International Dental & Medical Journal of Advanced Research (2020), 6, 1–5

META-ANALYSIS

Influence of diet on oropharyngeal cancer: A meta-analysis

Alberto Rodriguez-Archilla and Marta Calderer-Ortiz

Department of Stomatology, Oral Medicine Unit, Faculty of Dentistry, University of Granada, Colegio Maximo, s/n. Campus de Cartuja, Granada 18071, Spain

Keywords:
Case–control studies, Diet, Food, Mouth neoplasms, Risk factors

Correspondence:
Alberto Rodriguez-Archilla, Department of Stomatology, Oral Medicine Unit, Faculty of Dentistry, University of Granada, Colegio Maximo, s/n. Campus de Cartuja, Granada 18071, Spain. Phone: +34-958-244-085.
E-mail: alberodr@ugr.es

Received 12 April 2020;
Accepted 05 July 2020

doi:10.15713/ins.idmjar.110

Abstract

Background: The main risk factors related to oropharyngeal cancer (OFC) are tobacco and/or alcohol consumption, infectious agents, especially human papillomavirus, and others like dietary factors. The high intake of fruits, especially citrus fruit, and vegetables protects against OFC, while the consumption of processed meat and animal fats increases this risk.

Aim: This study aims to assess the possible influence of the diet on the OFC risk.

Methodology: A search for articles on OFC and diet was performed in the following electronic databases: PubMed (MEDLINE, Cochrane Library), Web of Science (WoS), and Spanish Medical Index (IME). From 125 potentially eligible articles, 111 were excluded for several reasons: Articles without full-text availability (45), studies with a sample size fewer than 100 subjects (16), studies in tumors with a location other than oral cavity and pharynx (11), studies carried out on patients with potentially malignant disorders (4), and studies without usable data (35). Finally, 14 studies were included in this meta-analysis. The data were analyzed using statistical software RevMan 5.3 (The Cochrane Collaboration, Oxford, UK). For dichotomous outcomes, the estimates of effects of an intervention were expressed as odds ratio (OR) using the Mantel-Haenszel (M-H) method with 95% confidence intervals.

Results: High consumption of the following foods reduced the probability of OFC: Vegetables (49%, $P < 0.001$), fruits (47%, $P < 0.001$), carrots (34%, $P < 0.01$), and pulses (13%, $P = 0.02$), but not significantly for fish (11%, $P = 0.39$) and dairy products (8%, $P = 0.62$). On the contrary, there was an increased risk of OFC with the consumption of bread (OR: 1.42, $P < 0.01$) or meat (OR: 1.36, $P < 0.01$), but not significantly for eggs (OR: 1.50, $P = 0.10$), pasta (OR: 1.24, $P = 0.44$), potatoes (OR: 1.12, $P = 0.44$), and cheese (OR: 1.12, P=0.61).

Conclusions: The consumption of vegetables, fruits, and pulses was foods with a protective effect against OFC.

Clinical significance: Dietary changes toward a healthier diet are an effective measure to prevent OFC.

Introduction

Oropharyngeal cancer (OFC) is the sixth most frequent tumor in the world, being responsible for approximately 3.5% of cancer deaths. The main risk factors related to this cancer are the consumption of tobacco and/or alcohol and infectious agents such as the human papillomavirus (HPV) in populations under 50 years of age.[1] Other potential factors such as chronic trauma or dietary factors have also been related to OFC. Numerous epidemiological studies revealed an inverse association between the intake of fruits and vegetables and OFC risk. The beneficial effect of vegetables and fruits has been attributed to various micronutrients, such as flavonoids, polyphenols, or fibers, with favorable effects on this cancer risk. These foods develop antioxidant effects, bind to carcinogens, and dilute them in the digestive tract. Furthermore, more frequent consumption of fruits and vegetables could be an indicator of a more affluent and balanced diet.[2]

Various epidemiological studies have found that high intake of fruits, especially citrus, and vegetables protects against OFC. However, studies of the effect of diet on OFC have reported conflicting results. Some observational studies have shown a protective effect with the consumption of some of them, especially

fruits and vegetables, while others have not shown this benefit. It remains to be clarified whether this benefit could vary with the different types and preparations, for example, cooked compared to raw foods.[3] The diet rich in fruits and vegetables protects against OFC and other cancer types. High consumption of fruits and vegetables also has protective effects against cancer of the esophagus, breast, prostate, colon, bladder, and lung. High dietary fiber intake is protective against colon cancer. In contrast, high consumption of red or processed meat is a risk factor for colon cancer, lung cancer, pancreatic cancer, stomach cancer, or prostate cancer. Moreover, a high intake of dairy products has been associated with an increased risk of developing prostate cancer and ovarian cancer. However, it has not been shown that the use of dietary supplements in the absence of nutritional deficiencies confers the same benefits as the regular consumption of fruits and vegetables, so they should never be used as substitutes for these foods.[4]

The purpose of this study was to assess the possible influence of diet on the risk of OFC.

Methodology

A search of case–control studies on diet and OFC was performed in the following databases: PubMed (MEDLINE, Cochrane Library), WoS, and the Science Information and Documentation database in Spain (InDICEs-CSIC) that include the Spanish Medical Index (IME). Studies evaluation was carried out by two reviewers (A.R.A. and M.C.O.) independently. After, they jointly agreed on the articles to include in this study. Search strategies were developed for each database with a combination of terms from Medical Subject Headings and free text. The search terms were as follows: "Mouth neoplasms," "diet," "case control studies," "oral cancer." After this initial search, 222 articles were found (97 in PubMed, 109 in WoS, and 16 in IME) between the years 1973 and 2020, 97 of them duplicates for having the same title and abstract, which left 125 potentially eligible articles. Exclusion criteria were as follows: (a) Articles without full-text availability (n = 45), (b) studies with sample sizes of <100 subjects (n = 16), (c) studies in non-OFC (salivary glands, esophagus, etc.) (n = 11), (d) studies carried out on patients with potentially malignant disorders (n = 4), and (e) studies with non-usable data (n = 35). After applying these criteria, 14 studies were included in this meta-analysis [Figure 1].

Statistical analysis

For the meta-analysis, data were processed with the RevMan 5.3 program (The Cochrane Collaboration, Oxford, UK). For dichotomous variables, the odds ratio (OR) with the Mantel-Haenszel (M-H) Chi-square formula and a 95% confidence interval (95% CI) was used. Heterogeneity was determined according to P values and the Higgins statistic (I^2). In cases of high heterogeneity, the random effects model was applied. $P < 0.05$ was considered as the minimum level of significance.

Results

Table 1 summarizes the characteristics of the study groups and the nutritional parameters considered in the 14 studies included in the meta-analysis.[5-18] The effect of a high intake of different foods on the OFC risk is shown in Table 2.

Twelve studies[5-8,11-18] considered the high consumption of vegetables, finding 49% reduction in the risk of OFC in subjects with an important vegetable intake, finding a highly significant statistical association (OR = 0.51, 95% CI: 0.41 to 0.65, $P < 0.001$).

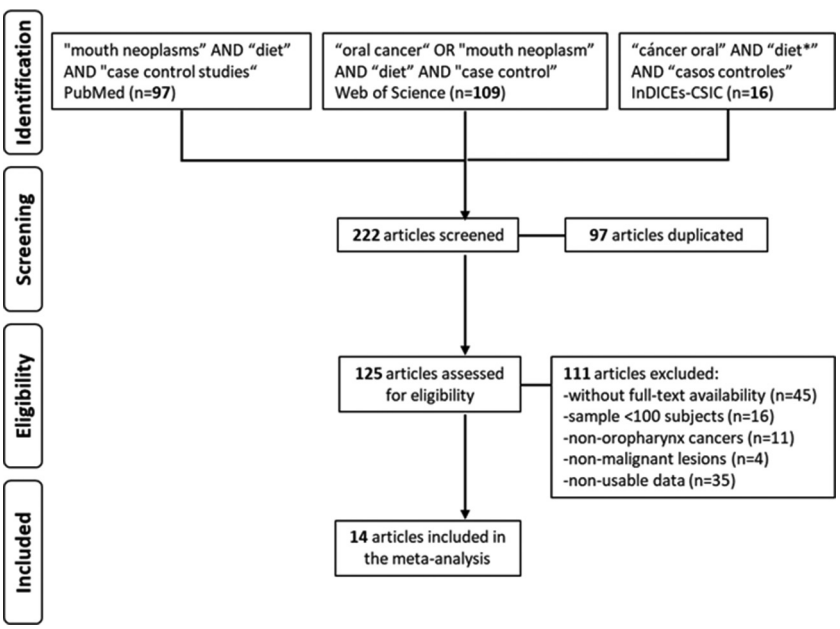

Figure 1: Study flow diagram

Table 1: Description of the 14 studies included in this meta-analysis

First author (year)	Country	OFC patients	Hospital-based controls	Food analyzed
Franceschi *et al.* (1991)[5]	Italy	*n*=302 (266 M, 36 F; X=59 yr)	*n*=699 (549 M, 150 F; X=58 yr)	Meat, fruits, eggs, dairy, potatoes, pasta, fish, cheese, vegetables.
La Vecchia *et al.* (1991)[6]	Italy	*n*=105 (89 M, 16 F; X=56 yr)	*n*=1169 (875 M, 294 F; X=55 yr)	Meat, fruits, eggs, dairy, pasta, fish, cheese, vegetables.
Oreggia *et al.* (1991)[7]	Uruguay	*n*=57 (57 M, 0 F)	*n*=353 (353 M, 0 F)	Meat, fruits, vegetables.
Fioretti *et al.* (1999)[8]	Italy	*n*=42 (10 M, 32 F; X=62 yr)	*n*=864 (442 M, 422 F; X=57 yr)	Fruits, dairy, pulses, fish, cheese, vegetables, carrots.
Rodriguez *et al.* (2004)[9]	Italy	*n*=137 (113 M, 24 F; X=42 yr)	*n*=298 (226 M, 72 F; X=42 yr)	Fruits, carrots.
Galeone *et al.* (2005)[10]	Italy	*n*=634 (634 M, 0 F; X=57 yr)	*n*=1252 (1252 F, 0 F; X=57 yr)	Meat, eggs, potatoes, fish.
Kreimer *et al.* (2006)[11]	USA	*n*=1670	*n*=1732	Meat, fruits, dairy, pulses, fish, cheese, vegetables.
Suzuki *et al.* (2006)[12]	Japan	*n*=385 (302 M, 83 F)	*n*=1925 (1510 M, 415 F)	Fruits, vegetables, carrots.
Asakage *et al.* (2007)[13]	Japan	*n*=96 (96 M, 0 F)	*n*=642 (642 M, 0 F)	Fruits, vegetables.
Garavello *et al.* (2008)[14]	Italy	*n*=805 (659 M, 146 F; X=58 yr)	*n*=2081 (1302 M, 779 F; X=58 yr)	Fruits, vegetables.
Toporcov *et al.* (2012)[15]	Brazil	*n*=296 (230 M, 66 F)	*n*=296 (230 M, 66 F)	Meat, fruits, eggs, dairy, fish, cheese, vegetables.
Bezerra *et al.* (2017)[16]	Brazil	*n*=133 (85 M, 48 F)	*n*=532 (340 M, 192 F)	Meat, fruits, eggs, pasta, potatoes, vegetables.
Gupta *et al.* (2017)[17]	Australia	*n*=187 (130 M, 57 F; X=56 yr)	*n*=240 (161 M, 79 F; X=58 yr)	Meat, fruits, dairy, fish, vegetables.
Chen *et al.* (2017)[18]	China	*n*=930 (588 M, 342 F)	*n*=2667 (1689 M, 978 F)	Meat, fruits, vegetables, eggs, dairy, pulses, fish, seafood.

OFC: Oropharyngeal cancer, *n*: Number of subjects, M: Males, F: Females, X: Mean age, yr: Years

Table 2: Influence of high intake of different foods on the risk of oropharyngeal cancer

Foods	*n*	OFC (%)	Cont. (%)	OR	[95% CI]	I^2 (%)	*P*-value
Vegetables[5-8,11-18]	12	35.3	44.7	0.51	[0.41–0.65]	82	<0.001*
Fruits[5-9,11-18]	13	23.2	37.5	0.53	[0.41–0.68]	88	<0.001*
Carrots[8,9,12]	3	13.5	19.6	0.66	[0.50–0.88]	0	0.04*
Pulses[8,11,18]	3	33.4	44.2	0.87	[0.77–0.98]	15	0.02*
Meat[5-7,10,11,15-18]	9	32.5	29.3	1.36	[1.10–1.68]	78	<0.01*
Bread[5,16]	2	36.9	30.1	1.42	[1.12–1.80]	0	<0.01*
Eggs[5,6,10,15,16,18]	6	37.5	37.2	1.50	[0.92–2.45]	95	0.10
Fish[5,6,8,10,11,15,17,18]	8	23.8	30.4	0.89	[0.69–1.16]	81	0.39
Dairy[5,6,8,11,15,17,18]	7	25.1	31.5	0.92	[0.66–1.28]	88	0.62
Cheese[5,6,8,11,15]	5	18.9	24.3	1.12	[0.72–1.74]	86	0.61
Potatoes[5,10,16]	3	36.7	34.3	1.12	[0.84–1.51]	62	0.44
Pasta[5,6,16]	3	35.8	25.1	1.24	[0.72–2.14]	81	0.44

n: Number of studies, OFC: Oropharyngeal cancer patients, Cont.: Controls, OR: Odds ratio, [95% CI]: 95% confidence interval, I^2: Higgins statistic for heterogeneity, *Statistically significant

Thirteen studies[5-9,11-18] evaluated the high consumption of fruits, observing a reduction in the risk of OFC of 47% in the subjects who ate a lot of fruit, also with a highly significant statistical relationship (OR = 0.53, 95% CI: 0.41–0.68, $P < 0.001$).

Regarding the high consumption of carrots, three studies[8,9,12] concluded that the high consumption of carrots represented 44% reduction in the risk of OFC. After statistical analysis, significant differences were found (OR = 0.66, 95% CI: 0.50–0.88, $P = 0.04$).

Other three studies[8,11,18] considered the high consumption of pulses. Patients with high consumption of pulses reduced their risk of OFC by 13%, with a statistically significant association (OR = 0.87, 95% CI: 0.77–0.98, $P = 0.02$).

Concerning to the high consumption of meat, nine studies[5-7,10,11,15-18] verified that the high meat consumption increased the probability of OFC by 1.36 times, finding statistically very significant differences (OR = 1.36, 95% CI: 1.10–1.68, $P < 0.01$).

Similarly, two studies[5,16] analyzed the possible risk of OFC associated with high consumption of bread, observing an increase in the risk of 1.42 times, with a statistically very significant association (OR = 1.42, 95% CI: 1.12–1.80, $P < 0.01$).

Six studies[5,6,10,15,16,18] found that high egg consumption had no relevant impact on OFC risk, and no statistically significant relationship was observed (OR = 1.50, 95% CI: 0.92–2.45, $P = 0.10$).

Eight studies[5,6,8,10,11,15,17,18] looked at the high consumption of fish, finding 11% reduction in the risk of OFC, although without reaching statistical significance (OR = 0.89, 95% CI: 0.69–1.16, $P = 0.39$). Seven studies[5,6,8,11,15,17,18] found that high consumption of dairy products reduced this risk by 8%, although without a statistically significant association (OR = 0.92, 95% CI: 0.66–1.28, $P = 0.62$).

OFC patients had a higher consumption of other foods such as cheese,[5,6,8,11,15] potatoes,[5,10,16] or pasta[5,6,16] than controls without the disease. Although there was an increased risk of OFC, no statistically significant differences were found ($P > 0.05$ in all cases).

Discussion

In the present meta-analysis on the possible influence of diet on OFC, data from 14 studies have been included.

Only between 5% and 10% of cancer cases have a genetic basis; while the remaining 90–95% are associated with environmental agents and other factors such as sedentary lifestyles, body mass index, health habits, and a poor quality diet with nutritional deficiencies or food shortage.[16]

The greatest risk factors for OFC are tobacco and alcohol consumption, with a dose-dependent relationship in the case of tobacco and having a multiplicative effect when both harmful habits act together. In addition to these two factors, infection with HPV is especially relevant.[19]

This study has focused on the analysis of another risk factor, the diet, which, in some studies, is considered independent of the previously mentioned factors. For some, dietary factors could directly intervene in the development of cancer through their carcinogenic metabolites; while others maintain that tobacco and alcohol can favor exposure of the oral cavity and pharynx to other carcinogens present in the diet.[8]

In the present study, the high intake of vegetables (OR: 0.51), fruits (OR: 0.53), carrots (OR: 0.66), or pulses (OR: 0.87) had a significant protective effect about OFC. The high consumption of fish (OR: 0.89) or dairy (OR: 0.92) also had a protective effect, although it did not reach statistical significance.

Various studies[6-9,15-17] highlighted the protective effect of these foods (vegetables, fruits, and cereals), relating it to the mechanical cleaning action they exert on the oral cavity, as well as the beneficial effect of substances sensitive to temperature like Vitamin C when these foods are eaten raw.[5] Although they are usually attributed a protective role, they could be considered as a non-specific indicator of a more oriented attitude toward a healthier lifestyle,[8] with good habits and a varied, balanced diet that implies good nutritional status.[14]

The anti-cancer effect of fresh fruits and vegetables on OFC can be attributed to its content of carotenoids, Vitamin A, Vitamin C, Vitamin E, folic acid, flavonoids, indoles, isothiocyanates, protease inhibitors, plant sterols, allium compounds, selenium, dietary fiber, and other antioxidants.[18] Furthermore, vegetables are an important source of glucosinolates, whose main degradation products (isothiocyanates and indoles) have been shown to have anti-cancer activity, thank to their antioxidant, antimutagenic, and antiproliferative properties.[17]

Folates are crucial for normal DNA synthesis and repair, and their deficiency can increase OFC risk by inducing an imbalance in DNA precursors. In particular, the decreased absorption of folic acid may also be due to a high intake of alcohol.[11] These same authors[11] maintain that the consumption of these foods would only have a beneficial effect against OFC in smokers and/or habitual drinkers, since some of its components, such as β-carotenes and Vitamins C and E, are capable of neutralizing reactive oxygen radicals that are increased in this population.[12]

Fish contain polyunsaturated fatty acids, especially omega-3, mineral salts, and proteins that could inhibit tumor progression through its anti-inflammatory effects and the inhibition of reactive oxygen species.[18] The omega-3 fatty acid is incorporated into cell membranes and influences various biological responses, such as suppression of neoplastic transformation, inhibition of cell growth, activating the immune system and inflammation, apoptosis, and antiangiogenesis.[11] The absence of a significant association between fish consumption and its possible protective effect on OFC could be due to several facts. Although fish are an important source of highly beneficial omega-3 fatty acids, it can also contain heterocyclic amines, which are potentially carcinogenic substances, especially when cooked at high temperatures.[15]

The role of dairy in carcinogenesis is controversial. Although milk contains animal fat, it is also rich in other compounds such as calcium, Vitamins D and A, or linoleic acid that have anti-cancer properties. Furthermore, cow's milk contains lactoferrin, which could act inducing apoptosis, inhibiting angiogenesis, and modulating the enzymatic capacity of carcinogens. Bovine lactoferrin inhibits processes such as oxidative DNA damage, cancer activation, cell proliferation and invasion, and angiogenesis, mechanisms directly involved in the appearance of OFC.[15]

In this study, the high intake of meat (OR: 1.36) or bread (OR: 1.42) behaved as a significant risk factor for OFC. High consumption of eggs (OR: 1.50), pasta (OR: 1.24), cheese (OR: 1.12), or potatoes (OR: 1.12) was also risk factors but not statistically significant.

Eating meat, especially red meat, is considered a risk factor for OFC.[15] Meats are foods with high protein content, rich in saturated fats in addition to other harmful substances such as nitrites, genotoxic heterocyclic amines,[10] and polycyclic aromatic hydrocarbons that increase the level of free radicals or react with DNA.[16] Lipids of animal origin can alter the composition of cell membranes, affecting their integrity and favoring the absorption of carcinogens from other foods.[11]

Regarding bread, few studies have analyzed the influence of its consumption on OFC risk and the results are contradictory. For some, it has no influence;[16] while for others, they carry some risk due to their high content of refined carbohydrates.[5]

This study has some limitations. Other foods such as spicy foods, hot foods (soups),[16] or hot drinks (coffee or tea) could not be evaluated.[7,17] These hot foods could cause recurrent thermal damage to the lining of the oral cavity. Furthermore, long-term exposure to methylxanthines can also negatively affect the anti-cancer action of saliva.[17]

Other important parameters possibly related to the risk of OFC such as the type of meat or fish, the way of preparing food (raw, cooked, fried, smoked, etc.), the type of oil (olive, sunflower, soybean, palm, coconut, etc.) or butter used for cooking, the temperature (>150°C), or the time (>2 min) when cooking.[10]

The high heterogeneity observed in some analyzes requires a careful interpretation of the results of this meta-analysis. Differences between the different included studies may be due to the design, the methods used for both collection and data analysis, or the characteristics of the study populations.

Conclusions

In this meta-analysis, high consumption of the following foods reduced the probability of OFC: Vegetables, fruits, carrots, or pulses, but not significantly for fish or dairy. On the other hand, there was an increased risk of OFC with the consumption of bread or meat, but not significantly for eggs, pasta, potatoes, or cheese.

Author Contribution

The two authors equally contributed to the manuscript.

Conflicts of Interest

None.

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, *et al*. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359-86.
2. Lucenteforte E, Garavello W, Bosetti C, La Vecchia C. Dietary factors and oral and pharyngeal cancer risk. Oral Oncol 2009;45:461-7.
3. Pavia M, Pileggi C, Nobile CG, Angelillo IF. Association between fruit and vegetable consumption and oral cancer: A meta-analysis of observational studies. Am J Clin Nutr 2006;83:1126-34.
4. Chainani-Wu N, Epstein J, Touger-Decker R. Diet and prevention of oral cancer: Strategies for clinical practice. J Am Dent Assoc 2011;142:166-9.
5. Franceschi S, Bidoli E, Barón AE, Barra S, Talamini R, Serraino D, *et al*. Nutrition and cancer of the oral cavity and pharynx in North-East Italy. Int J Cancer 1991;47:20-5.
6. La Vecchia C, Negri E, D'Avanzo B, Boyle P, Franceschi S. Dietary indicators of oral and pharyngeal cancer. Int J Epidemiol 1991;20:39-44.
7. Oreggia F, De Stefani E, Correa P, Fierro L. Risk factors for cancer of the tongue in Uruguay. Cancer 1991;67:180-3.
8. Fioretti F, Bosetti C, Tavani A, Franceschi S, Vecchia CL. Risk factors for oral and pharyngeal cancer in never smokers. Oral Oncol 1999;35:375-8.
9. Rodriguez T, Altieri A, Chatenoud L, Gallus S, Bosetti C, Negri E, *et al*. Risk factors for oral and pharyngeal cancer in young adults. Oral Oncol 2004;40:207-13.
10. Galeone C, Pelucchi C, Talamini R, Levi F, Bosetti C, Negri E, *et al*. Role of fried foods and oral/pharyngeal and oesophageal cancers. Br J Cancer 2005;92:2065-9.
11. Kreimer AR, Randi G, Herrero R, Castellsagué X, La Vecchia C, Franceschi S, *et al*. Diet and body mass, and oral and oropharyngeal squamous cell carcinomas: Analysis from the IARC multinational case-control study. Int J Cancer 2006;118:2293-7.
12. Suzuki T, Wakai K, Matsuo K, Hirose K, Ito H, Kuriki K, *et al*. Effect of d ietary antioxidants and risk of oral, pharyngeal and laryngeal squamous cell carcinoma according to smoking and drinking habits. Cancer Sci 2006;97:760-7.
13. Asakage T, Yokoyama A, Haneda T, Yamazaki M, Muto M, Yokoyama T, *et al*. Genetic polymorphisms of alcohol and aldehyde dehydrogenases, and drinking, smoking and diet in Japanese men with oral and pharyngeal squamous cell carcinoma. Carcinogenesis 2007;28:865-74.
14. Garavello W, Giordano L, Bosetti C, Talamini R, Negri E, Tavani A, *et al*. Diet diversity and the risk of oral and pharyngeal cancer. Eur J Nutr 2008;47:280-4.
15. Toporcov TN, Biazevic MG, Rotundo LD, de Andrade FP, de Carvalho MB, Brasileiro RS, et al. Consumption of animal derived foods and mouth and oropharyngeal cancer. Rev Panam Salud Publica 2012;32:185-91.
16. Bezerra KF, Douglas-de-Oliveira DW, Menezes-Silva R, Granville-Garcia AF, Alves PM, Nonaka CF, *et al*. Diet and squamous cell carcinoma of the oral cavity and pharynx: A case-control study. Pesqui Bras Odontopediatria Clin Integr 2017;17:e3732.
17. Gupta B, Bray F, Kumar N, Johnson NW. Associations between oral hygiene habits, diet, tobacco and alcohol and risk of oral cancer: A case-control study from India. Cancer Epidemiol 2017;51:7-14.
18. Chen F, Yan L, Lin L, Liu F, Qiu Y, Wang J, *et al*. Dietary score and the risk of oral cancer: A case-control study in Southeast China. Oncotarget 2017;8:34610-6.
19. Alves CG, Treister NS, Ribeiro AC, Brandão TB, Tonaki JO, Lopes MA, *et al*. Strategies for communicating oral and oropharyngeal cancer diagnosis: Why talk about it? Oral Surg Oral Med Oral Pathol Oral Radiol 2020;129:347-56.

How to cite this article: Rodriguez-Archilla A, Calderer-Ortiz M. Influence of diet on oropharyngeal cancer: A meta-analysis. Int Dent Med J Adv Res 2020;6:1-5.