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Food Mutagen and Thyroid Cancer

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Abstract

This article reviews the role of food mutagens in mutagenesis and carcinogenesis for thyroid cancer; it also discusses how to evaluate the effects of food mutagens. We tried to illustrate new scientific knowledge regarding food related factors by picturing and integrating new genotoxicological findings for food-borne mutagens/carcinogens and detailing contributions of modulation in thyroid cancer.

This review reports the association between dietary factors and thyroid cancer risk. Iodine-rich food such as fish and shellfish may provide a protective role in populations with insufficient daily iodine intake. The consumption of goitrogenic food, such as cruciferous vegetables, showed a positive association with risk.

The relationship between acrylamide, N-nitroso compounds, Polycyclic Aromatic Hydrocarbons, Alcohol intake and thyroid cancer has been the subject of many studies. Digestion, absorption, metabolism and excretion of fat deposits require oxidative metabolism, which create free radicals capable of causing DNA damage.

When considering the human diet, it should be recognized that foods contain both mutagens and components that decrease cancer risk such as antioxidants. Thus nutritionally related cancers ultimately develop from an imbalance of carcinogenesis and anticarcinogenesis. The best way to assess nutritional risks is through biomarkers, but there is no single biomarker that has been sufficiently validated.

Key words: Thyroid; cancer; food; mutagens; metabolism; anti oxidents; fibre; genetics;

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Introduction

Thyroid cancer is the most common endocrine malignancy with more deaths annually than all other endocrine cancers combined. Medical centers in many parts of

the world have noted an increasing frequency of cases of thyroid cancer.

The general impression has been that if there is a rising frequency, it was likely due to some environmental cause, namely, greater radiation exposure or some other toxic exposure. This concept was dealt with in the publication of a statistical analysis of data from the Surveillance Epidemiology and End Results (SEER) database by Davies and Welch [1].

Papillary thyroid cancer accounts for about two-thirds of both male and female cases, while follicular accounts for 10-20%, medullary for 5-10% and anaplastic for less than 5% [2].

This article review the role of food mutagens in mutagenesis and carcinogenesis for thyroid cancer; it also discusses how to evaluate the effects of food mutagens. There are data to indicate that food mutagens and carcinogens affect specific organs rather than affecting every organ in the body. Separate foods contain many substances that are likely to reduce cancer risks, such as antioxidants or some types of fibres. These are not reviewed herein, but it should be recognized that nutritionally related cancers occur through an imbalance of carcinogenesis and anticarcinogenesis [3].

Some of the studies we review investigated dietary factors that can possibly affect thyroid cancer risk, but the results were inconsistent due to diverse dietary patterns, eating habits, life-styles and other environmental risk factors. They investigated the role in thyroid cancer of food items rich in iodine such as seafood and vegetables containing goitrogens such as cruciferous vegetables. For instance, multi-ethnic groups living in iodine deficient regions with high intake of seafood showed either no association or lowered thyroid cancer risk [4, 5].

Table 1: showing carcinogens and activating enzymes

Carcinogen	Activating enzyme with genetic polymorphisms
Acrylamide	CYP2E1
N-Nitrosamines	CYP2E1
Polycyclic Aromatic Hydrocarbons	CYP1A, CYP1B
Alcohol	CYP2E1

Methods

A review of the literature concerning thyroid cancer was performed. This review focuses on evidence indicating that diet and nutrition can contribute to human thyroid cancer risks.

Several lines of evidence indicate that diet and dietary behaviours can contribute to human cancer risk. One way that this occurs is through the ingestion of food mutagens. Sporadic cancers result from a gene-environment interactions where the environment includes endogenous and exogenous exposures. The target organs for these agents are numerous, but there is target-organ specificity for each. Mutagenesis however is not the only pathway that links dietary exposures and cancers. There is growing evidence that epigenetic factors, including changes in the DNA methylation pattern, are causing cancer and can be modified by dietary components. Also DNA damage may be indirect by triggering oxidative DNA damage [3].

Dietary constituents reduce the risk, in some cases by decreasing the effects of food mutagens, or through carcinogenic detoxification, or protection of DNA from electrophilic carcinogen. Futhermore,

nutritionally related cancer ultimately developed from an imbalance of carcinogenesis and anticarcinogenesis process [3].

Diet and nutritional factors are one of several major causes of carcinogenesis. Carcinogenic processes themselves are known to involve multi steps process (initiation, promotion, progression) and influenced by various factors. Food mutagen is working through genotoxic and non-genotoxic pathway in carcinogenesis.

Genotoxic pathway works on the level of DNA causing DNA damage. Moreover, non-genotoxic pathway affects the cell through tumour promoters such as inflammation, immunosupression, free radical and so on. More exposure to both pathways, more risks of carcinogenesis [6].

Some risk factors relevant to thyroid cancer, but the results are inconsistent due to differences in dietary patterns, life-styles, nutrition, or other environmental risk factors among various ethnic groups. Some studies showed that dietary factors play a significant role in the cause of thyroid cancer, possibly influencing thyroid hormones that affect thyroid function.

Particularly, low iodine intake has been considered as a risk factor for thyroid disease and thyroid cancer. The regions where daily iodine intake is relatively insufficient with a high intake of fish showed a negative association with thyroid cancer risk.

Several micronutrients deficiency interacting with nutritional iodine may affect thyroid function in low income countries, and even occur in well nourished elderly population [7, 8]. Both chronic iodine deficiency and iodine excess may increase thyroid cancer risk [9].

Hyperglycemia, insulin resistance and obesity increase oxidative stress and stimulate mitogenic pathways of follicular thyroid cells [10]. The growth-promoting effect of insulin and insulin-like growth factor-I have also been proposed as a causal link between abnormal glucose metabolism and cancer risk and doubling in insulin-like growth factor-I concentration is associated with a relative risk of 1.48 (95% CI, 1.06–2.08) for differentiated TC in the EPIC study [11].

Thyroid nodularity has been associated with obesity, but data regarding associations of body composition parameters with specific ultrasound features of thyroid nodules are lacking. The aim of the present study was to assess associations between thyroid nodule ultrasound characteristics, lifestyle, and anthropometric parameters. Body fat accumulation and lack of exercise, used as surrogate markers of sedentary lifestyle, influence thyroid nodule size and could predict some ultrasonographic characteristics, like hypoechoicity and internal vascularity. Therefore, routine thyroid examination of obese patients and promotion of active lifestyle may be warranted to prevent thyroid nodule formation and possibly progression to malignancy [12].

Food Mutagen: Molecular Biology

Acrylamide

Acrylamide is classified as a probable human carcinogen based on animal studies and mechanistic insights. The Acrylamide is a chemical that naturally forms in starchy food products during every-day high-temperature cooking (frying, baking, roasting and also industrial processing, at +120°C and low moisture). The main chemical process that causes this is known

as the Maillard Reaction; it is the same reaction that 'browns' food and affects its taste. Acrylamide forms from sugars and amino acids (mainly one called asparagine) that are naturally present in many foods. Acrylamide also has many non-food industrial uses. It is also present in tobacco smoke [13].

Studies of rodents have shown positive dose-response associated between acrylamide exposure and cancer in multiple organs and tissues, among which were the mammary gland, skin, lungs, oral tissues, and thyroid gland [14, 15].

In occupational studies, no association was observed between exposure to acrylamide and risk of head-neck cancer [16, 17]. Several aspects of diet have been related to thyroid cancer and a poor diet accounted for ~40% of cases in Italy [18].

Among the other associations found, case–control studies conducted in Italy showed increased risk for refined cereal intake [19] , pasta or rice, bread, pastry, and potatoes [20], although the issue remains open to discussion [21,22]. Glycemic index and glycemic load are indicators of the physiological response to different carbohydrates in terms of plasma glucose and insulin responses [23].

Acrylamide is readily absorbed in the body and converted to glycidamide by epoxidation by the CYP2E1 (cytochrome P450 2E) enzyme. Both Acrylamide and glycidamide may be detoxified through direct conjunction to glutathione by glutathione-S-transferases and glycidamide by hydrolysis to glyceramide [24].

Nitrate, Nitrite and N-Nitrosamines

Ingested nitrate inhibits thyroid uptake of iodide by binding to the sodium-iodide symporter on the surface of thyroid follicles. This reduces the levels of the thyroid hormones triiodothyronine (T3) and thyroxin (T4), which increases thyroid stimulating hormone (TSH). TSH controls thyroid hormone production through a negative feedback loop [25, 26]. Chronic stimulation of the thyroid gland by TSH can lead to proliferative changes in follicular cells, including hypertrophy and hyperplasia as well as neoplasia [27, 28].

There is some evidence from human studies that exposure to elevated nitrate levels in drinking water is associated with increased thyroid volume and increased frequency of subclinical thyroid disorders [29, 30].

Nitrate and nitrite are also precursors in the endogenous formation of N-nitroso compounds, which are potent animal carcinogens that cause thyroid and many other tumours in animal models [31].

Ingestion of nitrate and nitrite has also been associated with increased risk of stomach, oesophagus, and other cancers in some epidemiologic studies [32].

Both nitrate and nitrite are capable to form nitrosamines, a large group of compounds with common carcinogenic mechanism. Humans are exposed to N-nitroso compounds in diet from a variety of cured meats and fish products [33, 34]. N-nitroso compounds, or heme iron are formed and carcinogenesis is promoted by increasing cell proliferation in the mucosa [35].

Sodium nitrite has been used as food addictive for preservation and as colouring substance in meat. N-nitrosamines may also derived from nicotine of tobacco smoking [33, 34].

Polycyclic Aromatic Hydrocarbons

Polycyclic Aromatic Hydrocarbons (PAH) compounds are formed during incomplete

combustion of organic matter. Smoked foods, e.g. ham, sausages, and fish may contain PAH, resulting from incomplete combustion in food processing. These compounds are also commonly found in tobacco smoking. In laboratory animal studies, diets with PAH consistently induce foregut tumours and can also induce lung tumours. In humans, there is some evidences for association of dietary PAH exposure with colon cancer. Animal and human studies suggest that dietary PAH is distributed to organ besides the locally exposed tissues, so it is plausible to consider that dietary PAH may contribute to lung or breast cancer risks [36].

Benzo(a)pirene is the best-characterized PAH compound available from the diet. Carcinogenesis mechanism is conducted through BaP adduct formation, after being activated by CYP1A and CYP1B enzymes. BaP adduct is associated with site-specific hotspot mutations in the p53 tumour suppressor gene. The mutations are observed in lung cancer of smokers [36].

Alcohol

The alcohol intake may increase the level of TSH, which regulates the growth and function of thyroid gland [37].

The elevation of TSH levels or changes in thyroid function could be a possible reason for an association between alcohol consumption and an increase in thyroid cancer risk [38]. Table 1 describes the association between the consumption of alcohol and thyroid cancer.

The exact mechanisms by which chronic alcohol ingestion stimulates carcinogenesis are not known. Experimental studies in animals support the concept that ethanol is not carcinogen but under certain experimental conditions is a cocarcinogen and/or tumour promoter. The metabolism of ethanol leads to the generation of acetaldehyde and free radicals. Evidence has accumulated that acetaldehyde is predominantly responsible for alcohol associated carcinogenesis.

Acetaldehyde is carcinogenic and mutagenic, binds to DNA and proteins, destructs folate and results in secondary hyperproliferation. It has also been shown that acetaldehyde interferes with the DNA repair process, where it directly inhibits O6methyl-guanyltransferase, an enzyme important for the repair of adducts caused by alkylating agents. Moreover, individuals with polymorphism tend to accumulate acetaldehyde products, resulting in increased cancer risk. Other mechanism is through the induction of cytochrome P-4502E1 (CYP2E1) that is associated with increased free radicals generation and activation of procarcinogens compounds contained in the alcoholic beverages to their ultimate carcinogens [36].

Conclusions

With this article, we tried to illustrate new scientific knowledge regarding food related factors by picturing and integrating new genotoxicological findings for food-borne mutagens/carcinogens and detailing contributions of modulation in thyroid cancer. The findings of this review may be of interest for medical staff who are currently undertaking studies and for those who will be performing research and studying about lung cancer.

The relationship between acrylamide, N-nitroso compounds, Polycyclic Aromatic Hydrocarbons, Alcohol intake, and thyroid cancer has been the subject of many studies. Digestion, absorption, metabolism, and excretion of fat deposits require oxidative metabolism, which create free radicals capable of causing DNA damage.

Carcinogenic processes themselves are known to involve multi steps process (initiation, promotion, progression) and influenced by various factors. Food mutagen is working through genotoxic and non-genotoxic pathway in carcinogenesis.

Genotoxic pathway works on the level of DNA causing DNA damage.

This article has focused on the most commonly studied food mutagens, but many others exist in food as do agents that reduce cancer risk. The integrated consideration of all of these remains problematic because of the complex nature of the exposure and the documentation of dietary habits, and each of our research methods has strengths and limitations.

Based on data from the American Institute for Cancer Research and World Cancer Research Fund, it is estimated that around 30-40 percent of all cancers could be prevented by healthy life-style and a good diet pattern [39].

Hence, a good knowledge of diet, nutrition, and life-style are important to reduce thyroid cancer risk and risks of cancer in general in the society.

Author's Contributions

All the authors conceptualised the review, designed the table contents question and developed the search strategy. Author G. Strano, and C. West conducted the literature search, summarised the review articles, prepared the first draft of the article.

All authors contributed to synthesis of the results of the final manuscript.

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Conflict of Interests

The authors' declare that there are no conflicts of interests.

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