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Food and Risk of Oral Cancer (Review)

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Abstract
Mouth is the first area for the food to be in contact with oral epithelia and it could cause a chain of events initiated thermal injuries (because of eating or consumption of hot food) leading to ulceration epithelial hyperplasia or dysplasia and end by carcinoma. The elaboration of the food makes it risque to evaluate the role of various dietary components about oral carcinogenesis. Broiling or frying foods and the utilization of microwave increase oral cancer chance. The way is too long in this field and it needs more studies to focus on oral cancer especially oral squamous cell carcinoma (OSCC). In this review we attempt to clarify the impact of some diet items on oral carcinoma.

Introduction:

Oral cancer cause is multifactorial no single causative agent or factor had characterized or accepted but both extrinsic and intrinsic agents may be at work. Oral mucosa works as a mechanical and immunological barrier. Contact with exogenous material implies the probability of an attack from a microorganism (fungi, bacteria parasite and viruses) and induction of microtrauma irritants toxins and carcinogens [1]. Oral cancer has a complex etiology and pathophysiology and is the indirect result of the interaction between environmental exposures and genetical factors. Nutrition and diet as environmental factors and determinants of growth and body composition can contribute to oral cancer [2]. SCC is approximately 90% of oral cancers which is seen typically on the tongue (usually posterior lateral and ventral surfaces) then the floor of the mouth clinically presented as a white lesion(leukoplakia) red (erythroplakia) white or a mix of the two (erythroleukoplakia) with an ulcer. OSCC has many variants verrucous cell

carcinoma spindle cell carcinoma basaloid SCC and adenosquamous cell carcinoma [1]. Most of patients complaint at the first clinical presentation is ulceration. The patient health education and elevation of diagnostic standards of the general practitioners play an essential role in the early detection of oral cancer [3]. To reduce oral cancer risk a healthy diet must be optimized; by diminishing animal-based fat red or processed meat. Eating more vegetables fruits and cereals the primary origin of vitamins and fibers should be sufficient in the everyday diet to provide vitamin C E antioxidants zinc β-carotene and folate all being an impact in the restraining of oral cancer. Also fried or boiled foods should be avoided because of the formation of heterocyclic amines (HCAs) that increases the risks of oral cancer [2]. This review tries to explain the effect of diet on oral carcinogenesis process. The primary nutrients provided by food are carbohydrates protein fat minerals and vitamins. For organizing meals the foods can broadly be divided into three groups. These are: 1) Energy yielding food. 2) Bodybuilding food. 3) Protective food [4 5]. Table 1 shows all the nutrients function of food groups. The principles of the healthy eating food pyramid must be followed to have a healthy diet [5]. Figure 1 shows the food pyramid.

Diet and risk of oral cancer
1- Fruits and vegetables
There are more than one hundred beneficial contents in fruits and vegetables such as fiber minerals vitamins and specific phytochemicals (such as flavonoids carotenoids terpenes indoles and sterols) that may prevent cancer [6]. Daily eating five or more portions of fruits and vegetables can diminish the risk of oral cancer [7]. The primary sources of polyphenols are apples and strawberries while potatoes lettuces and onions are the most crucial vegetable sources. The overall intake of polyphenol from fruits is about three times more than from vegetables. Apple contains phenolic acids and flavonoids. Apple has the second-highest antioxidant activity and the highest

level of free phenolic agents [8]. More frequent consumption of fruits (especially citrus fruit and apple) carrots fresh tomatoes and green peppers have an inversed association with the chance of getting oropharyngeal carcinoma [9]. Carotenoids colorful compounds of plants can dynamically decrease the cancer risk. Many studies show that the most potent protective agent is α-carotene then β-carotene. The overall intake of carotenoids was more protective than a high intake of a single carotenoid. The best source of α-carotene is yellow/orange vegetables like carrot pumpkin and winter squash [10]. Cruciferous vegetables (cauliflower broccoli cabbage Brussel sprout and turnip greens) are the essential origin of sulfur-rich compounds which have an anticarcinogenic effect [11]. Tomatoes are the primary source of lycopene (consisting primarily of all-trans isomers,) a most powerful antioxidants among dietary carotenoids. It is organized in individual buccal mucosa and enters the plasma immediately when consumed. They are found abundantly in red fruits and vegetables. Lycopene anticancerous impacts are through the regulation of gap junction communication [12].

2- Turmeric and ginger
From the Curcuma longa plant a polyphenol Curcumin (diferuloylmethane) is derived widely known as turmeric. For centuries it has been used extensively in Ayurvedic medicine as it is non-toxic with curative properties (like anti-oxidant anti-inflammatory analgesic and antiseptic activity). Curcumin possesses anti-cancer activities via its effect on mutagenesis oncogene expression cell cycle regulation apoptosis and metastasis. It has an anti-proliferative impact on oral cancer by inhibition of NF-κB and downstream gene products (involving COX-2 c-myc NOS Bcl-2 Cyclin D1 TNF-α interleukins and MMP-9). Also curcumin influences a set of growth factor receptors and cell adhesion molecules implicated in tumor growth angiogenesis and metastasis [13]. In oral precancerous lesions it used as a chemopreventive agent (like in leukoplakia submucosal fibrosis and lichen planus). Turmeric reduces the

micronuclei formation in exfoliated mucosal cells and circulating lymphocytes and this can help in oncotransformation prevention. It can stop and minimize the genesis of fibrosis by playing as an antifibrotic factor (by inhibiting inflammatory cell stimulation and preventing leukocyte influx) [12]. Ginger inhibits NF-κB signaling pathway and thus represses COX-2 expressions. It has dose-dependent cytotoxicity on oral carcinoma cells by activating caspase-3 mediated apoptosis [14]. The main compound of ginger is gingerol which converts to shogaols zingerone and paradol have anti-inflammatory , antiangiogenesis anticancer and anti-, antioxidant ,androgenic and hypoglycemic activities, and atherosclerotic pharmacological properties [15]. By downregulation of NF-κB that decreases the release of IL-8 and VEGF which are essential for angiogenesis ginger helps in the prevention of tumor growth and metastasis [12].

3-Onion and garlic
Allium cepa and Allium sativum consuming deem as markers of a healthier lifestyle because of their potential health benefits yet the specificities of these advantages are still opened to the argument [16]. In the Italian diet onion and garlic are often eaten or cooked with foods. The preventive effect of garlic and tomato against the carcinogenic process of hamster buccal pouch was reported [17]. Onion anticarcinogenic action may be due to their altitude content of organosulfur compounds or to their high antioxidant efficiency which is principally related to the great content of flavonoids [18]. For thousands of years garlic root bulb utilized for medicinal purposes. It rich in sulfur-containing amino acids and it contains several vitamins and micronutrients (that explained its action as anticarcinogenic). Diallyl sulfide which is responsible for its powerful taste and smell induce P-450 enzymes [19]. It also contains useful content for health (like selenium and arginine oligosaccharides flavonoids). In particular many human studies have proposed that people who eat more garlic possess a lower chance of mouth cancer [6].

Also a study from southern European populations (included several cancers oral cavity was one of them) shows a reverse association between the frequency of allium vegetable use and the risk of studied cancers [20].

4- Carbohydrates (whole grains bread cereals and pasta)
Rich-kind food plant foods is one of the foremost preventable factors of non-communicable diseases. The grasses seeds cultivated for food are called grains or cereals. Whole grains are the complete plant seeds and it is consist of bran germ and endosperm. Purified grains are nutritionally low because the milling process substantially reduced the nutrient contents of grains by removing the bran and germ (that rich in fiber protein micronutrients and phytochemicals) leaving a mainly starchy endosperm. Purified grains enriched with B vitamins (riboflavin niacin thiamin and iron) [21]. Dietary guidelines widely recommended whole grains intake (included brown rice bran or corn muffins whole wheat or barley and oatmeal shredded wheat or bran cereals). It has shown a favorable harmonic influence on insulin sensitivity lipid profile endothelial function antioxidant activity and inflammation [22]. Fibers are slowing digestion carbohydrates intake and the following glycemic reaction thus decreasing hyperinsulinemia and insulin- like growth factors (IGF). Dietary fiber scavenges nitrite a precursor for carcinogenic nitrosoamines. Fiber may bind carcinogens and thereby limit their contact with upper digestive tract epithelia. High- fiber foods generally tend to have a higher content of antioxidants [23]. Ma *et al.* found that cereal appears to have protection against oral carcinoma due to the effects of their riboflavin iron and magnesium contents [22].

5- Proteins
Barbaresco *et al.* in their systematic review found that a Western food pattern has a positive correlation with the higher contents of C-reactive proteins the primary biomarker of inflammation [24]. Rich glycemic and protein-dense foods (such as

dairy products) may increase advanced glycated end (AGEs) product formation which in turn leads to cellular injury at various levels. AGEs perhaps induce changes in the protein texture and its role aberrant cell signaling and irregular of extracellular matrix functions. Disturbances of the primary cell role imply the etiology of several cancers involving oral cancer. High protein dietary patterns have an association with decreased oral cancer risk [25]. Vegetarians had about fifty percent less chance to develop oral cancer compared to those who eat meat. Taking meat not more than 15% of the total calories per day is recommended. Oral cancer risk is reduced by minimizing the amount of animal-based products selecting leaner meats (such as fish chicken or turkey) and eating healthier proteins (such as beans and other plant-based protein sources) [26]. Protein has a protective effect against OSCC by eating white meat poultry seafood fish (contain a long chain of omega-3 polyunsaturated fatty acids) and shellfish [27]. Xu et al. found that the risk of oral and oropharynx cancer has an association with meat consumption in South Americans. Yet it would not be able in Asians or Europeans. Thus the variation in the association significantly differs across ethnic groups (due to differences in genetic background lifestyles and ecological factors). Processed meat that is preserved by smoking curing salting or by chemical preservatives play an essential role in tumorigenesis. This was due to (A) Production of potent mutagens during high-temperature cooking and meat processing or preservation (including N-nitroso compounds polycyclic aromatic hydrocarbons and HCAs). (B) Their enrich of saturated-fat and heme-iron ingredient [28]. Beef supply heme iron which is more bioavailable than non-heme iron. In rat experimental researches heme iron contributes to carcinogenesis by generating free radicals and inducing oxidative stress. A significant association of high processed meat consumption with a high chance of oral cancer was found but the relation between total meat red meat or white meat was not reported [29].

In Switzerland Levi et al. considered more consumption of eggs beef pork and processed meat as a relevant risk factor for oral carcinoma [30].

6-Milk and dairy products
The anticancerous feature of milk is attributed to its calcium and lactoferrin. Chen et al. in their hospital-based case-control study suggest that tea and milk consumption are independent protective factors for oral cancer among non-smoker/non-drinker with a synergistic effect between them (epigallocatechin gallate and lactoferrin interaction) [31]. Toporcov et al. study (on milk and dairy products) showed a protective effect against oropharyngeal cancer [32].

7- Coffee and tea
As one of the foremost vastly drunk beverages in the world coffee is the most favorite in people's lives. It contains polyphenols antioxidants anticarcinogenic constituents and other biologically active components that perhaps help in protection versus the evolution or progression of cancer besides its daily enjoyment [33]. Zhang et al. in their meta-analysis study had proposed that more coffee consumption might decrease the chance of oral cancer particularly in Europe [33]. Caffeine polyphenol caffeic acid and 2-coffee-specific diterpenes cafestol and kahweol protects against oxidative DNA damage promotes apoptosis and have anti-proliferative activity [34]. But the questions about 'How many cups of coffee one can drink a day?' 'What type of coffee does a person usually drink each day?' (Boiled coffee filtered coffee instant coffee decaffeinated coffee) "What are the brewing methods?". These must be more clarified in future studies to know its effect on OSCC. Tea is commonly consumed and more accessible than coffee. Relying on the degree of fermentation it can be green tea (non-fermented) oolong tea (semi-fermented) and black tea (totally fermented). Green tea contains catechins (antioxidant polyphenolic molecules) that appear very beneficial against cancer. Compared to green tea black tea has much fewer

catechins. Multiple in vitro studies have shown the potential of green tea polyphenols particularly EGCG in apoptosis induction reduction of cell growth and inhibition of angiogenesis in oral carcinoma cell lines [35]. Green tea was reducing oral leukoplakia size inhibiting cell micronucleated shedding [36]. Ede *et al.* study showed that green tea had reduced the hazard ratios of oral cancer in women [37]. Black tea has a great preservative influence in "ever" drinkers and that has been attributed to an antiproliferative action and apoptosis induction reducing micronuclei contents and chromosomal aberrations in mouth precancerous lesions [38]. In South America and parts of Europe maté (a tea-like beverage) consumed. It has an independent effect on the growth of oropharyngeal cancers. Yet the exact pathogenesis of maté in oral carcinoma is obscure. Many ideas have suggested for maté's carcinogenicity like thermal trauma dissolvent for chemical carcinogens and the existence of tannins and N-nitroso components [39].

8- Honey and sweeten syrup

Honey has nutritional and medical benefits due to its antimicrobial antiviral and antiparasitic activity. Its form of organic acids polyphenols proteins amino acids vitamins minerals and aromatic compounds. Effects of tualang honey (Local Malaysian honey) as an antiproliferative agent on OSCC were reported. It persued apoptosis by up-regulating p53 and by modifying the expression of pro and anti-apoptotic proteins reactivation of caspase-3 pathway due to its phenolic and tryptophan ingredients. Honey transduced the apoptotic signal via an initial depletion of intracellular non-protein thiols reducing the MMP by elevation of ROS generation which demands apoptosis. So honey regulates oral cancer cell line by inducing cell-growth arrest by cell cycle blockage at the sub-G1 phase [40]. There is speculation on an association between sweetened carbonated beverage consumption and cancer risk. Overall the feedbacks are promising regarding the relation between soft drinks and cancer risk [41]. Although the quality of many studies is quite weak by acceptable modern standards and no research has been performed with carbonated beverages consumption as the main hypothesis.

Micronutrients (vitamins and minerals)

Many micronutrients and minerals were taken from food like iron phosphorus vitamins B E K and selenium. Particular micronutrients decrease oral cancer development like vitamins A, C B_5, E ,carotenoids , phosphorus selenium and potassium. These antioxidants are essential in lowering free radical response [29]. Vitamin C reduces nitrosation by blocking nitrosamines formation acting as a chemopreventive factor and impacts the activity of leukocytes and macrophages. Vitamin C is also involved in the efficiency of cytochrome P450 which is essential in the procarcinogens metabolic activation and inactivation of efficient carcinogens. The association between vitamin C and oral carcinoma is established with few intakes of fruits and vegetables predisposed to an increased chance of getting oral carcinoma [42]. This was in line with Negri *et al*. study findings that showed significant protection from oral cancer with the following micronutrients: carotene vitamins C and E thiamine vitamin B6 folic acid niacin potassium and iron [39]. Some considered that the retinol blood levels and the quantities of dietary β-carotene ingestion are inversely proportional to the risk of OSCC and leukoplakia. Furthermore long-term therapy with retinoic acids and β-carotene has a relation with the regression of some leukoplakic lesions by a reduction of the severity of dysplasia within such conditions [1]. Vitamin E is an essential nutrient that serves as a chain breaking free radical trapping antioxidant, reacts with the lipid peroxide radical before the establishment of chains lipid peroxidation reactions occurs. Clinical medication with α-tocopherol a nontoxic antioxidant like β-carotene has shown considerable compact with oral pre-cancerous and cancerous lesions (23). The

primary natural origin of vitamin E is new vegetables and plant-derived oils cereals and nuts. It can prevent premalignant lesions modulate the effects of cancer chemotherapy and decrease the side effects of chemo-radiotherapy for cancer patients. Also vitamin E can inhibit reactions of the tobacco-specific nitrosamine which undergo specific activation and detoxification way. They may suppress oral cancer development through emulation of wild-type p53 downregulation of mutant p53 reactivation of heat shock proteins and an antiangiogenic action intermediated by blockage of TGF-α [43]. Selenium is a mineral that has anti-cancer features. Good origins of selenium are whole grains and legumes grown in selenium-rich soil nuts nutritional yeast brewer's yeast and sunflower seeds. It has shown that reduced selenium levels chiefly for men are a cancer risk [44]. Series of metabolic steps involve specific enzymes such as superoxide dismutase catalase and glutathione peroxidase rapidly eliminate toxic free-oxygen radicals. Correct selenium concentration in the plasma may represent a form of head and neck SCC chemoprevention [45].

Fats and oils

Studies showed that high-fat diets had a link to many types of cancer and saturated fat was particularly dangerous. Cutting out the fat is not the answer. Choosing fats wisely and eating them in moderation is the trick because some types of fat may protect against cancer. Saturated fatty acids are abundant in animal fat and plant-extracted oils (like sunflower grain oil and corn oil) that are full of linoleic acid (one of the N-6 polyunsaturated fatty acids / arachidonic acid is suggested to enhance cancer development). Oils derived from fish oils N-3 polyunsaturated fatty acids (especially eicosapentaenoic acid and docosahexaenoic acid) and that derived from olive oil (N-9 monounsaturated fatty acids/oleic acid) have protective effects against carcinogenesis [46].The most damaging fats that increase cancer risk are saturated fats and trans fats. Beef whole-

milk dairy products and eggs are rich in saturated fats. Hydrogenated oils are produced by adding hydrogen to vegetable oils to be more solid and fewer avails. Unsaturated fats are the best derived from plant sources such as olive oil canola oil nuts and avocados are liquid at room temperature and decrease the risk of cancer. Furthermore omega-3 fatty acids fight inflammation and support brain and heart health [26]. Regarding potential biologic mechanisms olive oil may have endogenous antioxidant properties that influence the risk of oral cancer. But it is not clear whether such antioxidant activity is due to oleic acid itself or the presence of other antioxidants like vitamin E and polyphenols. Low intake of soups cakes processed meats eggs and butter has an association with reduced risk for oral cancer [47]. In the Brazilian diet beside it is rich in high-fat bacon cheese eggs beef and pork meat are ordinarily supplied fried and hot which perhaps damage oral mucosa. Bacon is traditionally added to beans for flavoring which showed an increased risk of oral cancer. Also the risk of oral carcinoma has a relation with the constant intake of fried food and other rich-fat food which ordinary presented with creamy bechamel or sauté [48]. In Italy Franceschi *et al*. tick that the chance of developing oral cancer had an association with saturated fatty acids intake [49] which effect on cell membrane integrity increase in lipid peroxidase alteration of hormone levels especially estrogen and impairment of nutrient metabolism [48].

Cooking methods

Cooking food is alter the structure of the food destroy nutrients and enzymes and create byproducts. But for some food contents cooking improves the bioavailability of some nutrients and digestibility. It had been showed inverse relationships between the risk of upper digestive tract cancers and the consumption of both raw and cooked vegetables [50]. Cooking methods (like broiling frying , barbecuing and) produce the most massive rate of HCAs. Yet reducing HCAs can be done in different

ways (especially by using aluminum foil to wrap meat before roasting to avoid direct exposure to open flames stewing and boiling or partly cooked in the microwave) prior broiling frying or barbecuing meat [51]. Boiled beef together with sweet potato winter squash and rice showed an association with high oral cancer risk. While liver , raw vegetables whole vegetables citrus fruits and pulses were significantly protective foods. It is bearable that thermolabile ingredients present in plants   liable to high temperature overcooking. These agents' intake at a high temperature and it causes thermal damage   lead to ulceration trauma-induced hyperplasia epithelial dysplasia   and subsequent carcinoma [52].The first foodborne cancer-causing agents to be identified were benzo-[a]pyrene and related polycyclic aromatic hydrocarbons which formed during the grilling of meats and fishes [53]. Drinking alcohol with high monounsaturated animal-derived oil diets red or processed meat frying or broiling foods   and employment of microwave cooking increases the chance of oral carcinoma and salivary gland neoplasms [2].

Dietary pattern

Popular two main dietary patterns throughout the world are "Western " which is high-energy rich in french fries refined grains   and sweets/desserts [54] another pattern is the healthy "Prudent " mainly composed of fruit vegetables legumes fish and whole grains. Ethnic or country-specific diets have been identified like the "bean pattern" amongst Chinese women or Japanese race Korean Iranian Syrian and Lebanese patterns [25]. A study in Uruguay displayed an increase in oropharynx and larynx cancers among subjects adhering to the Western dietary pattern [55]. An increase in oral cancer risk demonstrated in multiple studies associated with patterns that had another nomenclature showed the same components of the Western diet. The

'Preferred' pattern has an association with an increased risk of oral carcinoma which composed of fermented foods fast foods and desserts rich in fat and sugar [56]. Likewise another study in Malaysia demonstrated that eating 'Traditional' pattern which included beverages and starches had a higher odds of oral carcinoma as well as with the 'Combination' pattern which consisted of dairy and meat [57]. Another case-control study had shown that increased risks of OSCC associated with a 'meat and fat' dietary pattern a 'pasta and pizza' pattern was inversely associated with risk of OSCC while a 'fruit and vegetable' pattern decreased OSCC risk [58]. So a higher chance of developing oral cancer related to sticking to a Western or western-like pattern which may be mediate inflammation degenerative diseases lasting by cancer. Traditional Syrian and high protein patterns were showed a significant lowering of the odds of oropharynx and larynx cancers [25]. Table 2 summarizes the association between food components and oral cancer which are mentioned in the earlier epidemiological studies.

Conclusion

A large variety of food is included in our daily meals for taste and flavor. Some foods are good for bodybuilding a source of energy or protective functions. Some foods nutrients and supplements have been associated with the development of oral cancer (carcinogenesis) or have been linked to cancer prevention. High consumption of healthy grains unsaturated fats   fruits and vegetables effective herbs and low use of animal and animal-based derivatives along with non-broiling non-frying methods might be the key to prevention of many types of human cancers including the oral cancers. More studies are needed in this field to focus on oral cancer especially oral squamous cell carcinoma.
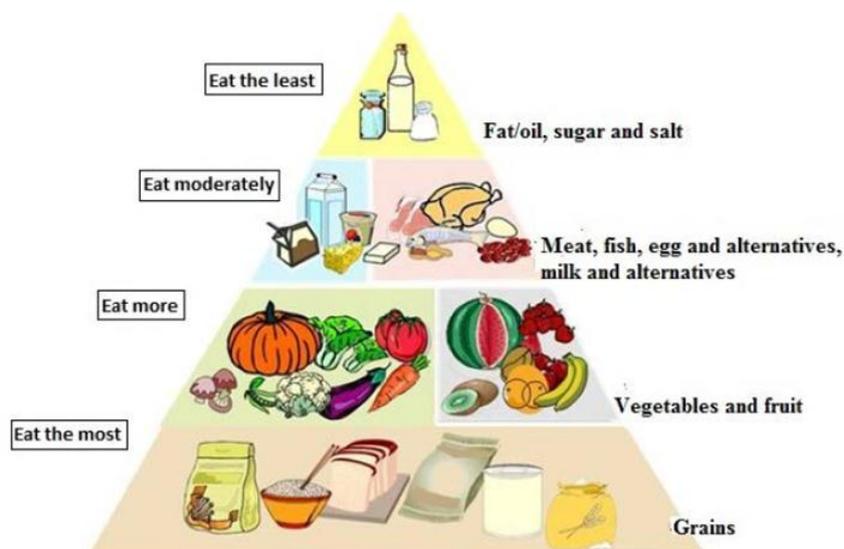
Fig.(1): Food pyramid [5]

Table (1):- Nutrients function provided by food groups [4].

Function	Major nutrients	Food groups
1. Bodybuilding	Proteins	− Milk meat chicken
		− Pulses
2. Energy giving	Carbohydrates fats	− Cereals
		− Fats sugar
3. Protective	Minerals vitamins	− Fruits vegetables

Table(2):- Summary of food components that decrease or increase the risk of oral cancer

Decrease the risk of oral cancer	Increase the risk of oral cancer
Phytochemicals:	− CRP
− Flavonoids	− N-nitros compounds
− Carotenoids (α-carotene β-carotene)	− AGEs
− Terpenes	− Trans fat and Saturated fat
− Indoles	(N-6 polyunsaturated fatty acids / arachidonic acid)
− Sterols	− Benzo-[a]pyrene
− Lycopene	− Polycyclic aromatic hydrocarbons
− Sulfur-containing compounds (glucosinolates) and (diallyl sulfide Allium)	− HCAs
Polyphenols:	
− Diferuloylmethane curcumin	
− EGCG	
− Caffeic acid 2-coffee-specific diterpenes cafestol and kahweol	
Gingerol	
Lactoferrin	
Vitamins (A C E B$_2$ B$_5$ and B$_6$) phosphorus folic acid thiamine niacin potassium magnesium iron and selenium	
Unsaturated fat:	
1. Fish oils N-3 polyunsaturated fatty acids (eicosapentaenoic acid docosahexaenoic acid)	
2. Olive oil N-9 monounsaturated fatty acids/oleic acid	

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