Citation: Javid, N., Asghar, S., & Yasmeen, Z. (2020). A Literature Review of The Epidemiology, Pathogenesis and Treatment of Thyroid Cancer. Global Immunological & Infectious Diseases Review, V(I), 32-38. https://doi.org/10.31703/giidr.2020(V-I).04

ISSN (Print): 2788-4961 | **ISSN (Online):** 2788-418X | **URL:** http://dx.doi.org/10.31703/giidr.2020(V-I).04

Pages: 32 – 38 | **DOI:** 10.31703/giidr.2020(V-I).04 | **Vol.** V, **No.** I (2020)

A Literature Review of The Epidemiology, Pathogenesis and Treatment of Thyroid Cancer

Nida Javaid * Sana Asghar† Zainab Yasmeen‡

Abstract *Among the endocrine malignancies, thyroid cancer is the most commonly occurring and increasing around the globe. Inspite of prognosis, about 5-10% people become victim of differentiated thyroid cancer. Cancer is basically uncontrolled division of cells. These rapidly developing cells become toxic for the body of patient once they start travelling from place to another because in such situation the early diagnosis even does not benefit while in case of localized cancer, chances of survival increase. In thyroid cancer, patient becomes aggressive abruptly with developing metastasis. In case of gene mutations, every patient got a different mutated gene from other against which several medicines have been under consideration. This review has been put together to overview the disease, its etiology, pathogenesis, and treatment methods.*

Key Words: Malignancies, Metastasis, Mutation, Victim, Localized

Introduction

Thyroid Cancer is a cancer that strikes the thyroid gland as the name indicates. It is located at the base of human throat and is shaped like a butterfly. This gland regulates the vital functions of the body and metabolism by the production of hormones - tri-iodothyronine (T3) and thyroxine (T4). Certain factors can result in the dysfunction of this gland. Any kind of damage to the gland can also lead to the formation of a tumor that can grow into a malignancy. The incidence of Thyroid Cancer has increased many folds in the past few decades, turning into an epidemic becoming a global health concern. New cases have risen up to 567,000 across 20 world regions as of 2018. It has gained ninth position out of 36 most common worldwide cancers, according to World Health Organization (WHO). (Bray et al., 2018).

Method

Online data bases were used to carry out a systematic literature review of epidemiology, pathogenesis, and treatment management of thyroid cancer. The articles reviewed were recovered from Google scholar, PubMed and Medline, the key terms of which were, "thyroid cancer epidemiology", pathogenesis of thyroid cancer" and "treatments used for thyroid cancer". The scientific publications till 2021 were kept under consideration. It was made sure to include only those publications can have focused on the etiology and treatment methods for coronavirus. Any publication that may be missed has been identified via screening of all reference lists.The articles worthy of inclusion are available for full-text review. The publications chosen were in English only.

Epidemiology of Thyroid Cancer

Thyroid Cancer is one of the leading types of cancers that affect the mankind. Its incidence has been increasing quite a lot in the past couple decades especially in volcanic areas. This cancer is basically a hormone-related also known as endocrine-related cancer that can be triggered by multiple reasons.

* Department of Pharmacy, Faculty of Biological Sciences, Quaid I Azam University, Islamabad, Pakistan.
Email: Nidajavid56@gmail.com *(Corresponding Author)*
† Department of Pharmacy, Faculty of Biological Sciences, Quaid I Azam University, Islamabad, Pakistan.
‡ Department of Pharmacy, Faculty of Biological Sciences, Quaid I Azam University, Islamabad, Pakistan.

The aetiology of Thyroid Cancer is variant. The most important ones are the focal point of this heading. These have been reviewed and included in this portion.

Nutritional deficiency – Iodine

The major contributors of triggering Thyroid Cancer have been filtered as to be low-intake of iodine, eating habits and risk factors that are related to lifestyle. Apart from this, exposure to noxious compounds, several pollutants, xenobiotics and sometimes, co-morbidities can be the reason for the development of Thyroid Cancer.

Foods rich in iodine, fruits and vegetables are defensive against Thyroid Cancer (Barrea et al., 2020). Less than required intake of these food items can increase the chances of having this cancer. According to a study, the incidence of Thyroid cancer was co-related with the consumption rate of "Qualified Iodized Salt" negatively, while it was co-related with "goiter prevalence" in a positive ratio. This shows that the areas where the populations have any kind of Iodine deficiency, even if its mild, can result in high incidence of Thyroid Cancer. It can be prevented if Iodine intake is kept normal and is maintained (Fan, Meng, Gao, and Liu, 2021).

Obesity

Since this cancer is attributed to hormonal imbalance, increased body weight or obesity can serve as a contributor to Thyroid Cancer. Studies and statistics have related the incidence of this cancer to obesity time and again. According to a study, about 16% of all Papillary Thyroid Cancers in the United States of America (2013-2015) were associated with obesity. These findings conclude that awareness about the relation of these two should be spread in order to avoid any further increase of this cancer in obese people or those who have unhealthy life-style (Kitahara and Sosa, 2020).

Exposure to high-risk Contaminants and Chemicals

Thyroid Cancer is also precipitated by chronic exposure to toxic substances. Those populations are more vulnerable to such exposures who have jobs close to such contaminants. These may be footwear and preservation manufacturing units, industries involved with pulp or paper or wood and populations involved in agriculture. Chemists as well as pharmacists are also prone to Thyroid Cancer since they are involved with a variety chemical that can trigger this cancer. Proximity to chemicals of chlorines, bromines, phenyls, and phenols. Other toxic substances are pesticides and heavy metals (Marotta et al., 2020). These chemicals interfere with the biological maintenance system- haemostasis and result in malfunctioning. Metals form a crucial part of diet but in very small amounts. Their presence in daily meals is essential for proper working of the body, however, if they are taken in high amounts, the same metals can be toxic. For example, Arsenic is a highly toxic metal as it has become a part of our drinking water, soil, diet, and environment. It is a well-known carcinogen, however, not all forms of arsenic possess harm to the endocrine glands but only its inorganic forms like methylated arsenic.

Another threat to endocrine glands is cadmium. Cadmium has the ability to substitute zinc transporters and hence, results in oxidative stress. This leads to tumor formation. (Malandrino et al., 2020).

Over-diagnosis of Thyroid Cancer

An interesting finding suggests that over-diagnosis and enhanced detection of Thyroid Cancer can aggravate this condition. A rise in about half the Papillary Thyroid Cancer has been linked back to this over-diagnosis. In view of these, American College of radiology, the American Thyroid Association (ATA) and US Preventive Services Task Forces has recommended that biopsy of very small or those nodules lacking non-suspicious features should

Exposure to high-risk contaminants and Chemicals

Thyroid Cancer is also precipitated by chronic exposure to toxic substances. Those populations are more vulnerable to such exposures who have jobs close to such contaminants. These may be footwear and preservation manufacturing units, industries involved with pulp or paper or wood and populations involved in agriculture. Chemists as well as pharmacists are also prone to Thyroid Cancer since they are involved with a variety chemical that can trigger this cancer. Proximity to chemicals of chlorines, bromines, phenyls, and phenols. Other toxic substances are pesticides and heavy metals (Marotta et al., 2020). These chemicals interfere with the biological maintenance system- haemostasis and result in malfunctioning. Metals form a crucial part of diet but in very small amounts. Their presence in daily

meals is essential for proper working of the body, however, if they are taken in high amounts, the same metals can be toxic. For example, Arsenic is a highly toxic metal as it has become a part of our drinking water, soil, diet, and environment. It is a well-known carcinogen, however, not all forms of arsenic possess harm to the endocrine glands but only its inorganic forms like methylated arsenic.

Another threat to endocrine glands is cadmium. Cadmium has the ability to substitute zinc transporters and hence, results in oxidative stress. This leads to tumor formation. (Malandrino et al., 2020).

Over-Diagnosis of Thyroid Cancer

An interesting finding suggests that over-diagnosis and enhanced detection of Thyroid Cancer can aggravate this condition. A rise in about half the Papillary Thyroid Cancer has been linked back to this over-diagnosis. In view of these, American College of radiology, the American Thyroid Association (ATA) and US Preventive Services Task Forces has recommended that biopsy of very small or those nodules lacking non-suspicious features should be avoided, same is suggested for screening of asymptomatic patients (Kitahara and Sosa, 2016).

Pathogenesis of Thyroid Gland Cancer

Thyroid cancer is divided into four main types that is papillary (PTC), anaplastic (ATC), medullary (MTC) and follicular (FTC). Among them papillary and follicular are major one and rest of two are minor ones. One of the theory regarding pathogenesis is that cancer stem like cells theory. According to this theory, phenotypically different cells can be generated if these are undergone with genetic and epigenetic transformation (Takano, 2014). Due to the discovery of genome sequence it has given better explanation of molecular mechanism of thyroid cancer (Mazzaferri, 1999). Majority of thyroid cancer is due to the dysregulation of mitogen activated protein kinase (MAPK) and phosphatidylinositol-3-kinase (PI3K)/AKT signaling pathways. The progression of PTC is due to activation of MAPK pathway due to the mutations of genes like BRAF and RAS genes and fusion of genes like RET/PTC and TRK (2). Not only environmental factors like ionizing radiations and exposure to organic and inorganic pollutants leads to development and aggravates the thyroid cancer but nutritional factors like deficiency of iodine also leads to worsen PTC (Han et al., 2019) for activation of FTC there are mutations in genes like RAS, PIK3CA and AKT1 and deactivating PTEN which regulates this pathway by negative feedback (2). MTC can be familial or sporadic; in both cases mutations in proto oncogene RET occurs (majority of familial greater than 98%) (Elisei et al., 2019) in ATC BRASH-K and N-RAS mutations accounts for only 19-45%and 9.5 -27% (Landa et al., 2016, Pozdeyev et al., 2018, Romei et al., 2018). Mutations in PTEN and PI3KCA are more frequent 15 -18%than well differentiated cancers (Landa et al., 2016).

Diagnosis

Thyroid cancer represents nearly 90% of endocrine cancers. Thyroid cancers are classified into different types. It includes “follicular adenoma (fa)”, “follicular

follicular variant of papillary thyroid carcinoma” (fvptc), “papillary thyroid carcinoma” (ptc), and “follicular thyroid carcinoma” (ftc). “Papillary thyroid carcinoma” is the most common among all lesions (Armanious et al, 2020).

Sometimes, diagnostic problems are encountered in which the difference between follicular variant of “papillary thyroid carcinoma” and other follicular-patterned lesions present challenges (Armanious et al, 2020).

To address these very common diagnostic challenges, many attempts have been made. Previous approaches, on the larger scale, have been restricted to the use of various immunohistochemical stains, individually or in the combine form. Upon investigation, several antibodies have been explored in which those included that are against ”HBME-1”, “CK19”, “galectin-3”, “galectin-1”, ”CITED-1”, “CD44”, “Trop-2”, “CD56”, and “TPO” with varied levels of success (Armanious et al, 2020).

Early diagnosis of thyroid cancer is very crucial as it leads to a lot of complications and leads to malignancy.

SAS1B

A study was conducted by group of scientists in China on “SAS1B (Sperm Acrosomal SLLP1 Binding protein)”. This protein was thought be used as a biomarker for identification of thyroid cancer. In this study two groups were studied. One of which was control group those having normal thyroid tissue and other was experimental group having abnormal cancerous thyroid tissue. Both the groups were tested for the presences of “SAS1B” protein by using “ELISA” method. Also, the results proved to be significant and

showed that abnormal cancerous cells contain "SAS1B protein" thus it is helpful for early diagnosis and is also the agent involved in oncogenesis (Yang et al., 2021).

Thyroidography

A recent study was conducted by Turkish scientist on an imaging technique "Thyroidography" that uses software of greater sensitivity and lower dose of X-ray for detection of calcification. In this study, patients aged 17 and older with primary thyroid related problems were selected. After that 3 techniques "USG", "DICOM" and "thyroidography" were used for evaluation of calcification in thyroid nodules. The results of all the techniques were compared from which it was inferred that "thyroidography" can detect macrocalcification with greater accuracy as compared to others. However, in case of malignancy, "thyroidography' has also proved to be the more reliable technique in identification of microcalcification as well. But for better diagnosis of thyroid cancer it is preferred to use both "thyriodography" and "USG" together (Aysan et al., 2019).

Mirna Markers

Also, a study was held in which "miRNA markers" were used to differentiate between the patients with thyroid cancer or any other disease related to thyroid. In the previous studies, it was found that downregulation of "miRNAs" generally occurs in case of thyroid cancer. Further, "RNA sequence analysis" was performed to identify new and known "miRNAs" to differentiate between different type of tumors. As a result of which it was found that it was not always the case some types of "miRNAs" were found to be overly expressed in cancer patients including miR-136, miR-21 and miR-127 that could serve as a biomarker for identification of thyroid cancer patients (Park et al., 2021).

Thyroid Cancer Treatment

A few methods for treatment of thyroid cancer can be applied/used.

Surgery

Surgery which is the majorly used method in all types of thyroid cancer but not used in those patients who suffer from anaplastic thyroid cancer.

This includes lobectomy i.e., the removal of one part/portion of thyroid by surgery or thyroidectomy i.e., the whole or portion of thyroid gland removal by surgery during an operation. When the entire thyroid gland is removed then it is known as total thyroidectomy (Singer, 1996) and on the other hand, the removal of major portion of thyroid gland is known as subtotal thyroidectomy.

Radioiodine

Thyroid cancer can be treated by using radioactive iodine (I-131). This radioiodine is administered into the body of sufferer in the form of liquid or as tablet. After absorption, these radioiodine constituents get access to cells of thyroid gland where they start accumulating (Higashi, Kudo and Kinuya, 2011) and emit radiations due to which the cancerous cells are destroyed while healthy cells remain unaffected.

External Beam Radiation Therapy

This method involves the use of high energy radiations or atoms to destroy the cancerous cells, or it may stop its growth and spread (Tubiana et al., 1985) (Brierley and Tsang, 1999). This method cannot be applied to treat the patients who suffer from differentiated thyroid cancer because they show better response to radioiodine therapy. It is more commonly exercised for medullary thyroid cancer and anaplastic thyroid cancer.

Chemotherapy

Cancer killing agents are administered IV, IM and orally. After absorption, these agents reach to the sites where tumor cells are present and then they are killed by anti-cancerous agents. This method of treatment proves beneficial in almost all kinds of thyroid cancers. Chemotherapy along with EBM (external beam radiation therapy) is basically preferred for the patients who suffer from anaplastic thyroid cancer or sometimes used for the patients who are at the advanced stage of thyroid cancer and are not responding to rest of the treatment methods.

Target Therapy

Unlike chemotherapy which destroy all the fast-developing cells without any control and specification, target therapy mainly destroys the cancerous cells following the specific pathways (Sherman, 2010).

Commonly Used Drugs

Drug	Disease
Vandetanib	Medullary Thyroid Cancer
Cabozantinib	Medullary Thyroid Cancer and second line agent for renal cell carcinoma (Degrauwe, Sosa, Roman and Deshpande, 2012) (Hoy, 2014)
Lenvatinib and sorafenib (two drug therapy)	Anaplastic Thyroid Cancer (non-responsive to radioiodine therapy) (Fallahi et al., 2013) (Cabanillas and Habra, 2016)
Dabrafenib and Trametinib	Anaplastic Thyroid Cancer / anaplastic thyroid cancer patients with BRAF gene mutation / incomplete surgical removal of tumor and advanced melanoma (Ballantyne and Garnock-Jones, 2013) (McGettigan, MSN, CRNP, AOCN®, 2014) (Subbiah et al., 2018)

Conclusion

Thyroid cancer cases are increasing day by day. It occurs due to a number of reasons like iodine deficiency in our diet, obesity and due to exposure to other contaminants. The need of the hour is to further understand the epidemiology of the disease in detail to minimize the patients suffering from thyroid cancer. Specific preventive measures must be taken to minimize the disease count. Population must be educated related to dangerous of the disease and what lifestyle should they adopt to protect themselves from thyroid cancer. More diagnostic techniques must be discovered that could help in diagnosis of thyroid cancer at an early stage. Also, better, improved and safer treatment methods can treat the patients suffering from thyroid cancer with better efficiency. Better treatment methods and improved diagnostic techniques for thyroid cancer will definitely lower the mortality rate and limit the number of patients suffering from this disease.

References

Armanious, H., Adam, B., Meunier, D., Formenti, K., & Izevbaye, I. (2020). Digital gene expression analysis might aid in the diagnosis of thyroid cancer. *Current oncology (Toronto, Ont.), 27*(2), 93–99.

Aysan, E., Aydin, O., Ercivan, M., Aksoy, D., & Yavuz, A. E. (2019). A New Imaging Technique for the Diagnosis of Thyroid Cancer: Thyroidography. *Journal of Investigative Surgery*, 1–6.

Ballantyne, A. & Garnock-Jones, K., (2013). Dabrafenib: First Global Approval. *Drugs, 73*(12), pp.1367-1376.

Barrea, L., Gallo, M., Ruggeri, R., Giacinto, P., Sesti, F., Prinzi, N., Adinolfi, V., Barucca, V., Renzelli, V., Muscogiuri, G., Colao, A. & Baldelli, R., (2020). Nutritional status and follicular-derived thyroid cancer: An update. *Critical Reviews in Food Science and Nutrition, 61*(1), pp.25-59.

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R., Torre, L. & Jemal, A., (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: *A Cancer Journal for Clinicians, 68*(6), pp.394-424.

Brierley, J. & Tsang, R., (1999). External-beam radiation therapy in the treatment of differentiated thyroid cancer. *Seminars in Surgical Oncology, 16*(1), pp.42-49.

Cabanillas, M. & Habra, M., (2016). Lenvatinib: Role in thyroid cancer and other solid tumors. *Cancer Treatment Reviews, 42*, pp.47-55.

Degrauwe, N., Sosa, J., Roman, S. & Deshpande, H., (2012). Vandetanib for the Treatment of Metastatic Medullary Thyroid Cancer. *Clinical Medicine Insights: Oncology, 6*, p.CMO.S7999.

Elisei, R., Tacito, A., Ramone, T., Ciampi, R., Bottici, V., Cappagli, V., Viola, D., Matrone, A., Lorusso, L., Valerio, L., Giani, C., Campopiano, C., Prete, A., Agate, L., Molinaro, E. & Romei, C., (2019). Twenty-Five Years Experience on RET Genetic Screening on Hereditary MTC: An Update on The Prevalence of Germline RET Mutations. *Genes, 10*(9), p.698.

Fallahi, P., Ferrari, S., Santini, F., Corrado, A., Materazzi, G., Ulisse, S., Miccoli, P. & Antonelli, A., (2013). Sorafenib and Thyroid Cancer. *BioDrugs, 27*(6), pp.615-628.

Fan, L., Meng, F., Gao, Y. & Liu, P. (2021) "Insufficient iodine nutrition may affect the thyroid cancer incidence in China," British Journal of Nutrition. *Cambridge University Press*, pp. 1–9.

Han, X., Meng, L., Li, Y., Li, A., Turyk, M., Yang, R., Wang, P., Xiao, K., Li, W., Zhao, J., Zhang, Q. & Jiang, G., (2019). Associations between Exposure to Persistent Organic Pollutants and Thyroid Function in a Case-Control Study of East China. *Environmental Science & Technology, 53*(16), pp.9866-9875.

Higashi, T., Kudo, T. & Kinuya, S., (2011). Radioactive iodine (131I) therapy for differentiated thyroid cancer in Japan: current issues with historical review and future perspective. *Annals of Nuclear Medicine, 26*(2), pp.99-112.

Hoy, S., (2014). Cabozantinib: A Review of Its Use in Patients with Medullary Thyroid Cancer. *Drugs, 74*(12), pp.1435-1444.

Kitahara, C. & Sosa, J., (2016). The changing incidence of thyroid cancer. *Nature Reviews Endocrinology, 12*(11), pp.646-653.

Kitahara, C. & Sosa, J., (2020). Understanding the ever-changing incidence of thyroid cancer. *Nature Reviews Endocrinology, 16*(11), pp.617-618.

Landa, I., Ibrahimpasic, T., Boucai, L., Sinha, R., Knauf, J., Shah, R., Dogan, S., Ricarte-Filho, J., Krishnamoorthy, G., Xu, B., Schultz, N., Berger, M., Sander, C., Taylor, B., Ghossein, R., Ganly, I. & Fagin, J., (2016). Genomic and transcriptomic hallmarks of poorly differentiated and anaplastic thyroid cancers. *Journal of Clinical Investigation, 126*(3), pp.1052-1066.

Malandrino, P., Russo, M., Gianì, F., Pellegriti, G., Vigneri, P., Belfiore, A., Rizzarelli, E. & Vigneri, R., (2020). Increased Thyroid Cancer Incidence in Volcanic Areas: A Role of Increased Heavy Metals in the Environment? *International Journal of Molecular Sciences, 21*(10), p.3425.

Marotta, V., Malandrino, P., Russo, M., Panariello, I., Ionna, F., Chiofalo, M. & Pezzullo, L., (2020). Fathoming the link between anthropogenic chemical contamination and thyroid cancer. *Critical Reviews in Oncology/Hematology, 150*, p.102950.

MAZZAFERRI, E., (1999). An Overview of the Management of Papillary and Follicular Thyroid Carcinoma. *Thyroid, 9*(5), pp.421-427.

McGettigan, MSN, CRNP, AOCN®, S., (2014). Dabrafenib: A New Therapy for Use in BRAF-Mutated Metastatic Melanoma. *Journal of the Advanced Practitioner in Oncology, 5*(3).

Park, J. L., Kim, S. K., Jeon, S., Jung, C. K., & Kim, Y. S. (2021). MicroRNA Profile for Diagnostic and Prognostic Biomarkers in Thyroid Cancer. *Cancers, 13*(4), 632.

Pozdeyev, N., Gay, L., Sokol, E., Hartmaier, R., Deaver, K., Davis, S., French, J., Borre, P., LaBarbera, D., Tan, A., Schweppe, R., Fishbein, L., Ross, J., Haugen, B. & Bowles, D., (2018). Genetic Analysis of 779 Advanced Differentiated and Anaplastic Thyroid Cancers. *Clinical Cancer Research, 24*(13), pp.3059-3068.

Takano, T., (2014). Fetal cell carcinogenesis of the thyroid: A modified theory based on recent evidence [My Opinion]. *Endocrine Journal, 61*(4), pp.311-320.

Tubiana, M., Haddad, E., Schlumberger, M., Hill, C., Rougier, P. & Sarrazin, D., (1985). External radiotherapy in thyroid cancers. *Cancer, 55*(S9), pp.2062-2071.

Yang, H. X., Yang, Y., Li, X. D., Miao, X. M., Yang, C., Zhi, D. F., Su, H., Yang, G., Gao, J., Du, C. G., Li, H. J., Song, Y. L., & Cao, G. F. (2021). The detection of SAS1B in serum provides clues for early diagnosis of thyroid cancer. *European review for medical and pharmacological sciences, 25*(3), 1410–1424.