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Iodine and Cancer

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Thyroid carcinomas are the most frequent endocrine malignancies. Among thyroid carcinomas the most frequent types are the differentiated forms (follicular, papillary or mixed papillary-follicular), whereas anaplastic thyroid carcinoma and medullary thyroid carcinomas are rare. Animal experiments have demonstrated a clear increase in incidence of thyroid epithelial cell carcinomas after prolonged iodine deficiency leading to a situation of the thyroid gland by thyrotropin and possibly other growth factors. However, the overall incidence of differentiated thyroid carcinoma is generally not considered to be influenced by the iodine intake of a population, whereas the distribution of the types of thyroid carcinoma seems to be related to the intake of iodine, with fewer of the more aggressive follicular and anaplastic carcinomas and more papillary carcinomas in iodine rich areas. Populations starting iodine prophylaxis demonstrate an increase in the ratio of papillary to follicular carcinoma. Because a population with higher iodine intake usually has fewer benign nodules in the thyroid gland and the incidence of thyroid carcinomas is similar to an iodine-deficient region, the diagnostic work-up of nodules in the thyroid gland may become affected. The incidence of other cancers, such as breast cancer, may be influenced by the iodine intake, but too few studies are available at present. The present article summarizes available data from both epidemiological studies, animal experiments, and basic gene transfection studies. The overall incidence for a relationship between iodine and cancer is poor and future studies are warranted.

Introduction

THE MOST FREQUENT endocrine gland malignancies are thyroid carcinomas accounting for approximately 0.5% to 1.5% of all malignancies. Thyroid carcinomas have a marked variability in aggressiveness from highly differentiated papillary carcinomas with a good prognosis, if found and treated early, to undifferentiated anaplastic cancers occurring mainly in older people and with a poor prognosis. Malignant tumors of the thyroid gland are of either follicular, parafollicular or stromal origin (1). The yearly incidence of thyroid carcinoma is approximately 20 to 50 per million inhabitants with approximately 5 deaths per million inhabitants per year (2). The review deals only with thyroid epithelial cell tumors, leaving out medullary and other rare cancers.

With conventional therapy the overall survival rate of thyroid carcinoma is high, usually exceeding 90%, in subgroups of patients with papillary carcinomas even close to 99%. Differentiated thyroid carcinomas may, however, relapse decades after apparently successful initial treatment, which makes life-long follow-up mandatory (2). The follow-up is justified by the availability of good markers for relapse (e.g., whole-body radioiodine uptake and serum thyroglobulin measurements) as well as a good prognosis after correct treatment (in most cases radioactive iodine).

The overall incidence of thyroid carcinoma is generally not considered to be influenced by the iodine intake of a population, whereas the distribution of the types of differentiated thyroid carcinoma may be related to the intake of iodine. The objective of the present article is to summarize available data on the possible relationship between iodine and the development of differentiated thyroid carcinoma, as well as the possible influence of iodine on other cancer types.

Types of Thyroid Carcinoma and Differential Diagnosis

The most frequent types of thyroid carcinoma are the differentiated forms (follicular, papillary or mixed papillary-follicular), whereas other forms such as anaplastic carcinomas, lymphomas, medullary thyroid carcinomas and secondary cancers are rare. The World Health Organization (WHO) classification of malignant thyroid tumors appears from Table 1.

Thyroid cancer has been described in all types of thyroid enlargements but most malignancies of the thyroid gland are found among nodules appearing "cold" on a thyroid scintigraphy. On the other hand, the majority of cold nodules are benign, leaving the clinician with a severe differential diagnostic problem. Clinically evident thyroid nodules and benign goiters occur frequently depending on the iodine intake

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Table 1. WHO Classification of Malignant Thyroid Tumors

Malignant epithelial tumors
Follicular carcinoma
Papillary carcinoma
Mixed papillary-follicular carcinoma
Undifferentiated carcinoma
Squamous cell carcinoma
Medullary carcinoma (C-cells)
Malignant nonepithelial tumors
Fibrosarcoma
Others
Other malignant tumors
Sarcoma
Malignant lymphoma
Malignant haemangiothelioma
Malignant teratoma
Secondary tumors
Unclassified tumors

in a population, with fewer nodules and goiters in iodine rich areas. Postmortem examinations and epidemiological surveys of populations with evaluation of the thyroid gland texture by ultrasound have revealed even more clinically nondetectable thyroid nodules. Most of these nodules are benign, and it is therefore a continuing challenge for the clinician to pick out the few malignant thyroid nodules needing surgery without overtreating a large number of patients not needing surgery. The general aim of this diagnostic procedure is to avoid too large economical costs for the society and too large risks of complications for the patient.

The diagnostic work-up may appear different in iodine-rich compared to iodine-poor regions because presence of a solitary thyroid nodule has a higher *a priori* likelihood of malignancy in iodine sufficient areas. In general, a rapidly growing mass in the thyroid gland is likely to be malignant (Table 2), but it has to be remembered that a cyst, a hemorrhage in a cyst or adenoma, subacute thyroiditis (de Quervain), or chronic thyroiditis of the Hashimoto type may all present as rapidly growing masses and all of them may also be firm and can even appear fixed on palpation. A single nodule in a male is more likely to be malignant compared to that in a female. Features strongly indicative of benign thyroid nodules include long duration without growth, multinodular or diffuse goiter, simple thyroid cyst, "hot" nodule on thyroid scintigraphy, high levels of antibodies to thyroglobulin and/or thyroperoxidase, a family history of benign goiter and a suppressed serum thyrotropin (TSH). Because of this complexity of the differential diagnoses it is therefore pertinent that all patients undergo a sufficient medical endocrinological evaluation before the decision for surgery.

Experimental Animal Studies

Experiments in the 1960s showed an increased development of thyroid carcinomas in various animals such as mice (3) and golden hamsters (4) fed on a low-iodine diet. Iodine-deficient Fisher rats were further shown to develop chromosomal abnormalities of the thyroid cells (5). The cancers described were both of papillary (3) and follicular (4) types. In the golden hamsters the spontaneous cancer types were both papillary and follicular, whereas the malignancies reported in the iodine-deficient animals were follicular adenocarcinomas (4). Only thyroid epithelial cells were involved. Initially, the thyroids showed hyperplasia and it was already then proposed that hyperplasia and cancer development were due to an overstimulation by TSH, which is the main growth factor for the thyroid gland although several others exist. Some of these growth factors such as epidermal growth factor and insulin-like growth factor I are probably required for TSH to induce its growth-stimulating effect (2). The results of these early studies have later been verified in other animal experiments and a model for thyroid tumorigenesis has been proposed (6,7).

Epidemiological Studies

Clinically evident thyroid nodules and benign goiters occur frequently in iodine-deficient areas. Epidemiological studies and animal experiments have demonstrated a relationship between iodine intake and the occurrence of benign nodules. The search for a similar relationship between the occurrence of malignant thyroid tumors and iodine intake has, however, been controversial and with conflicting results. The overall incidence of thyroid carcinoma is generally considered without influence from the iodine intake in a population (2), although a study from two regions in Italy has recently demonstrated a twofold increase in thyroid cancer incidence in an iodine-deficient area compared to an iodine-sufficient one (8). Contrary to this, the incidence of thyroid carcinoma was also increased in two areas of high iodine intake: Iceland (9) and Hawaii (10). This was initially linked to the iodine excess but may rather be due to the baseline volcanic nature of these islands. Thus, the natural radiation is higher in these volcanic areas, and radiation is known to increase the development of thyroid carcinomas, especially when the radiation occurs in childhood. This has been seen in adults in the United States after childhood neck irradiation for various benign diseases (11) and more severely so after the Chernobyl disaster in 1986 (12), a radiation disaster occurring in an iodine-deficient population. It is therefore quite possible (but not proven) that the thyroid carcinoma incidence would have been substantially higher in both Hawaii and Iceland, had the population in childhood not been protected by a high iodine intake.

Epidemiological studies have also tried to link the iodine intake of the population with the histologic type of thyroid carcinoma. The increased thyroid cancer incidence in Iceland was noted to be mainly of the papillary type (9). On the other hand, radiation is also known to cause thyroid carcinoma especially of the papillary type (2). In some studies, a negative

Table 2. Characteristics of Malignant Thyroid Tumors

Rapidly growing or painful thyroid nodule
Family history of thyroid cancer
Exposure to neck irradiation in childhood
Hoarseness
Firm and/or fixed nodule
Cervical adenopathy
Vocal cord paralysis

association was found between papillary carcinoma and the presence of endemic goiter (13,14), and the radiation induced thyroid cancer type found around Chernobyl was mainly papillary of a particular type (15).

More solid evidence for a change of type of thyroid carcinoma in relationship to iodine intake has come from studies in areas with previous iodine deficiency before and after iodine prophylaxis. In one such study from an area in Argentina the ratio of papillary to follicular carcinomas rose from 2.5:1 to 6.2:1 (16). Also, introduction of iodine prophylaxis in Switzerland increased the ratio of papillary to follicular carcinomas (17).

The importance of accurate histological typing in cancer epidemiology cannot be overemphasized, and great caution is needed in comparison of different types of thyroid tumors in different populations if not evidenced by the same pathologist. The reproducibility of the WHO classification has been questioned and a considerable observer variation has been reported, particularly as regards follicular and mixed papillary-follicular cancers (18). Differences in the detection and inclusion of occult thyroid cancers in the studies could also play a role in the observed cancer incidences. Finally, it should be noted that a concomitant selenium deficiency in iodine-deficient areas has not been taken into account. This will be important to do in future studies, because selenium deficiency in itself has recently been associated with an increased incidence of thyroid carcinoma (19).

All of the above reservations are probably reasons why comparison of thyroid carcinoma epidemiology in different populations and geographic areas are so difficult to perform and interpret, and why no specific solutions to the questions concerning environmental influence of iodine intake have been provided, despite a large number of studies over many years.

Iodine and Other Cancers

Iodine has also recently been mentioned as possibly interesting in the epidemiology of other types of cancer, in particular breast cancer. An association between thyroid and breast disease has long been suspected, and evidence has indicated a connection between thyroid diseases (e.g., autoimmunity) and breast cancer (20). More specific evidence was substantiated by the demonstration of the sodium iodide symporter (NIS) gene product (first cloned by Carrasco [21]) in breast tissue (22–27). This gave rise to suspect a relationship between iodine intake and breast cancer and/or benign breast disease. Indeed, Japanese women have been shown to have a lower incidence of breast cancer than that found in most other populations (28), and Japan has one of the highest iodine intakes in the world. It has, however, not been documented that iodine intake is the causative factor, but inorganic iodine has experimentally been shown to suppress breast cancer in Sprague-Dawley rats (29). No other epidemiological studies have as yet been published, and thus further epidemiological and experimental studies are needed for verification.

No other cancer types have been related to iodine intake, but none have been looked for so far. Interestingly, however, the NIS gene can be transferred into both thyrocytes as well as cells of other tissues (22–27,30,31), rendering these cells eligible to therapy with radioactive iodine (25,31,32). This has opened new possibilities for combined gene and targeted radiotherapy of some other cancer forms, where the organ is dispensible to the intact human organism such as prostate, breast and ovaries (22–27,32). Studies have so far been successful in cell lines and tumors transplanted into nude mice, while human patient studies have not yet been performed.

Conclusion

Available evidence from animal experiments, epidemiological studies and from the introduction of iodine prophylaxis has demonstrated a relationship between iodine intake and the types of thyroid carcinoma, while no clear evidence exists for a relationship between the overall cancer incidence and iodine intake. All the studies are in general hampered by difficulty in comparing populations since many factors have to be considered other than the iodine intake, such as ethnicity, other dietary factors (e.g., selenium), histological examination and radiation. Knowledge of all these factors have an influence also on the diagnostic work-up and management of patients in each population. In future studies, all of these factors should be taken into consideration.

The epidemiology of breast cancer may appear to be related to iodine intake, which is recommended for further study in the future. Finally, gene therapy involving transfer of the NIS gene to other cancer types is a promising tool for future imaging and treatment.

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