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DIET AS A POSSIBLE INFLUENCING FACTOR IN THYROID CANCER INCIDENCE: THE POINT OF VIEW OF THE NUTRITIONIST

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Comments from the Reviewer #1:

Comments to the Author

This paper report a point of view regarding the possible role of diet in thyroid cancer influence.

It is interesting and well-structured

Author's response: We are very grateful to the Reviewer for his/her appreciation of our findings and his/her most positive report. We are hopeful that the constructive suggestions and the proposed corrections will improve our exposition in the updated manuscript. All the corrections in the revised manuscript are made in yellow for the Reviewer's convenience.

I suggest to change the word "nutrizionist" in "nutritionist".

Author's response: We are apologize for the typing error. The term "nutrizionist" has been correctly changed to "nutritionist".

I suggest an English revision made by a native-spoken english.

Author's response: We thank the reviewer for the important observations, and we have done a thorough English grammar revision of the manuscript. Therefore, we have changed several lines that have highlighted in red for those deleted words and written in red for those added words for the Reviewer's convenience.

Some repetitions should be avoided. For example, pag 7/44, the first sentence should be deleted.

Author's response: We appreciate the reviewer's suggestion, and we have deleted that sentence. We have highlighted in red the deleted part for the Reviewer's convenience.

Please verify that all acronyms are correctly reported. Example: pag 8/44, line 18 PUFAs should be reported as (PUFAs).

Author's response: We thank the reviewer for that observation, and we have modified the text as suggested. We have verified that all acronyms are correctly reported and modified several lines (Page 9 lines 7, 9) that we have highlighted in yellow the added words and red the deleted ones for the Reviewer's convenience.

Regarding the study EPIC, could the authors specify if it evaluated quantity and/or quality of fish consumption?

Author's response: We value the reviewers' significant observation, and we have modified the text reporting detailed information on the quantity and quality of the fish analysed.

Pag 6/45, after the description of a meta-analysis (line 43) there is no reference.

Author's response: We have added the specific reference.

Pag 11/44, line 7: the sentence "In conclusion, the association between hypovitaminosis D and TC is still controversial" should be placed at the end of the section (line 23) as a conclusive remark.

Author's response: We appreciate the reviewer's important observation, and we have modified the text as his/her request. We have highlighted in yellow for the Reviewer's convenience.

Pag 14/44, line 16 Wie should be Wie et al.

Author's response: We thank the reviewer for that observation, and we have modified the text as his/her request (Page 15 line 16). We have highlighted in yellow for the Reviewer's convenience.

When reported "etc" should be removed

Author's response: We thank the reviewer for that observation, and we have modified the text as his/her request (Page 8 lines 14,15, Page 19 line 10). We have highlighted in red the deleted parts for the Reviewer's convenience.

Section "Conclusion". On the basis of the evidence described in the text the sentence "Significant associations between single nutrients or food and TC risk have been observed." seems too optimistic. I think that this sentence should be moderate.

Author's response: We value the reviewers' significant observation, and we have modified the text.

Page 15/44, line 27. The reference 114 should be associated with the more appropriate (in this context) "Hyun, Tae KyungRoles of polyphenols as dietary epigenetic modulators. MINERVA BIOTECNOLOGICA Volume: 31 Issue: 2

Author's response: As suggested by the Reviewer, we have added the appropriate reference.

Since there are too much references I suggest to remove the following numbers:

-19

-28

-40

-87

-89

-90

-96

-103

-105

-121

-132

-138

-139

-141

Please, remove "PubMed PMID: _____. Pubmed Central PMCID: _____. Epub _____" from the references list.

Author's response: Done.

TITLE: DIET AS A POSSIBLE INFLUENCING FACTOR IN THYROID CANCER INCIDENCE: THE POINT OF VIEW OF THE NUTRITIONIST

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Running title: Diet and Thyroid Cancer Risk.

Abstract

The incidence of differentiated thyroid cancer has been increasededing in the last decades all over the world. Different environmental factors are possible perpetrators of this exponential growthincrease. The nutritional factors are among the main environmental factors studied for thyroid cancer in recent years. The review aims of review is to give an overview among of the main dietary factors involved onin thyroid cancer risk, providing also specific nutrition recommendations as the point of view offrom the endocrinological Nutritionist point of view. Among single food, fish and shellfish are the majorprimary natural source of iodine in the human diet, andas well as selenium and vitamin D, all. These nutrients are essential for the synthesis of thyroid hormones; however, their consumption isare not consistently related to thyroid cancer risk. The high consumptionintake of fruit and vegetables, probably due to their vitamin and antioxidant content, shows a weak inverse association with thyroid cancer risk. No important effect on thyroid cancer risk of aAlcohol, meat, or other food-groups/nutrients emergedshowed no significant effect on thyroid cancer. In conclusions, to date, no definite an association among dietary factors, specific dietary patterns and thyroid cancer, as well as inand its clinical severity and aggressiveness have been found.

However, it is importantessential to underline that in the future, prospective studies should be carried out to specificallyprecisely evaluate the qualitative and quantitative intake of nutrients by patients, in order to establish with more confidence a potential correlation between food intake and the occurrence and development of thyroid cancer.

Keywords: Diet; Thyroid Cancer Risk; Mediterranean Diet, Vitamin D, Nutritionist.

TEXT

Introduction

Thyroid cancer (TC) is considered a rare disease since it constitutes <1% of all cancers [1]. However, it represents the most frequent endocrine cancer, affecting 5% of thyroid nodules, which have a prevalence of 20-50% in the general population, increasing due to the improvementimproved of diagnostic techniques and early diagnosis [2]. In particular, Ultrasound (US) and fine-needle aspiration are the most important diagnostic tool for the evaluation ofevaluating thyroid nodules [3-5].

TC has a greater prevalence in the female sex, with a 3:1 female-to-male ratio in most geographic regions and demographic groups. Although these tumors are veryrare in children, they affect a younger population than most malignancies, with a maximum incidence between 25 and 60 years [6]. Survival is very high, exceeding 90% at 5 years in differentiated forms [6]. Moreover, since the TC prognosis is excellent in most cases and the mortality rate remains very low, to date, there is a lot ofmuch interest in the personalized risk-based treatment [7].

TC generally originates from follicular cells and areis divided into papillary, follicular, anaplastic and medullary carcinoma [8]. Papillary carcinoma is the most frequent form of differentiated TC (DTC), comprising about 80% [9]. It has slow growth and can give rise tocause loco-regional lymph node metastases. In some patients, the tumor is multifocal and can affect both lobes of the thyroid gland [10]. Follicular carcinoma represents about 15% of differentiated DTC and can give rise toproduce distant metastases. Anaplastic carcinoma is a rare type of tumor, <1% of thyroid tumors, but it is particularly aggressive already at diagnosis with inadequatepoor response to conventional therapies [11]. Medullary carcinoma originates from parafollicular cells (or C cells), and the diagnosis is based on the basal or stimulated calcitonin dosage [12]. This tumor can occur in familial forms as the manifestation of genetic syndromes, such as multiple neoplastic syndrome type 2.

In the differentiated DTC, some recurrent genetic mutations have been found that specifically affect receptors with tyrosine kinase activity and their pathways: in particular BRAF (V600E) mutation, RET/PTC rearrangements RAS and pTERT mutations in papillary carcinoma and PAX8–

PPARγ rearrangements or RAS and pTERT mutations in follicular carcinoma [8,13]. Theseis mutations also justifyies the known relationship between exposure to ionizing radiation and increased TC incidenceof TC, since radiation induces double-stranded DNA breaks and genetic rearrangements [14].

As reported in clinical studies, the thyroid is particularly sensitive to the long-term effects of radiation exposure [15]. This association was evaluated in population-based case-control studies both of adolescents exposed to radiation following the Chernobyl accident and of subjects exposed to the atomic bombings of Hiroshima and Nagasaki, in whichwhere an increased incidence of TC was demonstrated [16]. The adverse effects of radiation in inducing TC have been reported in atomic bomb survivors from 62 to 66 years after exposure during their childhood [17]. Of interestRemarkably, Mesrine et al. prospectively analyzedin 86.960 women followed-up over 1990-2008, finding associations between nevi, baseline residential ultraviolet exposure, and thyroid cancer risk [18]. Results such asshowed that ultraviolet exposure level and the number of nevi were associated with nodules or histories of dysthyroidismthyroid disturbances, and the number of nevi was positively associated with TC risk (HR=1.7, 95% CI=1.0, 2.8; p=0.01). This risk was restricted to females with dietary iodine below the median intake. The authors concluded that TC risk was associated with the number of nevi and residential ultraviolet exposure [18].

In addition to ionizing radiation, the main risk factors known for TC are family history, female gender, and obesity [19, 20]. A family history of TC in first-degree relatives is associated with a 10-fold increased risk of non-medullary TC based on a large case-control study [21]. Although the incidence of this cancer incidence is significantly higher in women, no clear pathophysiological and hormonal mechanisms have been identified[22]. Some observational studies have shown an association between excess weight and increased TC risk of TC, both well-differentiated and anaplastic. In particular, a meta-analysis of 22 prospective studies showed that a high body mass index (BMI) is associated with an increased TC risk of TC, and that this association is even stronger in younger subjects than in elderly ones. The presence of obesity would also seem to be associated with TC with a worse prognosis (PMID: 26756356).

Beyond ionizing radiation, family history of TC, female gender, and obesity, other environmental factors seem to play a potential role in theTC's pathogenesis of TC, such as single foods or dietary patterns, including fish, vegetables, vitamin D, selenium and Mediterranean diet (MD) [20]. Of interest It is noteworthy that, nutritional and dietary patterns in recent years have gained high interest as possible promoters and modifiable risk factors for TC [20]., as well as They represent a majorsignificant objective of the dietetic and metabolic multidisciplinary rehabilitation in patients with obesity, aiminged to achieveat achieving a weight loss and the improvement of obesity-related cardiovascular and metabolic diseases [23]; beyond the drug therapy for obesity [24, 25].

In particular, the low dietary iodine intake was negatively associated towith increased TC risk of TC, favoring the development of more aggressive histotypes [20]. AlsoIn addition, the low dietary intake of selenium and vitamin D waswere associated with TC. However, but the evidence areis scarcevery limited, despite their well-known anti-cancer potentials of these nutrients, and the clinical usefulness of their dietary supplementation is still uncertain in this setting. DespiteConsidering thate single foods, fish, vegetables, and fruits might exert protective effects on TC risk; but the evidence is limited even in this case.,the evidence is scarce and albeit the The relationship between single foods and TC isremains difficult to examine. Although no clear linkrole between dietary factors and TC has been firmly established so far, some dietary patterns, in particular MD are supposed to play a role in thyroid carcinogenesis as well as in its stage and aggressiveness. In fact, diet rUnlike the study of individual foods or nutrients, diet because it is a complex interaction of single nutrients, foods and phytonutrients, and numerous individual compounds [26]. For this reason, the benefits of the dietary pattern are due tois a synergistic and/or accumulative effect of nutrients and foods which together, confer overall benefit [26]. In this context, in promotingto promote the reduction of TC risk, the focus should be on a healthy dietary pattern, in particularly the MD and not, on individual nutrients.

The present review summarizes the current epidemiological evidence on TC's nutritional risk factors for TC, with particular attention to MD, and provides the nutrition and dietetics guidance to

be followed by nutritionists for the reduction ofto reduce TC risk, paying particular attention to the MD.

Nutrition and Thyroid cCancer Risk

As we have seen previously, TC is among common endocrine carcinoma, and it increased rapidly worldwide during the past three decades [27]. Beyond genetic predisposition, TC risk is related to different factors such as radiation, thyroid disorders, hormonal and growth factors, obesity, and nutritional factor [27,28, 29].

Environmental carcinogens, probably higher in the last decades, including nutritional factors, may explain the high incidence of TC [30]. Previous evidence reported that some nutritional factors could possibly affect TC risk, but most of these data were inconsistent due to diverse dietary patterns, eating habits, lifestyles, and other environmental risk factors in the different populations studied. Of interest, the populations living in iodine sufficient regions with high fish consumption of fish showed either no relationship or lowered TC risk [27, 31]. Therefore, populations exposed to certain food types can have an increased or reduced TC risk compared with those who are not [27]. Most of the studies conducted whothat evaluated the relationship between TC risk and nutrition, have focused on single dietary factors, such as food items (fish, vegetables, etc) or nutrients (vitamin D, selenium, among others etc) [20]. In particular, some foods, including fish and other iodine-rich foods [27, 28], vegetables, and fruits and other polyphenols-rich foods [27, 28, 32-34], might have potential protective effects on TC risk. Contrariwise, high intake of meat, in particularly chicken, mutton, lamb [35], pork, and poultry [34, 36] were associated with a higher TC risk of TC.

The Mmain evidence for a single food

Fish and shellfish consumption

Fish and shellfish are an essentialimportant source offor different nutrients, such as iodine, selenium, and vitamin D, all crucialessential factors for the synthesizings of thyroid hormones [37].

To date, oOne of the well-established risk-modifying factors for TC is the dietary exposures [27, 28, 38]. Among these have been suggested intake of iodine-rich seafood [39, 40], goitrogenic vegetables [31, 41], Poly-Unsaturated Fatty Acids (PUFAs) [42], and alcohol [43]. Fish and shellfish are considered healthy foods in different dietary patterns, including MD [44], because of their content in iodine, selenium, the good fat n–3 Poly Fatty Acids (PUFAs) (eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)) and lipid-soluble vitamins, including retinol, vitamin D, and vitamin E [45].

In a recent EPIC (European Prospective Investigation into Cancer and Nutrition) study, Zamora-Ros et al. prospectively evaluated the association between quantity and quality of fish consumption and TC risk in a cohort of >500,000 men and women recruited in 10 European countries. In particular, based on quality, the fish was classified as: lean fish with <4 g/100 g of fat (e.g., cod, haddock, and plaice), and fatty fish with fat content between 4 and 14 g/100 g (e.g., salmon, tuna, and trout). While the amount of fish consumed was classified into: shellfish intake (including seafood such as prawn, crab, and mussels), fish and fish product intake (sum of lean and fatty fish and fish products), and total fish and shellfish intake, which was defined as the sum of intakes of fish, fish products, and shellfish. Dietary data were collected with quantitative or semiquantitative food frequency questionnaires that were developed and locally validated in EPIC previously. The results of the study reported no significant association between fish consumption and TC risk; likewise, no significant correlation was reported with the intake of any specific type of fish, fish product, or shellfish [46].

Thishe large study's results of this large study are also in agreement with a previous cohort study (24), a systematic review [47], a meta-analysis [38], and a pooled analysis of case-control studies

from the United States, Europe, Japan, and China [40]. In addition, fish is a rich source of n–3 PUFAs (EPA and DHA), that through their impact on prostaglandin synthesis, have anti-inflammatory properties and have been reported to be a protective factor in TC risk [48], in particular, an inverse association between PUFA intake and TC risk was showed in the EPIC study [42].

Vitamin D

Vitamin D, in addition to its main role in calcium homeostasis, can regulate (directly or indirectly), multiple signalling pathways involved in cellular proliferation and differentiation, apoptosis, inflammation, invasion, angiogenesis, and metastasis, with the potential to affect cancer development and growth [49], as well as reduce tumor-induced angiogenesis and invasiveness [50]. The most recognized anti-neoplastic effect of vitamin D is its ability to inhibit cell proliferation [51]. Besides its anti-proliferative effects, vitamin D also regulates inhibiting anti-apoptotic proteins (BCL-2 and BCL-XL) and inducing the expression of pro-apoptotic proteins (BAX, BAK, and BAD), the key mediators of apoptosis [49]. Beyond the importance of vitamin D in inflammatory processes associated to several chronic diseases, including obesity [52-54], polycystic ovary syndrome [55, 56], and psoriasis [57], the role of vitamin D's role has been determined in autoimmune and malignant thyroid diseases [58]. Different preclinical studies have shown growth arrest of TC after the administration of pharmacological doses of vitamin D in differentiated TC cell lines [59]. The main form of vitamin D, the vitamin D (subscript 3) (or cholecalciferol), is synthesized in the skin by 7-dehydrocholesterol reductase upon exposure to ultraviolet B (UVB) radiation, and can also be obtained from a few dietary sources (mainly fatty fish) [49] and meat [60]. In addition to the production of vitamin D, the indices of solar UVB irradiance can be associated with the genesis of some cancers. In particular, Grant has evaluated the cancer mortality rates for 48 continental Spanish provinces for 1978-1992 concerning respect to mortality rates for latitude (an index of solar UVB levels), reporting that nine cancers were significantly correlated with latitude, including TC thyroid cancer. In a Additionally, TC was associated with non-melanoma skin cancer, highlighting that the TC's development of TC can a

have different etiology [61]. In this context, an inverse association between UV-B exposure and non-skin cancer mortality, including TC, has been reported, probably through vitamin D, produced of exposure to the sun via the skin. Boscoe and Schymura showed the inverse relationships between UV-B exposure and TC (only in females), suggesting the vitalimportant role in maintainingce of adequate vitamin D levels linked to sun exposure [62].

Beyond TC risk, vitamin D also plays an indispensableimportant role in thyroid autoimmunity, improving the innate immune response and exerting an inhibitory action on the adaptive immune system [49]. Calcitriol, the activated (or hormonal metabolite of) vitamin D, has been reported to modulate the cytokine mileau to a more tolerogenic immune status [63]. Dutta et al. confirmed that anti-thyroid peroxidase antibody positivity is more prevalent in individuals with hypovitaminosis D and reported a negative correlation between anti-thyroid peroxidase antibody and serum 25-hydroxyvitamin D (25(OH)D). However, indespite the a large volume of evidence linking vitamin D with thyroid autoimmunity and cancer, meaningful clinical studies on the impact of vitamin D supplementation are needed [64].

Hashimoto's thyroiditis (HT) and differentiated DTC represents the most common autoimmune and malignant thyroid diseases [65], and hypovitaminosis D represents a prevalentjoint risk factor for HT [66] and differentiated DTC [67].

Sirtuins are the histone deacetylases that are involved in several metabolic pathways [68] and regulate post-translational modification of cellular regulator proteins on the energy status of the cell [69]. Recently, Sirtuin 1 has been shown to be regulated by vitamin D by deacetylation of forkhead box protein O3a (FOXO3a) [70]., tThe latter wasbeen reported as an important risk factor for TC [71], therefore suggesting a potential key role of vitamin D-SIRT1-FOXO3a signalling in immune regulation and TC. Recently, Roehlen et al. have genotyped the SNP's FOXO3a in 257 subjects with DTCdifferentiated thyroid carcinoma, 139 individuals with Hashimoto thyroiditis compared to 463 healthy controls [65]. The Aauthors have found that SNP's of FOXO3a, in particular rs9400239T and rs4945816C, independent of the vitamin D status, may constitute risk factors for Hashimoto

thyroiditis, indicating the implication of FOXO3a in the pathogenesis of autoimmune thyroid diseases. In addition,The anti-proliferative vitamin D effects on SIRT1 activity, show a keycritical role of the vitamin D-SIRT1-FOXO3a axis for protective vitamin D effects [65]. In addition, also sSome alterations of genetic variantsthat encode crucial enzymes for the synthesis, metabolism and degradation (DHCR7 rs12785878, CYP2R1 rs2060793, CYP24A1 rs6013897, respectively) of vitamin D, and they have been associated with serum levels of 25(OH)D and on the susceptibility to TC [72]. In particular,The case-control study done by Carvalho et al. in a case-control study investigated the effect of these variants in the vitamin D pathway and susceptibility to TC in 500 patients withdifferentiated DTC and 500 controls. The results of this study showed the association between DHCR7 rs12785878 and TC under, suggesting that DHCR7 polymorphisms due to its effect on circulating 25(OH)D levels, may be associated with an increased risk of TC [72].

Of interestRemarkbly, vitamin D has proven useful also as a prognostic tool for TC, as examined in 334 patients in a study of Sulibhavi et al. [73]. In this study, 25(OH)D levels showed no significant association to cancer stage, but subjects with hypovitaminosis D were more likely to have advanced disease. The results of this study suggests that hypovitaminosis D may have value as a negative prognostic indicator in papillary TC [73].

Although some studies have showned that higher 25(OH)D levels might protect against TC, other studies do not confirm this association, or have even indicated the opposite to be the case [74]. Very recently, in a meta-analysis of 14 articles, Zhao et al. investigated the association between deficit of vitamin D deficiency and TC. These metanalysis results of this metanalysis have showned that 25(OH)D levels were lower in patients with TC preoperatively compared tothan controls, concluding that lower 25(OH)D levels were associated with increased risk for TC and that hypovitaminosis D may act as a risk factor for TC [74]. In conclusion, the association between hypovitaminosis D and TC is still controversial.

Fruits and vegetables consumption

The fFruits and vegetables consumptionintake have been associated with a reduced risk of several tumors in case-control studies, but these relationships become weak or even null in cohorts studies [75, 76]. Nevertheless, the question of what is the optimal amount and type of fruit and vegetable consumption to reduce thecancer risk of cancer is still unanswered [75]. This issue is reflected by the fact that recommendations for dietary consumption vary globally. A weak one association between fruit and vegetable consumption or specific subtypes of fruits and vegetables and cancer risk cannot yet be excluded [76], but the current evidence is scarce [75]. Some studies reported inverse associations [75-77], whereas other studies found no clear association [75, 78, 79]. However, some of these may have had statistical power too low to detect a modest association.

Fruit and vegetables contain a variety ofvarious nutrients and phytochemicals, such as vitamins, antioxidants, flavonoids, and other unidentified compounds. All these nutrients could act alone or in synergy with each other through several biological mechanisms to reduce risk ofthe cancer risk[80]. In particular, the mechanisms by which fruits and vegetables could reduce the cancer risk are different: neutralization of reactive oxygen species (ROS) and reduce DNA damage through their antioxidants in fruit and vegetables [81]; detoxifying enzymes action by glucosinolates in cruciferous vegetables [82], among others.

Of interest, fruits and vegetables consumption through its fiber content content of fibre, may modulate the production of short-chain fatty acids (SCFAs) in the gut with a beneficial effect on gut microbiota [83, 84] and steroid hormone concentrations and hormone metabolism [81].

Currently, little is known about the association withbetween fruit and vegetables consumption and TC risk, particularly in prospective studies. Very recently, Zamora-Ros et al., in the EPIC study, evaluated the fruit and vegetable consumption and TC risk in over half a million participants, recruited between 1991 and 2000 with a mean follow-up period of 14 years. The results of tThis large study did not report a significant association between fruit and vegetable consumption and TC risk [41]. Of iInterestingly, the cruciferous vegetables have been studied more closely due asto containing glucosinolates, a diet source of thiocyanates and isothiocyanates that act as goitrogens [85] promoting

thyroid tumour growth in rats [86, 87]. Nevertheless, in two recent meta-analyses of retrospective studies, either no relationship or a positive association between cruciferous vegetables consumption and TC risk were evident [38, 88].

Alcohol consumption

The aAlcohol consumption is another important dietary factor on TC risk. In particular, evidence from several prospective [89-93] and case–control studies [94, 95] has reported a protective association between current moderate alcohol consumption and TC risk.

In a recent large study within the EPIC study, Sen et al. investigated baseline and lifetime alcohol consumption and risk of TC among 477.263 subjects (70% women), and 556 (90% women). The authors of this study observed that moderate alcohol consumption at recruitment was associated with a statistically significant lower risk of TC [43]. The potential mechanisms explaining the link between alcohol intake and TC risk are not well known and are complex. The Ddirect toxic effect of alcohol on the thyroid, has been suggested ofby some studies [96, 97].

Nevertheless, the potential effects of alcohol intake on the thyroid function should be considered speculative as there are much less studied. The free radicals generated by alcohol metabolism leadcause oxidative stress in tissues poorly metaboliszing alcohol, including thyroid, and leading to hypothalamus–pituitary–thyroid axis dysfunction and reducedtion of peripheral thyroid hormone concentrations [98].

Impact of resveratrol

There is an increasing interest in Phytochemical and TC treatment and other types of cancer Ssince there are still limitations for thise TC treatment, such as drug resistance or the unfavorable side effects from some treatment options, there is increasing interest on Phytochemical and TC treatment and other types of cancer [99]. The important anti-inflammation, anti-oxidation, and anti-cancer effects found in the Phytochemical (chemical substances produced by plants) have allowed

them to impact deeplyprofoundly in decreasing cell proliferation, angiogenesis, and invasiveness [100]. Resveratrol (3,5,4′-trihydroxy-trans-stilbene) is a phytochemical and a natural stilbenoid that haswith two aromatic rings with a methylene bridge. It can be found in grapes, blueberries, raspberries, and red wines,and in peanuts, pomegranates, and soybeans [101, 102]. Resveratrol has shown to be helpful in radioiodine therapy.

Additionally, it has shown to be helpful in radioiodine therapy [103, 104], due to its capacity to protect normal cells from reactive oxygen species (ROS) induced cytotoxicity by reducing them through the hydroxyl groups in the resveratrol's chemical structure., as it was reported by tTwo publications where it was highlighted the use of resveratrol as co-treatment with radioactive iodine therapy [105, 106]. Moreover, to its ROS scavenging effect, resveratrol has anti-thyroid cancer activities by regulating TC-specific signaling pathways to its ROS scavenging effect. Zheng et al. demonstrated that intragastric and intraperitoneal resveratrol administration of resveratrol efficiently reduced the frequency and severity of TC-related lesions such as hyperplasia and adenomas [107]. Resveratrol also influences thyroid function by enhancing iodide trapping and, by increasing thyroid-stimulating hormone (TSH) secretion via activation of sirtuins and the phosphatidylinositol- 4-phosphate 5 kinase γ (PIP5Kγ) pathway, positively affects metabolism [108]. These results imply that resveratrol improves retinoic acid sensitivity, enhances theradiotherapy's efficacy of radiotherapy, induces apoptosis or re-differentiation, and induces cancer stem cells differentiation [99].

White meat and Red meat

While cooking red meat at a high temperature, carcinogenic compounds such as heterocyclic amines (HCA), polycyclic aromatic hydrocarbons (PAH), N-nitroso compounds, or heme iron are formed [109].

From Wie et al.'s study done among 26,815 participants in cancer screening examinations from September 2004 to December 2008, there were selected 8,024 subjects who completed a self-administered questionnaire were selected. In September 2013, 387 cancer cases were classified from

the National Cancer Registry System, 387 cancer cases were classified, and the remaining individuals were included in the control group. From this study it was concluded that red meat consumption, Na intake and obesity (BMI ≥ 25 kg/m²) were positively associated with overall cancer incidence in men (HR 1.41, 95% CI 1.02, 1.94; P= 0.04), gastric cancer (HR 2.34, 95% CI 1.06, 5.19; P= 0.0365) and TC (HR 1.56, 95% CI 1.05, 2.31; P= 0.0270), respectively [110]. Also, an increased risk of TC associated with nitrate intake was reported in a cohort study of older women in Iowa. This study was a large prospective cohort of 490,194 men and women, ages 50-71 years, in 1995-1996. A 124-item food frequency questionnaire was used to determine the dietary intakes. During an average of 7 years of follow-up, they identified 370 incident TC cases (170 men, 200 women) with complete dietary information. Among men, increasing nitrate intake was positively associated with TC risk (relative risk [RR] for the highest quintile versus lowest quintile RR = 2.28, 95% CI: 1.29-4.04; p-trend <0.001). However, no trend with intake among women was observed (p-trend = 0.61). Nitrite intake was not associated with TC risk of TC for either men or women [111]. A systematic review and meta-analysis published onin 2015 concluded that no significant association was observed between nitrate exposure and theTC risk of TC, hyper- and or hypothyroidism. Additional research is needed to clarify the association between nitrate/nitrite exposures and both thyroid function and cancer [112]. On the other hand, high consumption of fresh fish seemed to have a protective effect against TC (OR=0.6; 95% CI: 0.3–1.0; *P*-trend <0.05). ButNevertheless, when fish products were processed, canned, or frozen, there was a strong positive association with TC (OR=3.0; 95% CI: 1.6–5.3; *P*-trend <0.01). Among other types of meat, high consumption of chicken (OR=3.0; 95% CI: 1.3–6.8; *P*-trend <0.01) as well as mutton and lamb (OR=1.8; 95% CI: 1.1–2.8; *P*-trend <0.01) showed a positive association with TC [35]. These studies suggests that several components like red meat, canned or frozen fish, high consumption of chicken, and processed meats like sausages, may influence TC risk.

Coffee and tea and other drinks

Coffee and tea are beverages consumed on a daily basis worldwide in adults. Both of them are rich sources of flavonoids and phenolic acids [113]. Polyphenols may play a role in cancer prevention, including TC, through the modulation of enzyme activities and signal transduction pathways related to cellular proliferation, differentiation, apoptosis, inflammation, angiogenesis, and metastasis (DOI: 10.23736/S1120-4826.19.02522-9) [114]. However, tThere is mucha lot of controversy for the caffeine and theophylline because of their negative and positive effects in carcinogenesis [115].

In the report by Alicandro et al., where they reviewed available evidence on coffee drinking and the risk of all cancers updated to May 2016, they concluded that coffee consumption is not associated with overall cancer risk [116]. The EPIC cohort, which included 476,108 adult men and women, coffee and tea intakes were assessed through validated country-specific dietary questionnaires, and during a mean follow-up of 14 years, 748 first incident differentiated DTC cases were identified. Coffee consumption (per 100 mL/day) was not correlated either with total differentiated DTC risk (HR: 1.00, 95% CI 0.97-1.04) or with the risk of TC subtypes. Tea consumption (per 100 mL/day) was not associated with the risk of total differentiated DTC (HR: 0.98, 95% CI 0.95-1.02). An inverse association was found with follicular tumor risk (HR: 0.90, 95% CI 0.81–0.99), but this association was based on a sub-analysis with a small number of cancer cases. In conclusion, in this large prospective study, coffee and tea consumptions were not associated with TC risk (PMID: 30535794) [114]. Hashibe et al., observed in the PLCO trial a decreased risk of endometrial cancer for coffee intake (RR=0.69, 95% CI=0.52-0.91 for ≥2 cups *per* day), and a decreased risk of cancer overall with tea intake (RR=0.95, 95% CI=0.94-0.96 for 1+ cups per day *vs.* <1 cup per day). This trial started in 1992 and ended enrollment in 2001. Approximately 155,000 women and men between the ages of 55 and 74 participate in this randomized study [117]. Michikawa et al., analyzed data from a prospective cohort of 100,507 persons, where green tea and coffee consumption were assessed via a self-administered questionnaire. During a mean 14.2-year follow-up, they documented 159 TC cases. They inferred that high green tea consumption could be associated with premenopausal

TC risk, but inversely correlatedassociated with postmenopausal TC risk [118]. Finally, Riza et al., in their study, they concluded that drinking herbal teas, especially chamomile ($P < 0.001$), protects from TC as well as other benign thyroid diseases. From these studies, it can be suggested to drink tea, especially chamomile, to prevent TC [119].

Soy Foods

Soy foodsThey have been considered as excellent replacements for dairy products, consideredrecognized as sources of high-quality protein and healthful fat and uniquely-rich sources of isoflavones (classified as phytoestrogens and selective estrogen receptor modulators). Soy foods were widely accepted because of the potential effects on health, such as the effectiveness in cardiovascular risk reduction, antioxidative effect of flavonoids may protect from cancer [120, 121], preventive roles in hypertension, hypercholesterolemia [122], bodyweight loss [123]. Nonetheless, there are reports of possible disruption of thyroid function and sexual hormones. A cross-sectional study of 11,688 women aged 30–50 years of North American Adventist church showed that high intake of isoflavones was related to increased risk of nulliparity and nulligravitynull gravity [124]. There are also reports of soy products into infant diet before 4 months of age and a 25% higher risk of menarche before 12 years of age [125]. About the thyroid gland disturbance, more long-term epidemiological studies are needed to verify soy-thyroid interaction in real conditions since in clinical trials; isolated isoflavones are used with a wide range of concentrations and heterogenic conditions [126]. In the multiethnic population-based case-control study of thyroid cancer conducted from the San Francisco Bay Area with 817 cases diagnosed between 1995 and 1998, 608 (74%) were examined. Phytoestrogen consumption was determined via a food-frequency questionnaire and a newly developed nutrient database. They reported that the consumption of traditional and nontraditional soy-based foods and alfalfa sprouts were associated with a reduced TC risk of TC [127]. In a recent study by Xiao et al., the association between dietary flavonoid intake and TC risk in 491,840 participants was investigated. It was reported that TC risk was not associated with the dietary intake

of isoflavones [128]. After analyzing carefully the results from these few studies carefully, it remains inconclusive the potential influence of isoflavones on TC risk.

Mediterranean diet

This dietary pattern is commonly used by the people living onin the Mediterranean coasts [129]. It is characterized by a higher intake of the majority of plant-derived foods, including vegetable and fruits, legumes, whole-grains, and extra virgin olive oil as the only source of fat, moderate alcohol consumption (especially red wine), moderate intake of animal protein (most represented by fish and dairy products), and very limitedminimal consumption of meat and highly processed foods [129]. Additionally, it is low in saturated fatty acids and provides high amounts of monounsaturated fatty acids and n-3 PUFAs, mainly derived from olive oil as alpha-linolenic acid and long-chain PUFAs from fish [130]. The foods and beverages of plant origins are widely rich in polyphenols, in particularly fruits, vegetables, spices, nuts. , etc) [131, 132]. The MD's beneficial effects of the MD are the high content in antioxidants and anti-inflammatory compounds, including polyphenols, to play a role in the preventingon of cancer [129, 133] and other diseases such as cardio-metabolic, neurodegenerative disorders[129], among others. There are sSeveral papers showing the antitumor effects of natural polyphenols [132], including anthocyanins from blueberries, epigallocatechin gallate from green tea, and resveratrol from red wine. All tThese functions are associated with cell survival, proliferation, differentiation, migration, angiogenesis, hormone activities, detoxification enzymes, and immune responses [132]. In spite ofDespite all the existing robust evidence regarding the MD and its advantages, more studies are needed to show a direct causal relationship ofbetween this diet and the reduction ofn TC risk. As it was reported by the EPIC cohort, which included 476,108 men and women from 10 European countries, no associations between dietary polyphenol consumption and TC risk wereas demonstrated [134].

The MD was associated with a lower risk of breast cancer [135, 136], gastroenteropancreatic neuroendocrine tumors aggressiveness [137-139], and other cancers [140, 141]. Nonetheless, there are only a few studies that link dietary patterns to TC [29, 34, 142]. In a case-control study of 113 subjects, Markaki

et al. [34] found that dietary patterns of fruits, raw vegetables, and mixed raw vegetables and fruits were negatively associated with TC (ORs 0.68, 0.71, 0.73, respectively).

Another study did not report any difference between traditional Polynesian diet (characterized by high consumption of fish, seafood, and fruits) and Western diet (characterized by high consumption of meat and starchy food), in 229 cases of differentiated DTC diagnosed, and 371 controls [142]. Very recently, Sangsefidi ZS et al., in a case-control study among 309 clinic-based participants in the northeast of Iran, evaluated the role of major dietary patterns on differentiated DTC. The only association reported in this study was that the western diet had 2.85 times more chance for differentiated DTC (OR=2.85, 95% CI=1.15-7.06) [29].

Dietary indications as Medical Prescription in the Reduction of Thyroid Cancer Risk: The Point of View of the Endocrinological Nutritionist

The current state of the dietary recommendations for the preventions of TC are lackingremains controversial, as the clinical studies' results of the clinical studies are inconsistent. However, based on current scientific evidence, we can give some dietary indications as a medical prescription to reduce in the reduction of TC risk, considering that the choice of food must be made by analyzing considering the presence of beneficial nutrients [20]. The principal dietary indications are summarized as follows:

1. Iodine intake and fish: Correction of iodine deficiency has shifted thyroid cancer subtypes toward less aggressive forms, without affecting thecancer's overall risk for cancer. High iodine intake seems to exert a protective effect against cancer;
2. Fruits and vegetables: They may provide a protective role for combiningthe combination of bioactive components with antioxidant activity, such as selenium and vitamin D, micronutrients, and phytochemicals. Eat 2 servings of fruits and at least 7.5 servings *per* day (600 g/d) of green-yellow and cruciferous vegetables (salads) *per* day;
3. Selenium, vitamin D: Despite the well-known anti-cancer activities and potentials, there is limited evidence on the association between either selenium or vitamin D deficiency and TC, as well as on the clinical usefulness of their supplementation in these patients;
4. Bodyweight: Obesity is associated with the incidence of various tumors, including differentiated DTC. An association between excessive weight and TC risk of TC, with more aggressive behavior, emerges from most of the studies.
5. Alcohol, red meat and dairy: To limit excess consumption of alcohol, meat, and dairy food even if no clear associations were found among the consumption of these foods on TC risk;
6. Don´t consume processed food;

7. Don´t consume frozen or canned fish or seafood;
8. Drink daily chamomile tea and herbal tea to prevent TC;
9. Adopt healthy lifestyle habits: Exercise 30 minutes daily or 1 hour every 2 days.

Most of these suggestions are potentially useful also for patients with thyroid cancer (Table 1)

Conclusion

Interesting Significant associations between single nutrients or food and TC risk have been described observed. Understanding the bidirectional relationships between dietary patterns and TC risk is also essential for delineating the risk profile from obesity **(Figure 1)**. Adopting a healthy lifestyle and the education regarding modifiable environmental factors (diet, nutrition, and physical activity) could have beneficial effects *per se* on reducing of TC risk. For achieving dietary-related goals, the skilled Endocrinological Nutritionist should play a central role during the endocrinological examination assessment considering dietary recommendations as like a real one medical prescription for the prevention of TC risk. On the basis of Based on its beneficial antioxidants and anti-inflammatories components, the MD could also presents health benefits also in TC's the prevention of TC. The advantageous beneficial effects of nutritional interventions promoting the Mediterranean food pattern could be extended to patients at risk of developing TC. Future well-designed dietary intervention trials on larger population samples are needed to define specific dietary guidelines forprevention of reducing TC risk.

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NOTES

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Abbreviations.

Abbreviations: Thyroid cancer (**TC**); body mass index (**BMI**); Mediterranean diet (**MD**); Poly-Unsatured Fatty Acids (**PUFAs**); eicosapentaenoic acid (**EPA**); docosahexaenoic acid (**DHA**); European Prospective Investigation into Cancer and Nutrition (**EPIC**); ultraviolet B (**UVB**); 25-hydroxyvitamin D (**25(OH)D**); forkhead box protein O3a (**FOXO3a**); short-chain fatty acids (**SCFAs**); reactive oxygen species (**ROS**); thyroid-stimulating hormone (**TSH**); phosphatidylinositol- 4-phosphate 5 kinase γ (**PIP5Kγ**); heterocyclic amines **(HCA)**; polycyclic aromatic hydrocarbons (**PAH**), relative risk (**RR**).

FIGURE

Figure 1: picture describing the known and potential factors involved in the correlation between Llifestyle patients and the development of thyroid cancer

TABLE

Table 1: Most of these suggestions are potentially useful also for patients with thyroid cancer

Table 1: Dietary suggestions for a correct lifestyle in thyroid cancer patients

✓ **Iodine intake and fish**	– A correct intake of iodine with the diet plays a protective role in the development of nodules and, therefore, potentially also thyroid carcinomas – High iodine intake seems to exert a protective effect against cancer
✓ **Fruits and vegetables**	– They may provide a protective role for the combination of bioactive components with antioxidant activity – Eat 2 servings of fruits and at least 7.5 servings per day (600 g/d) of green-yellow and cruciferous vegetables (salads) per day
✓ **Selenium, vitamin D**	– tThere areis limited evidences on the association between either selenium or vitamin D deficiency and TC
✓ **Obesity**	– Obesity is associated with the incidence of various tumors, including differentiated DTC – Weight loss is therefore recommended for patients with thyroid cancer
✓ **Alcohol, red meat, and dairy**	– No clear associations were found among the consumption of these foods on TC risk – In any case, it is advisable not to exceed with these foods in order to reduce the risk of obesity.
✓ **Adopt healthy lifestyle habits**	– It is recommended to perform physical exercise 30 minutes daily or 1 hour every 2 days
✓ **Nutritional status in patients treated with Tyrosine Kinase Inhibitors (TKI)**	– A close monitoring and management of weight loss is crucial to avoid withdrawal and to limit the need for dose reduction – eExpert nutritionist interventions are needed in patients affected with advanced TC treated with TKI

TITLE: DIET AS A POSSIBLE INFLUENCING FACTOR IN THYROID CANCER INCIDENCE: THE POINT OF VIEW OF THE NUTRITIONIST

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Running title: Diet and Thyroid Cancer Risk.

Abstract

The incidence of differentiated thyroid cancer has increased in the last decades all over the world. Different environmental factors are possible perpetrators of this exponential growth. Nutritional factors are among the main environmental factors studied for thyroid cancer in recent years. This review aims to overview the main dietary factors involved in thyroid cancer risk, providing specific nutrition recommendations from the endocrinological Nutritionist point of view. Among the single food, fish and shellfish are the primary natural source of iodine, selenium and vitamin D in the human diet. These nutrients are essential for the synthesis of thyroid hormones; however, their consumption is not consistently related to thyroid cancer risk. The high intake of fruit and vegetables, probably due to their vitamin and antioxidant content, shows a weak inverse association with thyroid cancer risk. Alcohol, meat, or other food groups/nutrients showed no significant effect on thyroid cancer. In conclusion, to date, no definite association among dietary factors, specific dietary patterns, and thyroid cancer, and its clinical severity and aggressiveness have been found. However, it is essential to underline that in the future, prospective studies should be carried out to precisely evaluate the qualitative and quantitative intake of nutrients by patients to establish with more confidence a potential correlation between food intake and the occurrence and development of thyroid cancer.

Keywords: Diet; Thyroid Cancer Risk; Mediterranean Diet, Vitamin D, Nutritionist.

TEXT

Introduction

Thyroid cancer (TC) is considered a rare disease since it constitutes <1% of all cancer [1]. However, it represents the most frequent endocrine cancer, affecting 5% of thyroid nodules, which have a prevalence of 20-50% in the general population, increasing due to improved diagnostic techniques and early diagnosis [2]. In particular, ultrasound and fine-needle aspiration are the most important diagnostic tools for evaluating thyroid nodules [3-5].

TC has a greater prevalence in the female sex, with a 3:1 female-to-male ratio in most geographic regions and demographic groups. Although these tumors are rare in children, they affect a younger population than most malignancies, with a maximum incidence between 25 and 60 years [6]. Survival is very high, exceeding 90% at 5 years in differentiated form [6]. Moreover, since the TC prognosis is excellent in most cases and the mortality rate remains very low, to date, there is much interest in the personalized risk-based treatment [7].

TC generally originates from follicular cells and is divided into papillary, follicular, anaplastic, and medullary carcinoma [8]. Papillary carcinoma is the most frequent form of differentiated TC (DTC), comprising about 80% [9]. It has slow growth and can cause loco-regional lymph node metastases. In some patients, the tumor is multifocal and can affect both lobes of the thyroid gland [10]. Follicular carcinoma represents about 15% of DTC and can produce distant metastases. Anaplastic carcinoma is a rare type of tumor, <1% of TC, but it is particularly aggressive already at diagnosis with inadequate response to conventional therapies [11]. Medullary carcinoma originates from parafollicular cells (or C cells), and the diagnosis is based on the basal or stimulated calcitonin dosage [12]. This tumor can occur in familial forms as the manifestation of genetic syndromes, such as multiple neoplastic syndrome type 2.

In DTC some recurrent genetic mutations have been found that specifically affect receptors with tyrosine kinase activity and their pathways, such as BRAF (V600E) mutation, RET/PTC rearrangements RAS and pTERT mutations in papillary carcinoma and PAX8–PPARγ

rearrangements or RAS and pTERT mutations in follicular carcinoma [8,13]. These mutations also justify the known relationship between exposure to ionizing radiation and increased TC incidence since radiation induces double-stranded DNA breaks and genetic rearrangement [14].

As reported in clinical studies, the thyroid is particularly sensitive to the long-term effects of radiation exposure [15]. This association was evaluated in population-based case-control studies of adolescents exposed to radiation following the Chernobyl accident and subjects exposed to the atomic bombings of Hiroshima and Nagasaki, where an increased incidence of TC was demonstrated [16]. The adverse effects of radiation in inducing TC have been reported in atomic bomb survivors from 62 to 66 years after exposure during their childhood [17]. Remarkably, Mesrine et al. prospectively analyzed 86.960 women followed up over 1990-2008, finding associations between nevi, baseline residential ultraviolet exposure, and TC risk [18]. Results showed that ultraviolet exposure level and the number of nevi were associated with thyroid nodules or history of thyroid disturbances, and the number of nevi was positively associated with TC risk (HR=1.7, 95% CI=1.0, 2.8; p=0.01). This risk was restricted to females with dietary iodine below the median intake. The authors concluded that TC risk was associated with the number of nevi and residential ultraviolet exposure [18].

In addition to ionizing radiation, the main risk factors known for TC are family history, female gender, and obesity [19]. A family history of TC in first-degree relatives is associated with a 10-fold increased risk of non-medullary TC based on a large case-control study [20]. Although this cancer incidence is significantly higher in women, no clear pathophysiological and hormonal mechanisms have been identified[21]. Some observational studies have shown an association between excess weight and increased TC risk, both well-differentiated and anaplastic. In particular, a meta-analysis of 22 prospective studies showed that a high body mass index (BMI) is associated with an increased TC risk, and that this association is even stronger in younger subjects than in elderly ones. The presence of obesity would also seem to be associated with TC with a worse prognosis [22] .

Beyond ionizing radiation, family history of TC, female gender, and obesity, other environmental factors seem to play a potential role in the pathogenesis of TC, such as single foods or

dietary patterns, including fish, vegetables, vitamin D, selenium and adherence to the Mediterranean diet (MD) [19]. It is noteworthy that nutritional and dietary patterns have recently gained high interest as possible promoters and modifiable risk factors for TC [19]. They represent a significant objective of the dietetic and metabolic multidisciplinary rehabilitation in patients with obesity, aiming to achieve a weight loss and the improvement of obesity-related cardiovascular and metabolic diseases [23], beyond the drug therapy for obesity [24, 25].

In particular, the low dietary iodine intake was negatively associated with increased TC risk, favoring the development of more aggressive histotype [19]. Moreover, the low dietary intake of selenium and vitamin D was associated with TC. However, the evidence is scarce, despite their well-known anticancer potential of these nutrients, and the clinical usefulness of their dietary supplementation is still uncertain in this setting. The relationship between single foods and TC remains difficult to examine. Although no clear link between dietary factors and TC has been firmly established so far, some dietary patterns, in particular, adherence to the MD are supposed to play a role in thyroid carcinogenesis as well as in its stage and aggressiveness. Unlike the study of individual foods or nutrients, diet is a complex interaction of single nutrients, foods and phytonutrients, and numerous individual compounds [26]. For this reason, the benefit of the dietary pattern is a synergistic and/or accumulative effect of nutrients and foods [26]. In this context, to promote the reduction of TC risk, the focus should be on a healthy dietary pattern, particularly the adherence to the MD and not, on individual nutrients.

The present review summarizes the current epidemiological evidence on TC's nutritional risk factors, with particular attention to adherence to the MD, and provides nutrition and dietetics guidance to be followed by nutritionists to reduce TC risk, paying particular attention to adherence to the MD.

Nutrition and TC risk

As previously reported, TC is among the common endocrine carcinoma, and it increased rapidly worldwide during the past three decades [27]. Beyond genetic predisposition, TC risk is related to different factors such as radiation, thyroid disorders, hormonal and growth factors, obesity, and nutritional factors [28].

Environmental carcinogens, probably higher in the last decades, including nutritional factors, may explain the recent increase in TC incidence [29]. Previous evidence reported that some nutritional factors could affect TC risk, but most of these data were inconsistent due to diverse dietary patterns, eating habits, lifestyles, and other environmental risk factors in the different populations. Of interest, the populations living in iodine sufficient regions with high fish consumption showed either no relationship or lowered TC risk [27, 30]. Therefore, populations exposed to certain food types can have an increased or reduced TC risk compared with those who are not [27]. Most of the studies conducted that evaluated the relationship between TC risk and nutrition have focused on single dietary factors, such as food items (fish, vegetables) or nutrients (vitamin D, selenium, among others) [19]. In particular, some foods, including fish and other iodine-rich foods [27], vegetables, and fruits and other polyphenol-rich foods [27, 31-33], might have potential protective effects on TC risk. Contrariwise, high intake of meat, particularly chicken, mutton, lamb [34], pork, and poultry [33, 35] , were associated with a higher TC risk.

The main evidence for a single food

Fish and shellfish consumption

Fish and shellfish are an essential source of different nutrients, such as iodine, selenium, and vitamin D, all crucial factors for the synthesis of thyroid hormones [36].

One of the well-established risk-modifying factors for TC is the dietary exposures [27, 37]. Among these have been suggested intake of iodine-rich seafood [38], goitrogenic vegetables [30, 39], poly-unsaturated fatty acids (PUFAs) [40], and alcohol [41]. Fish and shellfish are considered healthy foods in different dietary patterns, including MD [42], because of their content in iodine, selenium, healthy fat omega–3 PUFAs (eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)) and lipid-soluble vitamins, including retinol, vitamin D, and vitamin E [43].

In a recent European Prospective Investigation into Cancer and Nutrition (EPIC) study, Zamora-Ros et al. prospectively evaluated the association between quantity and quality of fish consumption and TC risk in a cohort of >500,000 men and women recruited in 10 European countries. In particular, based on quality, the fish was classified as: lean fish with <4 g/100 g of fat (e.g., cod, haddock, and plaice), and fatty fish with fat content between 4 and 14 g/100 g (e.g., salmon, tuna, and trout). While the amount of fish consumed was classified into: shellfish intake (including seafood such as prawns, crab, and mussels), fish and fish product intake (sum of lean and fatty fish and fish products), and total fish and shellfish intake, which was defined as the sum of intakes of fish, fish products, and shellfish. Dietary data were collected with quantitative or semiquantitative food frequency questionnaires that were developed and locally validated in EPIC. This study reported no significant association between fish consumption and TC risk; likewise, no significant correlation was reported with the intake of any specific type of fish, fish product, or shellfish [44].

This large study's results are also in agreement with a previous cohort study [45] , a systematic review [46], and meta-analysis [37]. Besides, fish is a rich source of omega–3 PUFAs (EPA and DHA), that, through their impact on prostaglandin synthesis, have anti-inflammatory properties and have

been reported to be a protective factor in TC risk [47]. In particular, an inverse association between PUFA intake and TC risk was showed in the EPIC study [40].

Vitamin D

Vitamin D, in addition to its central role in calcium homeostasis, can regulate (directly or indirectly), multiple signaling pathways involved in cellular proliferation and differentiation, apoptosis, inflammation, invasion, angiogenesis, and metastasis, with the potential to affect cancer proliferation [48] and invasiveness [49]. The most recognized antineoplastic effect of vitamin D is its ability to inhibit cell proliferation [50]. Besides its antiproliferative effects, vitamin D also regulates inhibiting antiapoptotic proteins (BCL-2 and BCL-XL) and inducing the expression of proapoptotic proteins (BAX, BAK, and BAD), the key mediators of apoptosis [48]. Beyond the importance of vitamin D in inflammatory processes associated with several chronic diseases, including obesity [51-53], polycystic ovary syndrome [54, 55], and psoriasis [56], vitamin D's role has been determined in autoimmune and malignant thyroid diseases [57]. Different preclinical studies have shown growth arrest of TC after the administration of pharmacological doses of vitamin D in differentiated TC cell lines [58]. The main form of vitamin D, the cholecalciferol (or vitamin D_3), is synthesized in the skin by 7-dehydrocholesterol reductase upon exposure to ultraviolet B (UVB) radiation and can also be obtained from a few dietary sources (mainly fatty fish) [48] and meat [59]. In addition to the production of vitamin D, the index of solar UVB irradiance can be associated with the genesis of some cancers. In particular, Grant has evaluated the cancer mortality rates for 48 continental Spanish provinces for 1978-1992 concerning mortality rates by latitude (an index of solar UVB levels), reporting that nine cancers were significantly correlated with latitude, including TC. Additionally, TC was associated with non-melanoma skin cancer, highlighting that TC's development can a have different aetiology [60]. In this context, an inverse association between UV-B exposure and nonskin cancer mortality, including TC, has been reported, probably through vitamin D, produced by exposure to the sun *via* the skin. Boscoe and Schymura showed inverse relationship between UV-B exposure and TC (only

in females), suggesting a vital role in maintaining adequate vitamin D levels linked to sun exposure [61].

Beyond TC risk, vitamin D also plays an indispensable role in thyroid autoimmunity, improving the innate immune response and exerting an inhibitory action on the adaptive immune system [48]. Calcitriol, the activated (or hormonal metabolite of) vitamin D, has been reported to modulate the cytokine milieu to a more tolerogenic immune status [62]. Dutta et al. confirmed that anti-thyroid peroxidase antibody positivity is more prevalent in individuals with hypovitaminosis D and reported a negative correlation between anti-thyroid peroxidase antibody and serum 25-hydroxyvitamin D (25(OH)D). However, despite the large volume of evidence linking vitamin D with thyroid autoimmunity and cancer, meaningful clinical studies on the impact of vitamin D supplementation are needed [63].

Hashimoto's thyroiditis (HT) and DTC represent the most common autoimmune and malignant thyroid disease [64], and hypovitaminosis D represents a prevalent risk factor for HT [65] and DTC [66].

Sirtuins are histone deacetylases involved in several metabolic pathways [67] and regulate posttranslational modification of cellular regulator proteins on the energy status of cell [68]. Recently, Sirtuin 1 has been shown to be regulated by vitamin D by deacetylation of forkhead box protein O3a (FOXO3a) [69]. The latter was reported as an important risk factor for TC [70], suggesting a potential key role of vitamin D-SIRT1-FOXO3a signaling in immune regulation and TC. Recently, Roehlen et al. have genotyped the SNP's FOXO3a in 257 subjects with DTC, 139 individuals with HT compared to 463 healthy controls [64]. The authors have found that SNP's of FOXO3a, in particular rs9400239T and rs4945816C, independent of vitamin D status, may constitute risk factors for HT, indicating the implication of FOXO3a in the pathogenesis of autoimmune thyroid diseases. The study authors conclude that, both rs4945816C and FOXO3a rs9400239T may constitute risk factors for TC, independent of the vitamin D levels. This underlines the role of FOXO3a in pathogenesis of autoimmune thyroid diseases. In addition, these evidence suggest that SIRT1 to be a crucial mediator

of anti-proliferative action and immune regulatory indicating that SIRT-FOXO3a is a downstream targets of vitamin D effects. Of interest, a combination of SIRT1 activators and vitamin D, could be a promising approach for novel anti-proliferative therapies also in TC[64]. Some alterations of genetic variants encode crucial enzymes for the synthesis, metabolism, and degradation (DHCR7 rs12785878, CYP2R1 rs2060793, CYP24A1 rs6013897, respectively) of vitamin D, and they have been associated with serum levels of 25(OH)D and on the susceptibility to TC [71]. The case-control study done by Carvalho et al. investigated the effect of these variants in the vitamin D pathway and susceptibility to TC in 500 patients with DTC and 500 controls. This study showed the association between DHCR7 rs12785878 and TC, suggesting that DHCR7 polymorphisms due to its effect on circulating 25(OH)D levels, may be associated with an increased risk of TC [71].

Remarkably, vitamin D has proven useful also as a prognostic tool for TC, as examined in 334 patients the study of Sulibhavi et al. [72]. In this study, 25(OH)D levels showed no significant association with cancer stage, but subjects with hypovitaminosis D were more likely to have advanced disease. This study suggests that hypovitaminosis D may have value as a negative prognostic indicator in papillary TC [72].

Although some studies have shown that higher 25(OH)D levels might protect against TC, other studies do not confirm this association or have even indicated the opposite to be case [73]. Very recently, in a meta-analysis of 14 articles, Zhao et al. investigated the association between vitamin D deficiency and TC. These metanalysis results have shown that 25(OH)D levels were lower in patients with TC preoperatively than controls, concluding that lower 25(OH)D levels were associated with an increased risk for TC and that hypovitaminosis D may act as a risk factor for TC [73]. In conclusion, the association between hypovitaminosis D and TC is still controversial.

Fruits and vegetables consumption

Fruits and vegetables intake have been associated with a reduced risk of several tumors in case-control studies, but these relationships become weak or even null in cohort studies [74, 75].

Nevertheless, the question of the optimal amount and type of fruit and vegetable consumption to reduce cancer risk is still unanswered [74]. This issue is reflected by the fact that recommendations for dietary consumption vary globally. A weak association between fruit and vegetable consumption or specific subtypes of fruits and vegetables and cancer risk cannot yet be excluded [75], but the current evidence is scarce [74]. Some studies reported inverse associations [74-76], whereas other studies found no clear association [74, 77, 78]. However, some of these may have had statistical power too low to detect a modest association.

Fruit and vegetables contain various nutrients and phytochemicals, such as vitamins, antioxidants, flavonoids, and other unidentified compounds. All these nutrients could act alone or in synergy through several biological mechanisms to reduce the cancer risk[79]. In particular, the mechanisms by which fruits and vegetables could reduce the cancer risk are different: neutralization of reactive oxygen species (ROS) and reduce DNA damage through their antioxidants [80]; detoxifying enzyme action by glucosinolates in cruciferous vegetables [81], among others.

Of interest, fruits and vegetables consumption through its fiber content may modulate the production of short-chain fatty acids (SCFAs) in the gut with a beneficial effect on gut microbiota [82, 83] and steroid hormone concentrations and hormone metabolism [80].

Currently, little is known about the association between fruit and vegetables consumption and TC risk, particularly in prospective studies. Very recently, Zamora-Ros et al., in the EPIC study, evaluated the fruit and vegetable consumption and TC risk in over half a million participants, recruited between 1991 and 2000 with a mean follow-up period of 14 years. This large study did not report a significant association between fruit and vegetable consumption and TC risk [39]. Interestingly, the cruciferous vegetables have been studied more closely due to containing glucosinolates, a diet source of thiocyanates and isothiocyanates that act as goitrogens [84] promoting TC growth in rats [85]. Nevertheless, in two recent meta-analyses of retrospective studies, either no relationship or a positive association between cruciferous vegetables consumption and TC risk were evident [37, 86].

Alcohol consumption

Alcohol is another important dietary factor for TC risk. In particular, evidence from several prospective [87-89] and case–control studies [90, 91] has reported a protective association between current moderate alcohol consumption and TC risk.

In a recent large study within the EPIC study, Sen et al. investigated baseline and lifetime alcohol consumption and risk of TC among 477.263 subjects (70% women), and 556 (90% women). They observed that moderate alcohol consumption at recruitment was associated with a statistically significant lower risk of TC [41]. In particular, compared with participants consuming 15 or more grams (approximately 1-1.5 drinks), subjects consuming 0.1-4.9 g of alcohol per day at recruitment, had a 23% lower risk of TC (HR=0.77; 95% CI=0.60-0.98)[41]. In addition, at recruitment non-consumers of alcohol were a similar risk for TC (HR=0.97; 95% CI=0.76–1.25) compared with consumers of 0.1–4.9 g per day. Among consumers for every 10 g of alcohol consumed per day, the risk of TC was lowered by 9% (HR=0.91; 95% CI=0.84–0.98) [41]. The potential mechanisms explaining the link between alcohol intake and TC risk are not well known. However, have been proposed different potential explanations for the effect for consumption of alcohol on decreased risk of TC. First, light-to-moderate alcohol intake is correlated with enhanced insulin sensitivity and reduced type 2 diabetes, a known risk factor for increased TC [92, 93]. Second, alcohol consumption is correlated with reduced prevalence of solitary thyroid nodules and goitre [94] , two important risk factors for TC [95]. Third, alcohol consumption have an effect on thyroid volume, thyroid function and the responsiveness of hypothalamic-pituitary-thyroid axis [95], which consequently lead to the modification of peripheral thyroid hormone concentrations. Of interest, alcohol decreases the thyroid-stimulating hormone (TSH) level since it acts reducing the responsiveness of the hypo–thalamic pituitary-thyroid axis to central stimulation. Nevertheless, the influence is elusive with regarding to the peripheral thyroid hormone concentrations on TC [95]. Fourth, alcohol intake could also potentially influence TC risk by altering sex steroid hormone levels [95].

Nevertheless, the potential effects of alcohol intake on thyroid function should be considered speculative as there are many less studied.

Impact of resveratrol

There is an increasing interest in phytochemical and TC treatment and other types of cancer since there are still limitations for this treatment, such as drug resistance or the unfavourable side effects from some treatment options [96]. The important anti-inflammatory, anti-oxidative, and anti-proliferative effects found in the phytochemical (chemical substances produced by plants) have allowed them to impact profoundly in decreasing cell proliferation, angiogenesis, and invasiveness [97]. Resveratrol (3,5,4′-trihydroxy-trans-stilbene) is a phytochemical and a natural stilbenoid with two aromatic rings with a methylene bridge. It can be found in grapes, blueberries, raspberries, red wines, peanuts, pomegranates, and soybeans [98, 99].

Additionally, it has been shown to be helpful in radioiodine therapy [100] due to its capacity to protect normal cells from ROS induced cytotoxicity by reducing them through the hydroxyl groups in resveratrol's chemical structure. Two publications highlighted the use of resveratrol as co-treatment with radioactive iodine therapy [101]. Moreover, resveratrol has anti-TC activities by regulating TC-specific signaling pathways due to its ROS scavenging effect. Zheng et al. demonstrated that intragastric and intraperitoneal resveratrol administration efficiently reduced the frequency and severity of TC through inhibiting proliferation and suppressing NF-κB mediated inflammatory reaction. [102].

Resveratrol also influences thyroid function by enhancing iodide trapping and increasing TSH secretion via activation of sirtuins and the phosphatidylinositol- 4-phosphate 5 kinase γ (PIP5Kγ) pathway, which positively affecting metabolism [103]. In this context, resveratrol would be favorable in the prevention of TC as it would improve retinoic acid sensitivity, enhance the radiotherapy's efficacy, would induce apoptosis, re-differentiation, and cancer stem cell differentiation. [96].

White meat and Red meat

While cooking red meat at a high temperature, carcinogenic compounds such as heterocyclic amines (HCA), polycyclic aromatic hydrocarbons (PAH), N-nitroso compounds, or heme iron are formed [104].

In Wie et al.'s study done among 26,815 participants in cancer screening examinations from September 2004 to December 2008, there were selected 8,024 subjects who completed a self-administered questionnaire. In September 2013, from the National Cancer Registry System, 387 cancer cases were classified, and the remaining individuals were included in the control group. From this study, it was concluded that red meat consumption, sodium intake, and obesity (BMI ≥ 25 kg/m²) were positively associated with overall cancer incidence in men (HR 1.41, 95% CI 1.02, 1.94; P= 0.04), gastric cancer (HR 2.34, 95% CI 1.06, 5.19; P= 0.0365) and TC (HR 1.56, 95% CI 1.05, 2.31; P= 0.0270), respectively [105]. An increased risk of TC associated with nitrate intake was reported in a cohort study of older women in Iowa. This study was a large prospective cohort of 490,194 men and women, aged 50-71 years, in 1995-1996. A 124-item food frequency questionnaire was used to determine the dietary intakes. During an average of 7 years of follow-up, they identified 370 TC cases (170 men, 200 women) with complete dietary information. Among men, increased nitrate intake was positively associated with TC risk (relative risk [RR] for the highest quintile versus lowest quintile RR = 2.28, 95% CI: 1.29-4.04; p-trend <0.001). However, no trend with intake among women was observed (p-trend = 0.61). Nitrite intake was not associated with TC risk for either men or women [106]. A systematic review and meta-analysis published in 2015 concluded that no significant association was observed between nitrate exposure and TC risk, hyper or hypothyroidism. Additional research is needed to clarify the association between nitrate/nitrite exposures and thyroid function and cancer [107]. On the other hand, high consumption of fresh fish seemed to have a protective effect against TC (OR=0.6; 95% CI: 0.3–1.0; *P*-trend <0.05). Nevertheless, when fish products were processed, canned, or frozen, there was a strong positive association with TC (OR=3.0; 95% CI: 1.6–5.3; *P*-trend <0.01). Among other types of meat, high consumption of chicken (OR=3.0; 95% CI:

1.3–6.8; *P*-trend <0.01) as well as mutton and lamb (OR=1.8; 95% CI: 1.1–2.8; *P*-trend <0.01) showed a positive association with TC [34]. These studies suggest that several components like red meat, canned or frozen fish, high consumption of chicken, and processed meats like sausages, may influence TC risk.

Coffee and tea and other drinks

Coffee and tea are beverages consumed daily worldwide in adults. Both of them are rich sources of flavonoids and phenolic acids [108]. Polyphenols may play a role in cancer prevention, including TC, through the modulation of enzyme activities and signal transduction pathways related to cellular proliferation, differentiation, apoptosis, inflammation, angiogenesis, and metastasis [109,110]. There is much for caffeine and theophylline because of their negative and positive effects in carcinogenesis [111].

In the report by Alicandro et al., where they reviewed available evidence on coffee drinking and the risk of all cancers updated to May 2016, they concluded that coffee consumption is not associated with overall cancer risk [112]. The EPIC cohort, which included 476,108 adult men and women, coffee and tea intakes were assessed through validated country-specific dietary questionnaires, and during a mean follow-up of 14 years, 748 DTC cases were identified. Coffee consumption (*per* 100 mL/day) was not correlated either with total DTC risk (HR: 1.00, 95% CI 0.97-1.04) or with the risk of TC subtypes. Tea consumption (*per* 100 mL/day) was not associated with the risk of total DTC (HR: 0.98, 95% CI 0.95-1.02). An inverse association was found with follicular tumor risk (HR: 0.90, 95% CI 0.81–0.99), but this association was based on a sub-analysis with a small number of cancer cases. In conclusion, in this large prospective study, coffee and tea consumption were not associated with TC risk [110]. Hashibe et al. observed in the PLCO trial a decreased risk of endometrial cancer for coffee intake (RR=0.69, 95% CI=0.52-0.91 for ≥2 cups *per* day), and a decreased risk of cancer overall with tea intake (RR=0.95, 95% CI=0.94-0.96 for 1+ cups *per* day *vs.* <1 cup *per* day). This trial started in 1992 and ended enrollment in 2001. Approximately

155,000 women and men between the ages of 55 and 74 participated in this randomized study [113]. Michikawa et al. analyzed data from a prospective cohort of 100,507 individuals, where green tea and coffee consumption were assessed *via* a self-administered questionnaire. During a mean 14.2-year follow-up, they documented 159 TC cases. They inferred that high green tea consumption could be associated with premenopausal TC risk but inversely correlated with postmenopausal TC risk [114]. Finally, Riza et al. reported that drinking herbal teas, especially chamomile ($p<0.001$), protects from TC as well as other benign thyroid diseases [115].

Soy Foods

They have been considered excellent replacements for dairy products, recognized as sources of high-quality protein and healthful fat and uniquely-rich sources of isoflavones (classified as phytoestrogens and selective estrogen receptor modulators). Soy foods were widely accepted because of the potential effects on health, such as the effectiveness in cardiovascular risk reduction, antioxidative effect of flavonoids may protect from cancer [116], preventive roles in hypertension, hypercholesterolemia [117], body weight loss [118]. Nonetheless, there are reports of possible disruption of thyroid function and sexual hormones. A cross-sectional study of 11,688 women aged 30–50 years of North American Adventist church showed that high intake of isoflavones was related to increased risk of nulliparity and null gravity [119]. There are also reports of soy products in infant diet before 4 months of age and a 25% higher risk of menarche before 12 years of age [120]. About the thyroid gland disturbance, more long-term epidemiological studies are needed to verify soy-thyroid interaction in real conditions since in clinical trials; isolated isoflavones are used with a wide range of concentrations and heterogenic conditions [121]. In the multiethnic population-based case-control study of TC conducted from the San Francisco Bay Area with 817 cases diagnosed between 1995 and 1998, 608 (74%) were examined. Phytoestrogen consumption was determined *via* a food-frequency questionnaire and a newly developed nutrient database. They reported that the consumption of traditional and nontraditional soy-based foods and alfalfa sprouts were associated with a reduced TC

risk [122]. In a recent study by Xiao et al., the association between dietary flavonoid intake and TC risk in 491,840 participants was investigated. It was reported that TC risk was not associated with the dietary intake of isoflavones [123]. After analyzing the results from these few studies carefully, it remains inconclusive the potential influence of isoflavones on TC risk.

Mediterranean diet

This dietary pattern is commonly used by people living on the Mediterranean coast [124]. It is characterized by a higher intake of the majority of plant-derived foods, including vegetable and fruits, legumes, whole-grains, and extra virgin olive oil as the only source of fat, moderate alcohol consumption (especially red wine), moderate intake of animal protein (most represented by fish and dairy products), and minimal consumption of meat and highly processed foods [124]. Additionally, it is low in saturated fatty acids and provides high amounts of monounsaturated fatty acids and omega-3 PUFAs, mainly derived from olive oil as alpha-linolenic acid and long-chain PUFAs fish [125]. The foods and beverages of plant origins are widely rich in polyphenols, particularly fruits, vegetables, spices, nuts [126]. The MD's beneficial effects are the high content in antioxidants and anti-inflammatory compounds, including polyphenols, to play a role in preventing cancer [124, 127] and other diseases such as cardio-metabolic, neurodegenerative disorders [124], among others. Several evidence show the antitumor effects of natural polyphenols, including anthocyanins from blueberries, epigallocatechin gallate from green tea, and resveratrol from red wine. These functions are associated with cell survival, proliferation, differentiation, migration, angiogenesis, hormone activities, detoxification enzymes, and immune responses. Despite all the existing robust evidence regarding the MD and its advantages, more studies are needed to show a direct causal relationship between this diet and the reduction of TC risk. As reported by the EPIC cohort, which included 476,108 men and women from 10 European countries, no associations between dietary polyphenol consumption and TC risk were demonstrated [128].

The MD was associated with a lower risk of breast cancer [129, 130], gastroenteropancreatic neuroendocrine tumors aggressiveness [131], and other cancers [132]. Nonetheless, only a few studies link dietary patterns to TC [28, 33, 133]. In a case-control study of 113 subjects, Markaki et al. [33] found that dietary patterns of fruits, raw vegetables, and mixed raw vegetables and fruits were negatively associated with TC (OR=0.68, 0.71, 0.73, respectively).

Another study did not report any difference between traditional Polynesian diet (characterized by high consumption of fish, seafood, and fruits) and Western diet (characterized by high consumption of meat and starchy food), in 229 cases of DTC diagnosed, and 371 controls [133]. Very recently, Sangsefidi ZS et al., in a case-control study among 309 clinic-based participants in the northeast of Iran, evaluated the role of major dietary patterns on DTC. The only association reported in this study was that the western diet had 2.85 times more chance for DTC (OR=2.85, 95% CI=1.15-7.06) [28].

Dietary indications as medical prescription in the reduction of TC Risk: the point of view of the endocrinological nutritionist

The current state of the dietary recommendations for the prevention of TC remains controversial, as the clinical studies' results are inconsistent. However, based on current scientific evidence, we can give some dietary indications as a medical prescription to reduce TC risk, considering that the choice of food must be made by analysing the presence of beneficial nutrients [19]. The principal dietary indications are summarized as follows:

1. Iodine intake and fish: Correction of iodine deficiency has shifted TC subtypes toward less aggressive forms without affecting cancer's overall risk. High iodine intake seems to exert a protective effect against cancer;
2. Fruits and vegetables: They may provide a protective role for combining bioactive components with antioxidant activity, such as selenium and vitamin D, micronutrients, and phytochemicals. Eating 2 servings of fruits and at least 7.5 servings *per* day (600 g/d) of green-yellow and cruciferous vegetables (salads) *per* day;
3. Selenium, vitamin D: Despite the well-known anti-cancer activities and potentials, there is limited evidence on the association between either selenium or vitamin D deficiency and TC, as well as on the clinical usefulness of their supplementation in these patients;
4. Body weight: Obesity is associated with the incidence of various tumors, including DTC. An association between excessive weight and TC risk, with more aggressive behavior, emerges from most of the studies.
5. Alcohol, red meat and dairy: To limit excess consumption of alcohol, meat, and dairy food even if no clear associations were found among the consumption of these foods on TC risk;
6. Don´t consume processed food;
7. Don´t consume frozen or canned fish or seafood;

8. Drink daily chamomile tea and herbal tea to prevent TC;
9. Adopt healthy lifestyle habits: Exercise 30 minutes daily or 1 hour every 2 days.

Most of these suggestions are potentially useful also for patients with TC (Table 1)

Conclusion

Interesting associations between single nutrients or food and TC risk have been described. Understanding the bidirectional relationships between dietary patterns and TC risk is also essential for delineating the risk profile from obesity **(Figure 1)**. Adopting a healthy lifestyle and education regarding modifiable environmental factors (diet, nutrition, and physical activity) could have beneficial effects *per se* on reducing TC risk. For achieving dietary-related goals, the skilled Endocrinological Nutritionist should play a central role during the assessment considering dietary recommendations as a real medical prescription for the prevention of TC risk. Based on its beneficial antioxidants and anti-inflammatories components, the MD could also present health benefits in TC's prevention. The advantageous effects of nutritional interventions promoting the Mediterranean food pattern could be extended to patients at risk of developing TC. Future well-designed dietary intervention trials on larger population samples are needed to define specific dietary guidelines for reducing TC risk.

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NOTES

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Abbreviations.

Abbreviations: Thyroid cancer (**TC**); differentiated thyroid cancer (**DTC**); body mass index (**BMI**); Mediterranean diet (**MD**); Poly-Unsatured Fatty Acids (**PUFAs**); eicosapentaenoic acid (**EPA**); docosahexaenoic acid (**DHA**); European Prospective Investigation into Cancer and Nutrition (**EPIC**); ultraviolet B (**UVB**); 25-hydroxyvitamin D (**25(OH)D**); Hashimoto's thyroiditis (**HT**); forkhead box protein O3a (**FOXO3a**); reactive oxygen species (**ROS**); short-chain fatty acids (**SCFAs**); thyroid-stimulating hormone (**TSH**); phosphatidylinositol-4-phosphate 5 kinase γ (**PIP5Kγ**); heterocyclic amines **(HCA)**; polycyclic aromatic hydrocarbons (**PAH**), relative risk (**RR**).

FIGURE

Figure 1: picture describing the known and potential factors involved in the correlation between lifestyle patients and the development of thyroid cancer

TABLE

Table 1: Most of these suggestions are potentially useful also for patients with thyroid cancer

Table 1: Dietary suggestions for a correct lifestyle in thyroid cancer patients

✓ **Iodine intake and fish**	– A correct intake of iodine with the diet plays a protective role in the development of nodules and, therefore, potentially also thyroid carcinomas – High iodine intake seems to exert a protective effect against cancer
✓ **Fruits and vegetables**	– They may provide a protective role for the combination of bioactive components with antioxidant activity – Eat 2 servings of fruits and at least 7.5 servings per day (600 g/d) of green-yellow and cruciferous vegetables (salads) *per* day
✓ **Selenium, vitamin D**	– There is limited evidence on the association between either selenium or vitamin D deficiency and TC
✓ **Obesity**	– Obesity is associated with the incidence of various tumors, including DTC – Weight loss is recommended for patients with thyroid cancer
✓ **Alcohol, red meat, and dairy**	– No clear associations were found among the consumption of these foods on TC risk – In any case, it is advisable not to exceed with these foods to reduce the risk of obesity.
✓ **Adopt healthy lifestyle habits**	– It is recommended to perform physical exercise 30 minutes daily or 1 hour every 2 days
✓ **Nutritional status in patients treated with Tyrosine Kinase Inhibitors (TKI)**	– A close monitoring and management of weight loss is crucial to avoid withdrawal and to limit the need for dose reduction – Expert nutritionist interventions are needed in patients affected with advanced TC treated with TKI