral cancer; SFA: saturated fatty acid; MUFA: monounsaturated fatty acid; PUFA: poly unsaturated fatty acid; FFA: trans fatty acid; FFQ: Food Frequency Questionnaire; PCA: principal component analysis; BMI: Body mass index; OR: Odds ratio; CI: confidence interval

Declarations

Ethics approval and consent to participate

All the participants gave written informed consent to participate in the study. The present study was conducted in terms of the principles of the revised Declaration of Helsinki, which is a statement of ethical principles that directs physicians and other participants in medical research involving human subjects. The participants were assured about their anonymity and confidentiality of their information. Moreover, the study was approved by the Institutional Review Board of Fujian Medical University (Approval number: 2011053; Approval date: March 10, 2011).

Consent for publication

The Institutional Review Board of Fujian Medical University.

Availability of data and materials

Available from authors on reasonable request.

Competing interests

All authors report no conflict of interest in regard to this work.

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Authors' contributions Conceptualization

Yi Fan contributed to study design, compiled the data, analyzed the data, assisted in interpretation, and wrote the paper; Qing Chen contributed to study design, assisted in interpretation, and critically reviewed drafts of the paper; Sijie Wang contributed to study design, assisted in interpretation, and critically reviewed drafts of the paper; Yu Qiu conceived the study, contributed to study design, assisted in interpretation, and critically reviewed drafts of the paper. All authors have read and approved the manuscript.

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Supplementary

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Figures

Figure 2

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Figure 3

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