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Thyroid Cancer, Risk Factors, Clinical Features, Prognosis, and its Incidence Preference in Saudi Populations: Review

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Abstract

The aim of this review was to discuss Thyroid cancer incidence, risk factors, and clinical features and prognosis. Within the diverse cancers reported, the epidemiology of thyroid cancer increased 3-fold in the latest years which may be due lifestyle changes, lack of cancer awareness, lack of screening, and early cancer investigations and detection programs in addition to genetics and deficiency of iodine and vitamin D. The cause of thyroid cancer is unknown, but because the thyroid gland is very sensitive to radiation, exposure to radiation can cause precancerous changes. For unclear reasons, thyroid cancer like almost all diseases of the thyroid, occurs about 3 times more often in women than in men at any age, but the risk peaks earlier for women at 40 to 50 years. Several inherited conditions have been linked to different types of thyroid cancer but some patients with thyroid cancer do not have inherited conditions or a family history of the disease. Four general types of thyroid cancer were explained, Papillary, Follicular, Medullary, and Anaplastic. Over the last decade, the incidence of Papillary and Follicular thyroid cancers increased at the same time.
Keywords: Hypothyroidism, thyroid cancer, hormones, TSH, cyclooxygenase-2

Introduction

The incidence of thyroid cancer which is the most common endocrine malignancy increased by 98% in the USA.[1-5] As the incidence of thyroid cancer rises, it is important to determine what preventive measures and risk-reduction approaches could be utilized to reduce thyroid cancer–related morbidity and mortality, as well as the cost of care.[6-8] Thyroid cancer is a malignancy arising from the thyroid parenchymal cells. Its incidence is steadily increasing worldwide, while the mortality rate has remained stable over the past several years. The clinical behavior of thyroid cancer is highly variable, from indolent, slowly progressing tumors to highly aggressive tumors with high mortality rates. There are various new cutting-edge treatment options for advanced thyroid cancer, while there is also evidence against the overtreatment of low-risk thyroid cancers. Hence, a thorough understanding of the types of thyroid cancer and its management is of paramount importance in providing the appropriate treatment to the patient.[9,10] This article reviewed the incidence, etiology, pathophysiology, diagnosis, types, and treatment of thyroid cancer and highlights the role of interprofessional communication in optimizing the care of these patients.

Thyroid Cancer Incidence in Saudi Arabia

Thyroid cancer is defined as one of the most prevalent endocrine malignancies and had worldwide is spread in women after breast cancer.[3,7] Its incidence has increased over the last few decades; however, mortality rates have steadily declined. Even so, the death rate from thyroid cancer has increased faster than that of any other malignancy in both men and women. Increased risk factors include genetic factors, age, environmental and lifestyle changes, radiation exposure, smoking, alcohol intake, pregnancy, oral contraceptives, and high levels of thyrotropin.[11] Over the past years, thyroid cancer rates in the female population in the Kingdom of Saudi Arabia (KSA) increased. During the last three decades, Saudi Arabia has experienced important demographic, economic, and cultural changes.[12] These changes have impacted clinical practice, pathological classification, and management tools with respect to health conditions, including thyroid cancer.[13] The Saudi National Cancer Registry has reported a significant increase in the incidence of thyroid cancer in both males and females.[14,15] A material understanding of thyroid cancer trends is critical in the planning of national cancer prevention and control strategies. In forming a national Saudi health policy, an awareness of age and sex-specific mortality rates and trends is essential for all health conditions. The increasing incidence of thyroid cancer and its etiology is still not clear. Flemban et al., (2022) estimate thyroid cancer incidence and mortality trends in Saudi Arabia.[16] They reported that 23,846 cases (17,220 females and 6626 males) were diagnosed with thyroid cancer in Saudi Arabia from 1990 to 2019. The incidence is higher in females than in males and over these 30 years, the incidence exponentially increased by 15-fold for females and 22-fold for males which may be due to the increased development in detection and diagnosis. In conclusion, increased awareness and diagnosis especially in the male population of Saudi Arabia is recommended. The increase in thyroid cancer cases of male proportion of Saudi Arabia increased worldwide but the reason for this phenomenon is not fully clear (He et al., 2016).[17] It might be attributed to higher exposure to known risk factors for thyroid cancer in Saudi Arabia, such as exposure to radiation, obesity, and smoking in addition to improvements in diagnostic techniques and methods in addition to family history of the disease.[12,18,19] Among the Saudi population, a correlation between thyroid cancer diagnosis and previous family incidence was found (Alamoudi et al., 2011).[20] Exposure to heavy metals, fungicides and pesticides like DDT (dichloro-diphenyl-trichloroethane), hexachlorobenzene and 2, 4-dichloro-phenoxyacetic acid may cause hypothyroidism or thyroid cancer.[19] Some pesticides had structural similarities to the thyroid hormones which disrupt the thyroid function by binding to thyroid protein receptors.[21,22]

Tamam et al. (2021) showed that multiple exposures of the head, neck, or chest region to X-ray significantly increased cancer risk due to genetic alterations.[23] Different studies have also failed to detect the possible factors that cause thyroid cancer while other studies have included broad population groups based on occupation and general exposure to chemicals during work.[24-26] A career in radiology is rarely pursued by women and they reported low levels of interest in a radiology career among females and the percentage of female workers in the agriculture industry is very low. Thus, male occupational exposure to thyroid cancer risk is higher compared to females. Thus, the percentage of regional and distant disease was high in male patients (40%), compared with 28% among females. From 2000 and 2010, about 53% of all male cases exhibited regional and distant metastasis at diagnosis, compared with 22% of female cases (Fielding et al., 2007) and 3% of male thyroid cancer cases had medullary carcinoma compared with 0.8 % of female cases.[27] Hussain et al., 2013, also found a higher incidence of medullary carcinoma in males than females in Saudi Arabia.[28] They found that 4.41% of male thyroid cancer cases between 2000 and 2010 were diagnosed with medullary carcinoma, compared with 1.6% among females (Hussain et al., 2013) while a higher percentage of anaplastic thyroid cancer in males (2.57%) compared with females (1.09%)[28]. Thus, phenotypes are more likely to be found in males diagnosed with thyroid cancer in Saudi Arabia, and this helps to explain the phenomenon of increasing male thyroid cancer deaths. The increase in the male thyroid cancer death rate is higher than that of females over the same study period. Overall, thyroid cancer cases increased by 169% and mortality by 87%. In South Korea, the incidence was greater among females than males, decline in male cases especially in Kazakhstan, while in 2017 mortality rate was the highest in Ethiopia and in the Philippines.[19] They reported that there were regional variations in the incidence and mortality of thyroid cancer in Saudi Arabia. Thus, further investigations into thyroid cancer stratified by region, histologic characteristics, grade, and risk factors are needed in the future.

Types of Thyroid Cancer

In some cases there are single or multiple growths (nodules) on the thyroid gland, Ultrasonography is used to measure the size of the gland and determine whether the growths are solid or fluid-filled (cystic). In this condition, cancer usually causes small growths (nodules) to grow within the thyroid gland. However, most thyroid nodules are not cancerous. Nodules are more likely to become cancerous if the nodule is solid rather than fluid-filled (cystic) if the nodule does not produce thyroid hormone, if the nodules are hard, if the nodule is growing rapidly, and if nodules occur in a man.[29] A painless lump in the neck is usually the first sign of thyroid cancer. A larger cancer may press on nearby tissues in the neck, causing hoarseness, coughing, or difficulty breathing. The cause of thyroid cancer is unknown, but because the thyroid gland is very sensitive to radiation, exposure to radiation can cause precancerous changes. Thyroid cancer is most common in people who have had radiation to the head, neck, or chest to treat benign cancers often in childhood (although radiation therapy for noncancerous conditions is no longer used). There are four general types of thyroid cancer: Papillary, Follicular, Medullary, and Anaplastic. Thyroid cancers include papillary, follicular, Medullary and anaplastic cancer. Papillary and follicular cancers are considered differentiated cancers, and patients with these tumors are often treated similarly despite numerous biologic differences.[30-32]

Papillary thyroid cancer is the most common type of thyroid cancer, accounting for 80 to 90% of all thyroid cancers. This cancer affects women three times more often than men. Papillary cancer is more common in the 30–30 age group. Age 60, but it grows and spreads more quickly in people who are older. People who have had radiation therapy to the neck have the greatest risk of developing papillary cancer. Papillary cancer grows within the thyroid gland, but sometimes it can spread (metastasizes) to nearby lymph nodes. If left untreated, papillary cancer may spread to more distant sites in the body. Papillary carcinoma is almost always treatable. For large nodules (especially those larger than 4 cm), most or all of the thyroid gland is usually removed. Radioactive iodine is often given to destroy any remaining or cancerous thyroid tissue. Thyroid hormone is also given in large doses to inhibit the growth of any remaining thyroid tissue. Similarly, if the nodules are smaller than 4 centimeters, it must be removed with the tissue surrounding it (hemithyroidectomy or thyroidectomy). They have very small papillary thyroid cancers that are unlikely to spread to nearby tissues. During intensive monitoring, the patient undergoes an ultrasound of the thyroid gland every six months to check for any spread of cancer.[33-36]

Follicular thyroid cancer accounts for about 10% of all thyroid cancers and is more common among older people. Follicular cancer is also more common in women than in men. Follicular carcinoma is more aggressive than papillary carcinoma and tends to spread (metastasizes) through the bloodstream, moving cancer cells to different parts of the body. Follicular carcinoma is treated surgically by removing as much of the thyroid gland as possible and destroying any remaining thyroid tissue, including metastases, if present, with radioactive iodine. Follicular carcinoma is usually treatable, but less so than papillary carcinoma.[34,35]

Medullary thyroid cancer accounts for about 4% of all cancers of the thyroid gland. It usually begins in the thyroid gland, but in a different type of cell that produces thyroid hormone. This cancer has its origin in the C cell, which is usually found throughout the thyroid gland, it secretes the hormone calcitonin, which helps control the level of calcium in the bloodstream. Cancer produces excessive amounts of the hormone calcitonin. Because medullary thyroid cancer can also produce other hormones, it may cause unusual symptoms. This cancer tends to spread (metastasize) through the lymph vessels to the lymph nodes, and through the blood to the liver, lungs, and bones. Treatment requires surgical removal of the thyroid gland. Additional surgery may be needed to determine whether the cancer has spread to the lymph nodes. Radioactive iodine is not used to treat this type of cancer. More than two-thirds of patients with medullary thyroid cancer are treated as part of a course of treatment. Multiple endocrine neoplasia syndrome. Because medullary thyroid cancer is often familial, people undergo genetic testing to identify the cancer-causing gene mutation. If a mutation is identified, doctors may recommend further testing of family members, and some family members may undergo thyroidectomy before cancer develops.[34-36]

Anaplastic thyroid cancer makes up about 2% of all thyroid cancers and is most common in older women. This cancer grows very quickly and usually results in a large, painful lump in the neck. This cancer also tends to spread throughout the body. About 80% of people with anaplastic carcinoma die within 1 year, even if they are treated. Treatment for anaplastic carcinoma may involve surgery to remove the thyroid gland (and sometimes surrounding tissue), radiation therapy, chemotherapy, or a combination of these in some people. Radioactive iodine is not useful in treating this type of cancer.[31,37]

Control the Levels of Thyroid Hormones and Risk Factors of Thyroid Cancer

There is a complex mechanism that controls the levels of thyroid hormones in the body. First, the hypothalamus, located just above the pituitary gland in the brain, secretes thyrotropin, which causes the pituitary gland to produce thyroid-stimulating hormone (TSH). TSH controls the production of thyroid hormones. The pituitary gland slows or speeds up the release of TSH, depending on whether the levels of thyroid hormones in the blood are too high or too low.[37-41]

Many factors increase the risk of thyroid cancer which include the female sex as thyroid cancer occurs more often in women than in men. Experts think it may be related to the hormone estrogen. The female sex generally has higher levels of estrogen in their bodies. Also, exposure to high levels of radiation increases the risk of thyroid cancer and certain inherited genetic syndromes can increase the risk of thyroid cancer including familial medullary thyroid cancer, multiple endocrine neoplasia, Cowden syndrome, and familial adenomatous polyposis. Types of thyroid cancer that sometimes run in families include medullary thyroid cancer and papillary thyroid cancer.[37,42]

Imaging of the Thyroid Gland and Nodules

In the presence of thyroid nodules, several tests were needed. The first tests are generally thyroid function tests, in which blood levels of thyroid-stimulating hormone (TSH), the thyroid hormones T4 (thyroxine, or tetraiodothyronine) and T3 (triiodothyronine) are Iodothyronine). Sometimes tests are done to detect thyroid antibodies.[43] If blood tests show an overactive thyroid gland, imaging of the thyroid gland is done to determine whether the nodules are producing thyroid hormones. Hormone-producing nodules ("hot" nodules) are almost always not cancerous. Hypothyroidism or Hashimoto's thyroiditis, or if the nodules are not of the "hot" type, the doctor will usually do a fine-needle biopsy. In a fine-needle biopsy, a sample of the nodule is removed and then examined under a microscope. This procedure is not very painful and can be done in a doctor's office, and may use a local anesthetic and ultrasonography to guide where the needle will be inserted. Ultrasonography is also done to determine the size of the large nodule, whether it is solid or fluid-filled, and to check for the presence of other nodules.[31,37]

Potential Diagnostic Method, Stages, and Treatment Options of Thyroid Cancer

Tests and procedures used to diagnose thyroid cancer include a physical exam of the neck to feel for changes in the thyroid, such as a lump (nodule) in the thyroid. Thyroid function blood tests measure blood levels of thyroid-stimulating hormone (TSH) and hormones produced by the thyroid gland. Ultrasound uses high-frequency sound waves to create pictures of body structures. To create an image of the thyroid, the ultrasound transducer is placed on the lower neck. Removing a sample of thyroid tissue (biopsy) and the sample is sent to a lab for analysis to examine the tissue sample under a microscope and determines whether cancer is present. A radioactive iodine scan uses a radioactive form of iodine and a special camera to detect thyroid cancer cells in your body. This test is most helpful for papillary and follicular thyroid cancers. The cancer stage is indicated with a number between 1 and 4.[31,37,44] A lower number usually means the cancer is likely to respond to treatment, and it often means the cancer only involves the thyroid. A higher number means the diagnosis is more serious, and the cancer may have spread beyond the thyroid to other parts of the body. Different types of thyroid cancer have different sets of stages. For instance, medullary and anaplastic thyroid cancers each have their own set of stages. Differentiated thyroid cancer types, including papillary, follicular, Hurthle cell, and poorly differentiated, share a set of stages. For differentiated thyroid cancers, your stage may vary based on your age.[34-36]

Nonsteroidal Anti-Inflammatory Drug Use and Risk of Thyroid Cancer

Cyclooxygenase-2 (COX-2) has been closely associated with tumor growth and metastasis in a number of cancer types such as lung, breast, colorectal, and cervical cancer.[45-48] Patients with chronic lymphocytic thyroiditis were three times more likely to have thyroid cancer, suggesting an association between chronic inflammation and cancer development.[49,50] Overexpression of COX-2 has been observed in thyroid follicular cells of patients with Hashimoto's thyroiditis but not in normal thyroid or multinodular goiter tissue.[51] Several studies have demonstrated overexpression of COX-2 in papillary thyroid cancer (PTC) compared with normal thyroid and multinodular goiter tissue.[52,53] In addition, the expression of COX-2 is associated with older age, lymph node metastasis, and advanced stage in patients with thyroid cancer.[54,55]

In vitro studies of thyroid cancer cell lines have shown that a selective inhibitor of COX-2, NS-398, can inhibit proliferation and reduce cellular migration and invasion.[56,57] In esophageal cancer, COX-2 expression has also been shown to be associated with anti-apoptosis. These findings suggest many roles of COX-2 in thyroid cancer development and the potential of COX-2 as a chemo-preventive and therapeutic target. This approach has been studied most notably in colorectal cancer. Chan et al. (2005) analyzed a large prospective cohort study of 82,911 women enrolled in the Nurses' Health Study and reported a multivariate relative risk of 0.77 among women with regular long-term aspirin use.[58] The use of aspirin and the multivariate RR was also found to be dose-dependent, and a similar trend was seen for NSAIDs as well. Given the findings of *in vitro* studies and the promising results of this study in colorectal cancer, aspirin, and NSAID use may reduce thyroid cancer incidence. While the evidence strongly supports the chemo-preventive effect of NSAIDs in colorectal cancer, there is no population-based study that addresses whether NSAIDs may reduce the risk of thyroid cancer.[59] It was hypothesized that the incidence of thyroid cancer would be lower in individuals taking NSAIDs which may reduce the risk of thyroid cancer in a large prospective population-based cohort. Patel et al. (2015) reported that the use of non-aspirin NSAID or aspirin was not associated with a reduced incidence of thyroid cancer. The pooled analysis confirms the protective association between thyroid cancer incidence and smoking and alcohol use and the higher risk of thyroid cancer associated with obesity and female sex.[60]

Tissue analysis of thyroid cancer has shown that COX-2 expression is upregulated in patients with thyroid cancer compared with adjacent normal thyroid tissue (Specht et al., 2002), and these findings were validated with immunohistochemistry findings showing COX-2 expression to be higher in patients with PTC.[28,61] Furthermore, chronic inflammation with increased expression of COX-2 has been associated with cancer and thyroid cancer.[49,50,62,63] Thus, it was postulated that NSAID use could potentially reduce inflammation and reduce the risk of cancer, as demonstrated in colorectal cancer. Therefore, NSAID use could potentially reduce the risk of thyroid cancer, which has financial and health-related consequences. However, the present analysis did not reveal a reduced risk of thyroid cancer with NSAID use in a population-based cohort study. This may be due to many factors including an older median age, short duration of known NSAID use, and relatively short duration of follow-up period. In the Nurses' Health Study, Chan et al. (2005) did not see a relative risk reduction of colorectal cancer incidence until patients were ingesting aspirin or NSAIDs for at least a decade.[58] The increasing incidence of thyroid cancer has been associated with the detection of occult disease by numerous authors. Udelsman et al. (2014) showed that the incidence rates were significantly correlated with the density of endocrinologists and the employment of cervical ultrasonography.[64] Access to care is associated with the incidence of PTC, as documented by Morris et al. (2013) in an analysis of the Surveillance, Epidemiology, and End Results database.[65] In that study, thyroid cancer incidence was significantly higher in those older than 65 years of age (annual percentage change 8.8%) compared with those younger than 65 (annual percentage change 6.4%) who do not have universal healthcare. Increasing access to healthcare may explain the negative association with obesity. Obesity may be a surrogate for increased use of healthcare resulting in an increased incidence of thyroid cancer due to increased imaging use. Morbidly obese patients have an 81% greater per capita healthcare expenditure compared with normal-weight adults. Among the reasons for increased expenditures, morbidly obese adults had increased office-based visits and outpatient hospital care.[66-68] Likewise, smoking and alcohol may be associated with a lowered incidence by lower healthcare access or use by that subset of patients. The lack of association between NSAID use and thyroid cancer incidence might be explained by the presence of these confounding factors. Nevertheless, the protective effects of smoking and alcohol have to be weighed against the well-documented known associated diseases, especially given the low morbidity of thyroid cancer and excellent prognosis for early-stage disease.

Analysis of patients with occupational radiation exposure has shown that total duration of occupation, employment below the age of 20, and therapeutic, and nuclear medicine procedures were not associated with thyroid cancer incidence.[67,69,70] In summary, the use of NSAIDs was not associated with a reduced risk of thyroid cancer. The data analysis confirms that obese patients have a higher risk of thyroid cancer and that current smoking and moderate alcohol use are associated with a lower risk of thyroid cancer. Therefore, contrary to the chemo-preventive effects of NSAIDs in colorectal cancer, the present analysis does not support the use of NSAIDs to reduce the risk of thyroid cancer.

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