

“Papillary Thyroid Carcinoma Gender Disparity in Najran City”

Researchers:

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Abstract

Cancer gender disparity in incidence, disease aggressiveness and prognosis has been observed in a variety of cancers. Thyroid cancer is one of the fastest growing cancer diagnoses worldwide. It is 2.9-times more common in women than men. The less aggressive histologic subtypes of thyroid cancer, which is Papillary thyroid carcinoma are more common in women, whereas the more aggressive histologic subtypes have similar gender distribution. Papillary thyroid cancer is the most common type of thyroid cancer, accounting for approximately 80% of the cases. Its incidence has nearly doubled over the last 30 years and is thought to be due in part to earlier diagnosis of subclinical disease. The aim of this study the gender differences in the Papillary thyroid cancer within the population of Najran city in Saudi Arabia.

1 Chapter1: Literature review

1.1 Definition of Thyroid gland

Thyroid gland is a gland that makes and stores hormones that help regulate the heart rate, blood pressure, body temperature, and the rate at which food is converted into energy. Thyroid hormones are essential for the function of every cell in the body. They help regulate growth and the rate of chemical reactions (metabolism) in the body. Thyroid hormones also help children grow and develop[1].

The thyroid uses iodine, a mineral found in some foods and in iodized salt, to make its hormones. The two most important thyroid hormones are thyroxine (T4) and triiodothyronine (T3). Thyroid stimulating hormone (TSH), which is produced by the pituitary gland, acts to stimulate hormone production by the thyroid gland. The thyroid gland also makes the hormone [calcitonin](#), which is involved in calcium metabolism and stimulating bone cells to add calcium to bone[1].

1.2 Anatomy of thyroid gland

The thyroid gland is located in the lower part of the neck, below the Adam's apple, wrapped around the trachea (windpipe). It has the shape of a butterfly: two wings (lobes) attached to one another by a middle part called the isthmus (figure 1-A). The thyroid gland weighs 10 to 20 grams in normal adults. Thyroid volume measured by ultrasonography (US) is slightly greater in men than women it increases with age and body weight. It decreases with increasing iodine intake. The thyroid is one of the most vascular organs in the body. Thus, US measurements of thyroid volume and even nodule size can differ markedly from the size after devascularisation and resection. The normal thyroid gland is immediately caudal to the larynx and encircles the anterolateral portion of the trachea. The thyroid is bordered by the trachea and esophagus medially and the carotid sheath laterally. The sternocleidomastoid muscle and the three strap muscles (sternohyoid, sternothyroid, and the superior belly of the omohyoid) border the thyroid gland anteriorly and laterally. It consists of two lobes connected by a narrow isthmus. Each lobe is pyramidal in shape, with its apex directed upward and its base directed downward. The isthmus is the narrow part of the gland connecting the two lobes. A small pyramidal lobe projecting upward from the isthmus is often present to the left of the midline[2].

The arterial blood supply to the thyroid gland is primarily from the right and left superior and inferior thyroid arteries, derived from the external carotid arteries and thyrocervical trunk, respectively. The venous drainage consists of the superior, middle, and inferior thyroid veins that drain into the internal jugular vein and innominate vein[2].

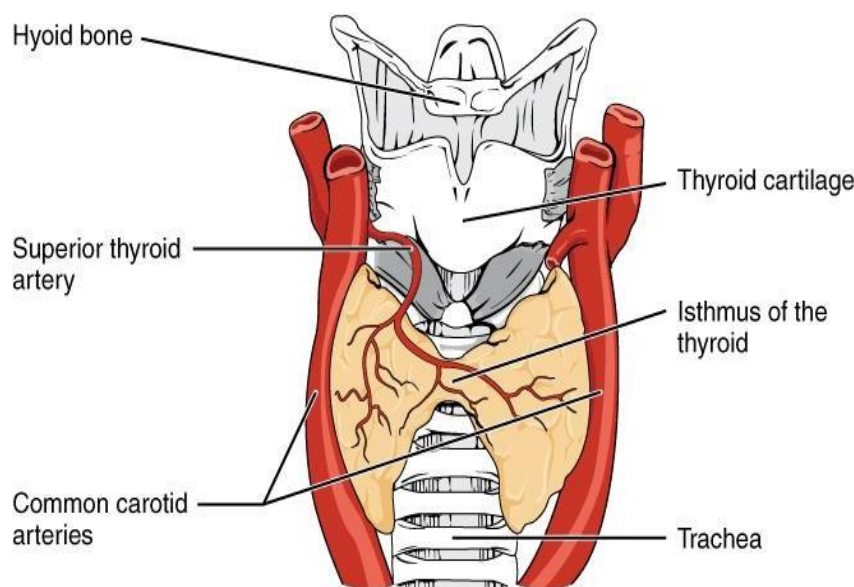


Figure 1-A: human thyroid viewed from the front.

Histology of the thyroid glands

At the microscopic level, there are three primary features of the thyroid, first discovered by Geoffery Websterson in 1664, which are follicles, follicles cells and Parafollicular cells (Figure 1-B).

1.2.1 Follicles

The thyroid is composed of spherical follicles that selectively absorb iodine (as [iodide](#) ions, I⁻) from the blood for production of thyroid hormones, and also for storage of iodine in [thyroglobulin](#). Twenty-five percent of the body's iodide ions are in the thyroid gland. Inside the follicles, in a region called the [follicular lumen](#), colloid serves as a reservoir of materials for thyroid hormone production and, to a lesser extent, acts as a reservoir for the hormones themselves. Colloid is rich in a protein called [thyroglobulin](#).

1.2.2 Follicular cells

The follicles are surrounded by a single layer of [follicular cells](#), which secrete [T3](#) and [T4](#). When the gland is not secreting T3 and T4 (inactive), the epithelial cells range from low columnar to cuboidal cells. When active, the epithelial cells become tall columnar cells.

1.2.3 Parafollicular cells

Scattered among follicular cells and in spaces between the spherical follicles are another type of thyroid cell, [parafollicular cells](#) (also called "C cells"), which secrete [calcitonin](#).

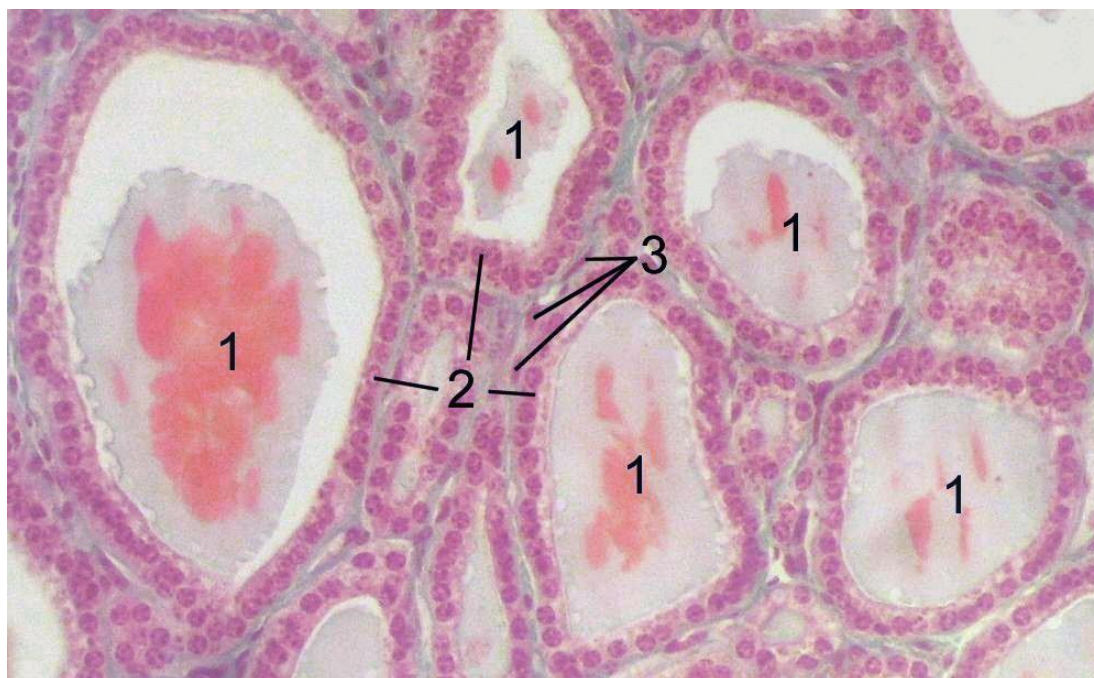


Figure 1-B: Section of thyroid glands under the microscope. (1) Follicles, (2) Follicles cells, (3) endothelial cells.

1.3 Synthesis of the thyroid hormone

The metabolic effects of the thyroid hormones are due to unbound or free T4 and T3. T3 is the more important and is also produced in the periphery by conversion from T4. T3 is quick acting (within a few hours) whereas T4 acts more slowly (4-14 days)[1, 3].

Thyrotropin-releasing hormone (TRH) increases the secretion of thyrotropin (TSH), which stimulates the synthesis and secretion of triiodothyronine (T3) and thyroxine (T4) by the thyroid gland. T3 and T4 inhibit the secretion of TSH, both directly and indirectly by suppressing the release of TRH. T4 is converted to T3 in the liver and many other tissues by the action of T4 monodeiodinases. Some T4 and T3 is conjugated with glucuronide and sulfate in the liver, excreted in the bile, and partially hydrolyzed in the intestine. Some T4 and T3 formed in the intestine may be reabsorbed. Drug interactions may occur at any of these sites[1, 3].

1.4 How the Thyroid Gland Works?

The thyroid is part of the endocrine system, which is made up of glands that produce, store, and release hormones into the bloodstream so the hormones can reach the body's cells. The thyroid gland uses iodine from the foods we eat to make two main hormones: Triiodothyronine (T3) and Thyroxine (T4).

It is important that T3 and T4 levels are neither too high nor too low. Two glands in the brain—the hypothalamus and the pituitary communicate to maintain T3 and T4 balance.

The hypothalamus produces TSH Releasing Hormone (TRH) that signals the pituitary to tell the thyroid gland to produce more or less of T3 and T4 by either increasing or decreasing the release of a hormone called thyroid stimulating hormone (TSH).

So, when T3 and T4 levels are low in the blood, the pituitary gland releases more TSH to tell the thyroid gland to produce more thyroid hormones. However, if T3 and T4 levels are high, the pituitary gland releases less TSH to the thyroid gland to slow production of these hormones.

1.5 What is the important of the Thyroid Gland?

T3 and T4 travel in your bloodstream to reach almost every cell in the body. The hormones regulate the speed with which the cells/metabolism work. For example, T3 and T4 regulate your heart rate and how fast your intestines process food. So if T3 and T4 levels are low, your heart rate may be slower than normal, and you may have constipation/weight gain. If T3 and T4 levels are high, you may have a rapid heart rate and diarrhea/weight loss[4].

The thyronines act on nearly every cell in the body. They act to increase the [basal metabolic rate](#), affect [protein synthesis](#), help regulate long bone growth (synergy with [growth hormone](#)) and neural maturation, and increase the body's sensitivity to [catecholamines](#) (such as [adrenaline](#)) by [permissiveness](#). The thyroid hormones are essential to proper development and differentiation of all cells of the human body. These hormones also regulate [protein](#), [fat](#), and [carbohydrate metabolism](#), affecting how human [cells](#) use energetic compounds. They also stimulate vitamin metabolism. Numerous physiological and pathological stimuli influence thyroid hormone synthesis.

Thyroid hormone leads to heat generation in humans. However, the [thyronamines](#) function via some unknown mechanism to inhibit [neuronal](#) activity; this plays an important role in the [hibernation](#) cycles of [mammals](#) and the [moulting](#) behaviour of [birds](#). One effect of administering the thyronamines is a severe drop in [body temperature](#).

1.6 Disease of the thyroid glands

A thyroid disease is a medical condition impairing the function of the [thyroid](#). Different thyroid diseases include Hashimoto's thyroiditis, hyperthyroidism and hypothyroidism. These diseases have a large range of symptoms and affect all ages[5].

1.6.1 Functional disorders

Imbalance in production of [thyroid hormones](#) arises from dysfunction of the [thyroid gland](#) itself, the [pituitary gland](#), which produces [thyroid- stimulating hormone](#) (TSH), or the [hypothalamus](#), which regulates the pituitary gland via [thyrotropin-releasing hormone](#) (TRH)[6]. Concentrations of TSH increase with age, requiring age-corrected tests. Hypothyroidism affects between three and ten percent of adults, with incidence higher in women and the elderly. The thyroid gland dysfunctional disorders can be categorized into different class, which are; Hypo-function or Hypothyroidism diseases, hyper-function or Hyperthyroidism diseases, Nodular abnormalities or [Goitre](#) and Tumours.

1.6.2 Thyroid tumours

Thyroid cancer accounts for approximately 1% of total cancer cases in developed countries. It affects all age groups, although it is rare in children. Thyroid tumors are more frequent in women than in men. Despite their relative rarity they exhibit a wide range of morphological patterns and biological behavior, which may explain the great interest in these neoplasms of both pathologists and clinicians[7].

1.6.2.1 Classification of the thyroid tumour based on the histological features

The thyroid gland contains two major types of epithelial cells: the follicular cells, which convert iodine into thyroxine and triiodothyronine, and the parafollicular or C-cells, which secrete calcitonin. Thyroid tumors can originate from these very different kinds of cells or from nonepithelial stromal elements, and architectural, cytologic and histogenetic features have been taken into consideration for neoplasms classification. According to the World Health Organization (WHO)1 primary thyroid tumors are classified

as epithelial and nonepithelial, benign or malignant, with a separate category for lymphomas and miscellaneous neoplasm. A slightly different classification scheme has been adopted by the Armed Forces Institute of Pathology (AFIP)², giving priority to the cell of origin and incorporating, in each cell type, special tumor types and subtypes designated as "variants"^[7].

The traditional classification of thyroid cancer as well differentiated carcinomas (papillary and follicular) characterized by relatively good prognosis, or poorly differentiated carcinomas (follicular, anaplastic) associated with aggressive behavior, metastases and death, is no longer applicable since certain morphologic variants of papillary carcinoma are associated with poor prognosis. In addition, the existence of true mixed forms of papillary and follicular cancers has been disproved, while new entities such as "mixed follicular-parafollicular carcinoma" have emerged ^[7].

Tumors of follicular cells and their variants.

1.6.2.1.1 Follicular Adenoma

Follicular adenoma is defined as a benign encapsulated tumor with follicular cell differentiation showing a uniform pattern throughout the confine nodule (Figure 1-C). The fibrous capsule varies in thickness, but is usually thin. Follicular adenomas are solitary tumors with a solid, homogeneous cut surface, but hemorrhage and cystic degeneration are not uncommon. Their size is highly variable, ranging from 1 cm to over 10 cm. On the basis of microscopic features, several variants have been described, including oncocytic adenoma (Hürthle cell adenoma), adenoma with clear cell change, atypical adenoma, hyalinizing trabecular adenoma, adenoma with bizarre nuclei and rare types such as adenoma with adipose (adenolipoma) or cartilagenous (adenochondroma) metaplasia^[7].

1.6.2.2 A.1.2. Follicular Carcinoma

Most authors agree that only follicular tumors that exhibit vascular and/or capsular invasion should be regarded as follicular carcinomas⁸. Depending on the degree of their invasiveness, follicular carcinomas have been divided into two major categories: minimally invasive or encapsulated (the most common), and widely invasive. The frequency of follicular carcinoma among thyroid malignancies ranges from 5-10% in non-iodine-deficient areas to 30-40% in iodine-deficient areas ^[7].

Macroscopically, follicular carcinomas do not differ appreciably from follicular adenomas. The fibrous capsule surrounding the tumor tends to be thicker and more irregular than in adenomas. Minimally invasive follicular carcinoma is an encapsulated tumor showing capsular and/or vascular invasion only on microscopic evaluation, while the widely invasive neoplasm shows lack of complete encapsulation, extensive areas of invasion to the adjacent thyroid tissue and/or widespread blood vessels infiltration^[7].

1.6.2.3 Papillary Carcinoma

Papillary carcinoma is the most common type of thyroid cancer, comprising approximately 80% of all primary thyroid malignancies¹⁵. Classical or non-otherwise specified (NOS) papillary carcinoma is characterized by the formation of papillae and a set of distinctive nuclear features (optically clear appearance, overlapping, pseudoinclusions and nuclear grooves) (Figure 1-C). The size of papillary carcinoma is extremely variable with a mean diameter of 2-3 cm². A clinically detected tumor is usually confined to the thyroid, is presented as a fairly well circumscribed or infiltrative neoplasm and has an indolent course. Its mode of spread is most commonly via lymphatics within the thyroid leading to

"multifocal" disease and to cervical node metastases. Indeed, 50% or more of papillary carcinomas have nodal metastases at initial diagnosis. There are several histologic variants of papillary carcinoma, some of which are associated with a more guarded prognosis[7].

1.6.3 Tumour of C-cell and their variants

1.6.3.1 Medullary Carcinoma

Medullary thyroid carcinoma is a malignant tumor of the thyroid, which shows evidence of C-cell differentiation and usually contains calcitonin (Figure 1-C). It accounts for up to 10% of all malignant thyroid tumors. The variants of medullary carcinoma are: glandular (composed in part of tubular or follicular structures and may resemble follicular carcinoma), papillary (exhibiting true papillary pattern of growth), small cell (resembling the intermediate variant of small cell carcinoma of the lung), and giant cell (occasionally present or focal areas with giant cell formation). Less common are the clear cell, melanotic (pigmented), oncocytic (oxyphilic), squamous, amphicrine (calcitonin and mucin-producing cells) and paraganglioma-like variants[7].

1.6.3.2 Mixed follicular-parafollicular Carcinoma

Mixed medullary and follicular carcinoma are rare neoplasms which show morphologic features of both follicular and C-cell differentiation⁴¹. The dual differentiation has also been noted in their metastatic sites. These neoplasms must be distinguished from the follicular variant of medullary carcinoma and from medullary carcinoma with entrapped normal follicles. Thus, WHO is very strict in defining them as "tumors showing both the morphologic features of medullary carcinoma together with immunoreactivity for calcitonin and the morphologic features of follicular carcinoma together with immunoreactivity for thyroglobulin[7].

Whether these tumors represent collision tumors or arise from a stem cell capable of dual differentiation into follicular and C-cell elements is the subject of several excellent reports in the recent literature[7-9].

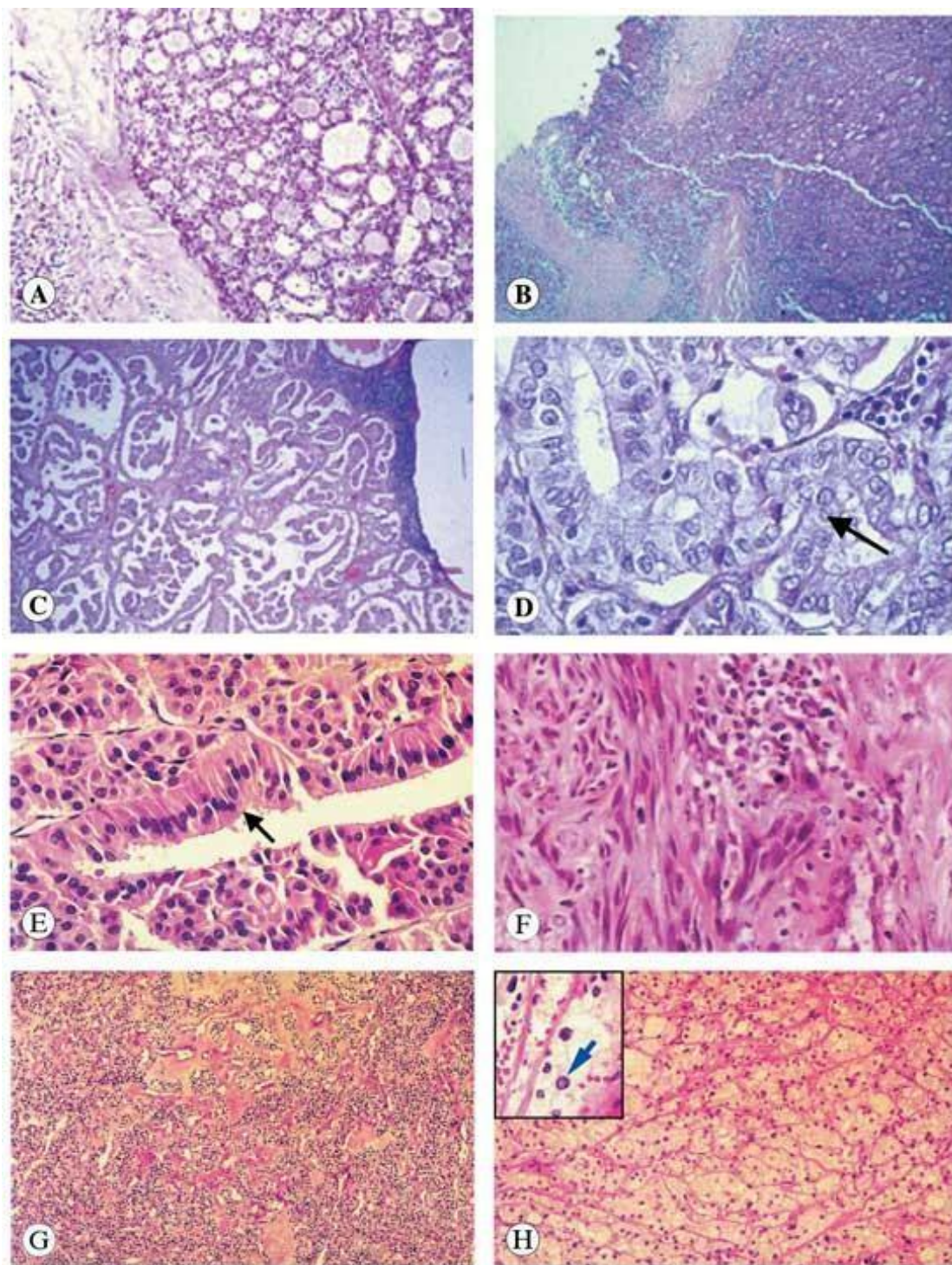


Figure 1-C: Histology of Thyroid Tumors.

A. Follicular adenoma, B. Follicular carcinoma with capsular penetration. C. Papillary carcinoma metastatic to a lymph node, D. Higher magnification showing optical clear, overlapping and grooved (arrow) nuclei. E. Tall cell variant papillary carcinoma, lined by tall cells (arrow). F. Undifferentiated carcinoma with elongated tumour cells. G. Medullary carcinoma. H. Papillary carcinoma with clear cell changes

Aims of the study:

We have four different aim in this study which are:

1. To study the rate of the papillary thyroid carcinoma incidence in Najran area
2. To study the differences in the incidence rate of papillary thyroid carcinoma between male and female.
3. To know which male aged group associated with highest rate of papillary thyroid carcinoma incidences
4. To know which female aged group associated with highest rate of papillary thyroid carcinoma incidences

2 Chapter2: material and methods

2.1 Data source

The data for the rate of papillary thyroid carcinoma incidence were obtained from the histopathology department of the king Khalid hospital for the period between January 2022 to November 2023.

2.2 Ethical consideration

A primary permission was obtained firstly from Najran university, then a consent litter was addressed to king Khalid hospital, in which the study was performed.

2.3 statistical analysis

Statistical analyses were performed using version6 of GraphPad Prism6.

3 Chapter3: Results

3.1 Distribution the incidence of Papillary thyroid carcinoma within male group

The incidence of papillary thyroid carcinoma for male patients was calculated by using the percentage equation. Thus, 42% of the male cases were with average age between 31 to 40 years, followed by 18.75% for the age group between 41 to 50 years. importantly, the age group between 61 to 70 years has the lowest number of papillary thyroid carcinoma incidence between male with 6.25%. Intestinally, the age groups between 21-30 and 41 to 50 has similar number of incidence with 12.5% percent (Figure 3-A).

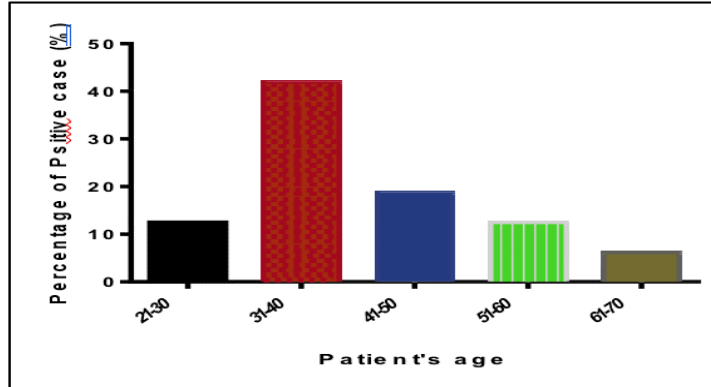


Figure 3-A: Percentage of positive case of Papillary thyroid carcinoma (Male)

3.2 Distribution the incidence of Papillary thyroid carcinoma within female group

In contrast to the male cases, the highest incidence of papillary thyroid carcinoma for female group was recorded for those with age group between 41 to 50 years, followed by 29% for the age group between 51 to 60 years. In the other hand, tow age groups between 21 to 30 and 31 to 40 have the lowest number of papillary thyroid carcinoma incidence for female group with 17.6% (Figure 3-A).

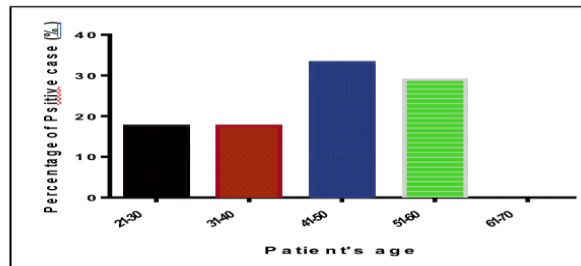


Figure 3-B: Percentage of positive case of Papillary thyroid carcinoma (female)

3.3 Distribution the incidence of Papillary thyroid carcinoma within both male and female groups

The highest incidence of papillary thyroid carcinoma for both sex groups was recorded for the 31 to 40 age group with 59.6%. In contrast, the age group between 61 to 70 has the lowest number of incidence with percent of 6.25%.

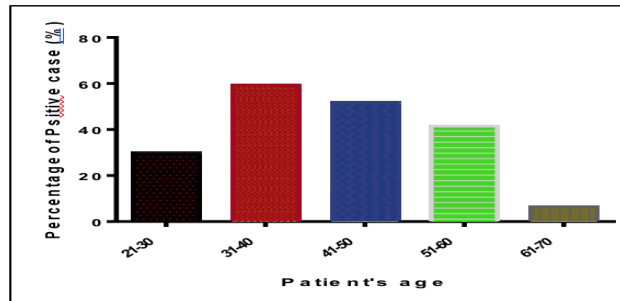


Figure 3-C: Percentage of positive case of Papillary thyroid carcinoma (both male and female)

3.4 Gender Differences in Papillary thyroid carcinoma

The disparities observed between men and women with respect to the incidence of Papillary thyroid carcinoma were studied in this project. It has been noticed that the rate of papillary thyroid cancer among woman is more than three-times higher than men (Figure 3-D). Interestingly, there were no difference between the average age of male and female groups (Figure 3-E).

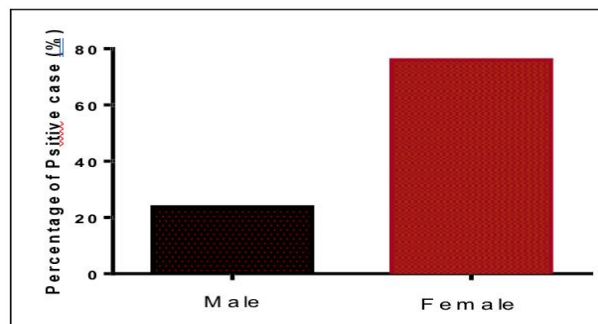


Figure 3-D: Comparison the percentage of Papillary thyroid carcinoma positive case between male and female

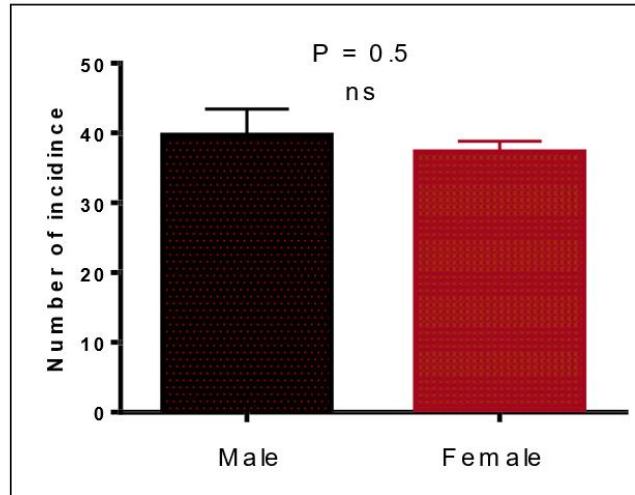


Figure 3-E: Comparison the average of the male and female patients age for Papillary thyroid carcinoma cases

3.5 Comparison the number of incidence of Papillary thyroid carcinoma for the peroid between 2013 to 2015

Figure 3-F, illustrates a significant and gradual decrease the incidence of thyroid cancer from 28 cases in the 2013 to 22 case in the 2014 then finally 14 cases in the 2015.

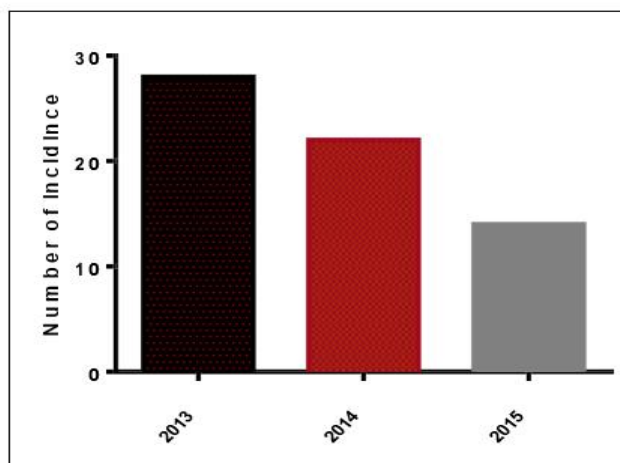


Figure 3-F: The incincince of Papillary thyroid carcinom case for each year

Chapter4: Discussion:

This study has shown that the rate of papillary thyroid cancer among woman is more than three-times higher than men, with a peak of the incidence for the age group between 41 to 50 (the premenopausal period). These findings come in agreement different others studies that focus to study the gender differences in thyroid cancer[10-12].

The female predominance of papillary thyroid cancer and its peak incidence occurring in premenopausal women suggests that female sex hormones may be involved in the development of thyroid cancer. In addition, an association of papillary thyroid cancer with breast cancer, a malignancy also predominantly affecting women, has long been established. Several studies have found an increased risk of thyroid cancer in individuals with a history of breast cancer[13, 14] and, conversely, an increased risk of breast cancer in those individuals with a history of thyroid cancer has also been observed[14, 15]. It has therefore been suspected that breast cancer, commonly an estrogen-responsive malignancy, and thyroid cancer may share some common etiological factors.

The influence of gender on thyroid cancer has remained an area of controversy. There is a significantly higher thyroid cancer incidence in women, while men appear to have a worse prognosis, although this is partly due to a more advanced cancer stage at presentation. However, numerous *in vitro* and animal studies suggest a possible role for sex steroids in thyroid cancer tumorigenesis and progression.

Recent study has suggested that Saudi female are suffering from a sever deficiency in vitamin D compare to men. That deficiency is due to the lack of exposure to the sun light [16]. Thus, the Role of vitamin D deficiency cannot be excluded as risk factor behind this increase in the

.incidence of female with papillary thyroid carcinoma. interestingly, a number of studies have linked the deficiency of Vitamin D with a number of cancer[17-19]. Excitingly, a very recent one has approved the association between Vitamin D deficiency and papillary thyroid carcinoma [20].

The last of our study showed a significant and gradual decrease the incidence of thyroid cancer from 28 cases in the 2013 to 22 case in the 2014 then finally 14 cases in the 2015. A few reasons can be suggested for this decline such as Improve the standard of living Education and awareness of health community for the people in Najran city. The reluctance of patients to other hospitals cannot be ignore.

Our understanding of the environmental and genetic susceptibility for thyroid cancer will improve and can serve to help identify factors influencing thyroid cancer gender disparity. High-throughput approaches, such as genome-wide single-nucleotide polymorphism analyses, may help identify new susceptibility loci for thyroid cancer, which could serve to explain the gender disparity found in thyroid cancer.

To conclude, our results illustrated that the rate of papillary thyroid cancer among woman is more than three-times higher than men, with a peak of the incidence for the age group between 41 to 50 (the premenopausal period). A number of limitations are identified in this study such as the size of the sample and localization of the study data which was selected from a single hospital, and this is unlikely to represent the real prevalence of thyroid cancer in Najran city. So, this study need be expanded targeting different number of hospital and with large number of sample.

4 References

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"سرطان الغدة الدرقية الحليمي التفاوت بين الجنسين في مدينة نجران"

الباحثون:

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وقد لوحظ وجود تفاوت بين الجنسين في الإصابة بالسرطان وعدوانية المرض والتشخيص في مجموعة متنوعة من أنواع السرطان. يعد سرطان الغدة الدرقية أحد أسرع تشخيصات السرطان نموًا في جميع أنحاء العالم. وهو أكثر شيوعًا عند النساء بنسبة 2.9 مرة مقارنة بالرجال. الأنواع الفرعية النسيجية الأقل عدوانية من سرطان الغدة الدرقية، وهي سرطان الغدة الدرقية الحليمي، أكثر شيوعًا عند النساء، في حين أن الأنواع الفرعية النسيجية الأكثر عدوانية لها توزيع مماثل بين الجنسين. سرطان الغدة الدرقية الحليمي هو النوع الأكثر شيوعًا من سرطان الغدة الدرقية، وهو ما يمثل حوالي 80% من الحالات. وقد تضاعف معدل الإصابة به تقريبًا خلال الثلاثين عامًا الماضية، ويُعتقد أنه يرجع جزئيًا إلى التشخيص المبكر لمرض تحت الإكلينيكي. تهدف هذه الدراسة إلى الفروق بين الجنسين في سرطان الغدة الدرقية الحليمي لدى سكان مدينة نجران في المملكة العربية السعودية.