Epidemiology of thyroid cancer: A review with special reference to Gulf Cooperation Council (GCC) States

A. S. Al-Zahrani 1,2, K. Ravichandran 2

1 Gulf Center for Cancer Registration,
2 Biostatistics & Epidemiology Department, King Faisal Specialist Hospital & Research Center, Riyadh, Kingdom of Saudi Arabia.

Abstract

A wide variation in incidence of thyroid cancer according to age, sex, ethnicity and geographic region was observed. In general, it occurs more frequently in women than men and a substantially higher rate was observed particularly during fertile period of women compared with men of the same age. Papillary carcinoma is the most prevalent histological type, irrespective of gender and conditions like iodine level. Over the years the incidence of thyroid cancer, especially papillary type, increases around the world. Ionizing radiation, in particular radiotherapy to head and neck region was the most established risk factor for thyroid cancer. Goiter, miscarriage or abortion (particular in the first pregnancy) may also predispose to thyroid cancer risk. Cigarette smoking and use of contraceptives may be modifier of thyroid cancer risk.

In all the GCC states thyroid cancer is the second most common cancer except in Bahrain and Kuwait (where it stands third). During the five year period (1998-2002) 549 male and 1898 female thyroid cancers were diagnosed in all the GCC states. Papillary carcinoma is the predominant histological type followed by follicular carcinoma in both gender. Among female, Qatar has the highest incidence with an age standardized incidence rate of 13.5 per 100,000 followed by Kuwait (7.7), Bahrain (7.6), Emirates (6.0), Oman (5.9), and Saudi Arabia (5.0). There were at least 2.6 female thyroid cancer cases (in Kuwait) for each male thyroid cancer case and this goes up to 6.6 in Bahrain. Incidence of thyroid cancer in the GCC states is closer or higher than that of some of the developed countries.

Key words

Thyroid cancer, Epidemiology, GCC states.

Introduction

In 2002, cancer of thyroid comprises 1.3% (141,013 cases) of all cancers worldwide with an estimated annual Age Standardised incidence Rate (ASR) of 3.3 per 100,000 among women and 1.3 per 100,000 among men (1). Although thyroid cancer is relatively rare neoplasm, it is the most common endocrine malignancy (2) and accounts for 0.5% of all deaths caused by malignant tumours (1). Thyroid cancer is heterogeneous in terms of histology, clinical presentation, treatment response and prognosis (3).

Little is known about the epidemiology of thyroid cancer in the Middle East and in particular Gulf Cooperation Council (GCC) states. Previous studies on epidemiology of thyroid cancer from the GCC states are very limited and from few states only (4, 5). The purpose of this review is to provide an account of our present knowledge about the epidemiology of thyroid cancer with a special emphasis pertaining to GCC states.

Variations in incidence

Gender

Approximately a three-fold higher incidence of thyroid cancer in females compared to males, across all countries and ethnicity, was observed (2) but this varies among morphological types and by age (6). A female predominance among childhood and adolescent was also observed by a study from Europe based on the largest ever assembled database on these age groups (7).
Age

Although thyroid cancer is rare in children and adolescents, it is one of the frequent cancers in these age groups (3). According to Pettersson et al (6), in Sweden, the incidence of papillary cancer in women increased steeply up to age 50 and leveled off above this age, but in males, a steady increase was observed up to age 75. While papillary and follicular carcinomas strike mainly younger age groups, anaplastic tumours are rare before 50 years of age. Furthermore, the sharp increase seen in female papillary thyroid cancer in Sweden during the fertile part of life was not seen for female follicular thyroid cancer and the incidence of follicular carcinoma increases slowly with age and reaches its highest level around 60 years of age for both men and women (3). On the other hand, a substantially and consistently higher (three times) incidence rates of thyroid cancer in men compared with women during the period between puberty and menopause was observed by Sakoda et al (8). A study by Lundgren et al (3) shows differentiated non-medullary thyroid cancer is more common among women, particularly during the fertile period of women’s life. A descriptive study from Japan suggests papillary, follicular, and medullary carcinomas are more common in the fifth and sixth decades of life while anaplastic carcinoma is more common in the elderly (9).

Geographic variations

Comparison of incidence around the world showed low rates in some European countries (Denmark, Netherland, UK, Ireland) and high rates in Iceland and Hawaii (2). Data on childhood and adolescent cases of thyroid cancer also showed a marked difference (7). More than 3-fold variation among women and less than 2-fold variation among men was observed even within 8 French cancer registries (10), and among 8 registries in Switzerland (11).

Ethnicity

Variations in the incidence of thyroid cancer among ethnic groups were also observed. In Hawaii, where the world’s highest incidence rate were reported, Filipino had highest ASR of 19.4 per 100,000 among females followed by Hawaiian (11.0), Whites (7.6), Japanese (7.3) and Chinese (6.7). Whereas among males, again, Filipino had highest ASR (5.0 per 100,000) followed by Hawaiian (4.6), Chinese (4.6), Whites (4.0) and Japanese (1.9) (2). A comparison of ethnic-specific incidence rates for groups living in Hawaii with people of the same ethnic backgrounds living in other geographic areas showed that Hawaii residents generally have much higher rates. Furthermore, Rossing et al (12) when compared the incidence rates of women residing in US by US-born and foreign-born Chinese, Japanese, and Filipino found that the thyroid cancer incidence rates were elevated for women born in Asia but not for those born in the US. In a later study by Haselkorn et al (13) indicates that the high thyroid cancer incidence rates observed in the Southeast Asian women in the US can be largely attributed to the higher prevalence of goiter or thyroid nodules in this group compared with others. This was observed consistently in both younger and older women and whether the comparison group was Northern Asian or Caucasian women. Indeed, the data from this study shows dietary patterns also contribute the differences in incidence rate but to much lesser degree compared to goiter or thyroid nodules.

The diversity in incidence of thyroid cancer among the various ethnic groups seems to bear a direct relationship with the genetic susceptibility, however, it is unlikely that this will account fully for the increased risk of thyroid cancer. The fact that higher rates observed for all residents of Hawaii, irrespective of ethnicity, and rates were elevated for women born in Asia but not for those born in the US suggest that persons residing in one or more regions have been exposed to environmental and lifestyle influences that have increased or decreased their subsequent risk of thyroid cancer.

Time trend

Different publications from many countries have described thyroid cancer time trends, confirming that incidence has been increasing over the past 6 decades. Pettersson and colleagues (6) described an increase of thyroid cancer in Sweden over the period 1958–1981, a mean annual change of 1.9% and 1.2% in the ASR of women
and men, respectively. The increase was mainly in papillary carcinoma especially in women (4.9%) and men (2.1%). These authors also mention a smaller increase for follicular cancer and a decrease in anaplastic cancer. A two fold increase of incidence in both sexes was observed in Norway (14) over the period 1955 to 1989 even though a decline was observed in the last 5-year period, especially among females. The reason for this is not clear, although radiation treatment during childhood and dietary habits may possibly be involved. According to Leenhardt et al (15) the increased incidence of thyroid cancer observed in France is mainly due to papillary type with an epidemic of microcarcinomas. A latest study, based on SEER data, showed a 2.4 fold increase in the incidence of thyroid cancer in US between 1973 and 2002. Virtually the entire increase was attributed to an increase in incidence of papillary thyroid cancer which increased from 2.7 to 7.7 per 100,000 and there was no significant change in the incidence of follicular, medullary, and anaplastic types (16). Similar increase in incidence was observed in Japan (9), England and Wales (17), Canada (18) and Switzerland (19). Incidence of thyroid carcinoma increased, also among children and adolescents by 3% per year largely due to papillary carcinoma in Europe (excluding Belarus) during 1978-1997 (7).

In addition to the well known risk factor of thyroid cancer, radiation exposure in childhood and adolescence, increased diagnostic activity as well as changes in surgical and pathological practices (18, 20, 21) and changes in the histological classification (20) has long been suspected to be of etiological importance in the observed increase of thyroid cancer incidence.

In the GCC States thyroid cancer is the fifth most common cancer (22). Between January 1998 and December 2002 there were 2,447 (5.8% of all cancers) incidence thyroid cancer cases reported from all GCC States among its nationals. Of the 2,447 cases 549 were male and 1,898 were female with a male to female ratio of 1: 3.5. During this five year period thyroid cancer was the second most common cancer (after breast) in all the GCC states among GCC national women except in Bahrain (where it stands third after breast and lung) and Kuwait (where it stands third after breast and colorectal). Among female, Qatar reported the highest incidence with an ASR of 13.5 per 100,000 followed by Kuwait (7.7), Bahrain (7.6), UAE (6.0), Oman (5.9), and KSA (5.0). There were at least 2.6 female thyroid cancer cases (in Kuwait) for each male thyroid cancer case and this goes up to 6.6 in Bahrain [Table 1]. The male to female ratio in the GCC

<table>
<thead>
<tr>
<th></th>
<th>Emirates</th>
<th>Bahrain</th>
<th>Saudi Arabia</th>
<th>Oman</th>
<th>Qatar</th>
<th>Kuwait</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cancer cases</td>
<td>715.0</td>
<td>942.0</td>
<td>15223.0</td>
<td>2365.0</td>
<td>374.0</td>
<td>1309.0</td>
</tr>
<tr>
<td>Thyroid cancer cases</td>
<td>16.0</td>
<td>9.0</td>
<td>417.0</td>
<td>47.0</td>
<td>13.0</td>
<td>47.0</td>
</tr>
<tr>
<td>%</td>
<td>2.2</td>
<td>1.0</td>
<td>2.7</td>
<td>2.0</td>
<td>3.5</td>
<td>3.6</td>
</tr>
<tr>
<td>CIR</td>
<td>0.8</td>
<td>0.8</td>
<td>1.1</td>
<td>1.0</td>
<td>2.5</td>
<td>2.3</td>
</tr>
<tr>
<td>ASR</td>
<td>1.5</td>
<td>1.1</td>
<td>1.7</td>
<td>1.7</td>
<td>3.4</td>
<td>3.7</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cancer cases</td>
<td>787.0</td>
<td>951.0</td>
<td>14694.0</td>
<td>2070.0</td>
<td>383.0</td>
<td>1662.0</td>
</tr>
<tr>
<td>Thyroid cancer cases</td>
<td>78.0</td>
<td>59.0</td>
<td>1421.0</td>
<td>171.0</td>
<td>47.0</td>
<td>122.0</td>
</tr>
<tr>
<td>%</td>
<td>9.9</td>
<td>6.2</td>
<td>9.7</td>
<td>8.3</td>
<td>12.3</td>
<td>7.3</td>
</tr>
<tr>
<td>CIR</td>
<td>4.0</td>
<td>5.8</td>
<td>3.8</td>
<td>3.9</td>
<td>9.5</td>
<td>5.7</td>
</tr>
<tr>
<td>ASR</td>
<td>6.0</td>
<td>7.6</td>
<td>5.0</td>
<td>5.9</td>
<td>13.5</td>
<td>7.7</td>
</tr>
<tr>
<td>Sex Ratio (M:F)</td>
<td>1 : 4.9</td>
<td>1 : 6.6</td>
<td>1 : 3.4</td>
<td>1 : 3.6</td>
<td>1 : 3.6</td>
<td>1 : 2.6</td>
</tr>
</tbody>
</table>

Table 1: Total number, percentage, average annual Crude Incidence Rate (CIR), Age Standardised incidence Rate (ASR) per 100,000 of thyroid cancer in the GCC states by gender: 1998-2002.

Epidemiology of thyroid cancer, Al-Zahrani et al.

states is consistent with the female predominance reported in other studies, however, was higher especially in UAE and Bahrain than elsewhere reported.

Incidence of thyroid cancer in the GCC States is closer or higher than that of some of the developed countries. For example, Qatar has the rate next to Hawaii, where the world’s highest incidence was reported (2). Kuwait and Bahrain reported incidence closer to that of Finland and higher than that of Australia, while UAE, Oman, and KSA reported higher incidence than that of UK (Fig. 1).

Fig. 1: Comparison of ASR of Thyroid cancer in the GCC States with selected countries.

Source: Five Year Cancer Incidence Report for the Gulf Cooperation Council Countries, 1998-2002 (22) and GLOBOCAN (1).

In general the incidence of thyroid cancer in GCC states increases with age however, unlike in other studies, a step increase only up to 35 years in females and 50 years in males was observed (Fig. 2a-2b) and there were 38 (1.6%) cases under 15 years of age.

Fig. 2a: Average annual Age Specific Incidence Rates of Thyroid Cancer in the GCC states, 1998-2002: Male.


Fig. 2b: Average annual Age Specific Incidence Rates of Thyroid Cancer in the GCC states, 1998-2002: Female.


In the GCC States a high proportion of cases (99.3%) were diagnosed by the microscopic verification method, however, cytological methods accounts for only 6.6% and remainder (92.7%) by histology of primary or secondary sites. The four major histological types (Papillary, follicular, medullary and anaplastic carcinoma) together accounts for 100% of total male cancers in Emirates, Bahrain and Qatar; 95.4%, 93.4% and 90.5% in Saudi Arabia, Kuwait and Oman. Whereas, among females a more consistent pattern than males was observed and these four types together accounts for 94.8% in GCC states with a range from 91.5% in Bahrain to 97.9% in Qatar.

Radiation

Epidemiological studies have revealed several factors that affect the risk of developing thyroid cancer. As per the pooled analysis of seven studies (five cohort and two case control studies) ionizing radiation in particular radiotherapy to head and neck region is the most widely accepted factor (23). The thyroid gland is highly sensitive to radiation-induced oncogenesis. This is verified by numerous reports from survivors after the bombings of Hiroshima and Nagasaki, several atomic-bomb tests (Nevada, Novaja Semlja and Marshal Island) and the accident at Chernobyl plant as well as medical use of radiation for benign diseases in childhood (24). In children, the risk is maximal when radiation exposure occurs below the age of 5 years, this risk decreases with older age, and above the age of 15–20 years the risk is only slightly or even not significantly
increased and no study has evidenced an increased risk for the exposure after the age of 45 years. Also, there appears to be a dose-response relation between the risk of thyroid cancer and exposure to radioactive radioiodine, and particularly for persons less than 15 years of age the dose-response was best described even down to 0.1 Gy. The excess relative risk began to decline about 30 years after exposure but was still elevated at 40 years. Moreover, after radiation exposure during childhood thyroid cancer incidence is 2–3 times higher in females than in males (23).

A birth-cohort effect observed in the time trend in both sexes, which closely follows the introduction of radiation treatment of benign childhood conditions in the head and neck region between 1920 and the 1950s in the US suggest that radiation treatment in the head and neck is largely responsible for the observed increase of thyroid cancer (25). In Northern region of England a significant increase in the incidence of thyroid cancer after the Chernobyl accident was detected and the increase was greater in the area received heaviest fallout, supporting a causal relationship of the temporal and spatial changes in incidence consistent with the Chernobyl accident (26). Similarly, the peak of thyroid cancer risk observed in women born in 1952-1955 is consistent with a carcinogenic effect of fallout radiation from atmospheric nuclear weapon tests, since these women were children in the late 1950s and early 1960s when fallout radiation was greatest in England and Wales (17).

No risk of thyroid cancer was found on who received I131 either as therapy or diagnostic purposes and the risk was not related to time since exposure or age at exposure (27, 28). However, a very strong dose-response relationship was observed between radiation exposure, mainly I131, in childhood (younger than 15 years) and the risk of a subsequent thyroid cancer by a population-based case control study from Belarus and the Russian Federation (29). The doses for each subjects is this study were estimated based on their whereabouts and dietary habits at the time of the accident and in following days, weeks, and years and their likely stable iodine status at the time of the accident. The cohort study from Ukraine, the most heavily contaminated area of Chernobyl accident, has clearly demonstrated a strong and positive relationship between thyroid dose from radioactive iodines and subsequent thyroid cancer risk, with an excess RR of 5.2 per Gy among those exposed as children and adolescents. These results indicate that the carcinogenic effects of childhood exposure to radioactive iodines do not differ substantially from those of external irradiation (30).

In the absence of reliable data on childhood radiotherapy in the GCC states it will be difficult to attribute the high incidence to this practice. The hypothesis regarding the effect of environmental contamination linked to the first Gulf War (1990-1991) following the Iraqi occupation of Kuwait can not be ruled out and has to be studied further in detail.

**Iodine**

Research on the relationship between iodine exposure and thyroid cancer risk is both complex and controversial. Differences in iodine intake may be one factor explaining the geographic variation, high iodine intake being associated with a slightly increased risk of developing thyroid cancer (24). Elevated incidence rates of thyroid cancer are reported from the areas where iodine intake was high (Hawaii, Iceland) (31), conversely, the high rates of thyroid cancer occurring in Hawaii or Iceland are not observed in Japan, yet high dietary iodine intake is typical (32) and, however, ethnic Japanese living in Hawaii have incidence rates for thyroid cancer up to 2-fold higher than those occurring in Japan (2).

Many epidemiological studies suggest dietary iodine, especially fish and shellfish as an etiological factor for thyroid cancer. However, associations between dietary iodine consumption and thyroid cancer risk have been mixed with no discernable pattern and often inconsistent within a given study (33). The study which quantified dietary iodine exposure (34) concludes that iodine exposure appears to have, at most, a weak effect on the risk of papillary thyroid cancer even after incorporating a biomarker of long-term (1 year) iodine exposure. Another study, based on urinary excretion levels of iodine, did not find
different incidence between iodine sufficient and deficient countries, also, both the iodine sufficient (Northern Europe) and deficient (Southern Europe) countries have the highest incidence rates (7).

Several papers have described that more papillary carcinomas are being observed in adequate or high iodine intake areas and a higher frequency of follicular and anaplastic thyroid cancer are being observed in iodine deficient areas (35). An investigation of iodine prophylaxis over a time span of 40 years from the region of Salta, Argentina, where goiter is common, found papillary carcinomas formed the largest group of tumors with a significant increase in their proportion in the later 25 year period (a period well after salt iodination) than with the first 15 year period (5 year before prophylaxis) (44 vs. 60%), while the percentage of follicular and undifferentiated carcinomas decreased and medullary carcinoma remained about the same. The ratio of papillary to follicular carcinoma rose from 1.7:1 in the first period to 3.1:1 in the second period (35). In Austria also an increase in the relative proportion of papillary carcinoma with a concurrent drop in anaplastic type has been recorded following the introduction of iodine supplementation in iodine deficient regions (36). In contrast to all these, a study from Sweden based on the cases diagnosed between 1958-1981 founds incidence of both papillary and follicular carcinoma increased during the study period with largely similar trends in iodine deficient and iodine sufficient areas, nevertheless after iodinization of the food supply, which was started in 1936 and enhanced in 1966 (37).

Goiter

Goiter was strongly and consistently associated with thyroid cancer (38). According to studies from Italy, Switzerland, US, Japan and China goiter was associated with a 4 to 7 fold increase in the risk of thyroid cancer (38). A cohort study from San Francisco observed a RR of 3.4 for persons who had history of goiter, after a median follow-up of 20 years (39). Regardless of prior radiation exposure, women who ever had a goiter were at increased risk of developing thyroid cancer. Women who had ever developed a goiter had 17 times the risk of developing follicular cancer and almost 7 times the risk of developing papillary cancer as compared with women who never had a goiter and the risk was elevated even among women who had a history of goiter many years prior to diagnosis (40).

A study from two endemic goiter areas of Poland confirms a significant decrease in elevated thyroid stimulating hormone (TSH) concentration in newborns, increase in urinary iodine concentration among schoolchildren and no further increase in thyroid cancer incidence rate since 1999 after restoring iodine prophylaxis in 1997, in contrast to the observed increased goiter prevalence in schoolchildren and adults, elevated TSH levels in newborns in the early 1990s and an increase in thyroid cancer incidence since 1992 due to iodine prophylaxis suspension in 1980 (41). Thyroid cancer patient data from the endemic goiter area of Algeria showed anaplastic and follicular carcinoma were more frequent (14% and 42%, respectively) when compared with those from the non-endemic area (6% and 38%, respectively) (42).

In the GCC states, studies on goiter are very few. Endemic goiter was more prevalent (24%) in mountainous, rural, high altitude areas of Asir Region, Southwestern Saudi Arabia (43). Further, prevalence of goiter among school children in high altitude areas of 3150 meters was significantly higher than the prevalence among their counterparts in low altitude areas of 500m. This finding was persistent among school children of all educational levels. However, the distribution of goiter in this region was patchy and differs from area to area. A cross sectional survey of primary-school children conducted in Bahrain showed only 1.7% had goiter (44). A study from UAE using the prevalence of raised TSH levels (> 5 micro U/ mL whole blood) during 1998 and 1999 found the ratio of TSH profile and goiter rate in schools in a 1994 study were discrepant, although there was good correlation between the ratio of TSH profile and urinary iodine (45).

Reproductive and menstrual factors

Literature on the association between reproductive characteristics of women and
thyroid cancer occurrence are inconsistent. Several studies indicates no risk, on the other hand, some found increased risk\(^{(38, 39)}\).

**Parity**

Among the various reproductive factors, parity has received the most attention. As regards to the number of pregnancies and the risk of thyroid cancer, bulk of the evidence suggests that there is a positive relationship. According to a prospective birth cohort study on Norwegian women of reproductive age and a case control study from Japan, the risk of thyroid cancer increased with the increasing number of pregnancies\(^{(46, 47)}\). The relationship appears most pronounced for the follicular type and this stronger effect is consistent with the fact that the general female preponderance of thyroid cancer is more pronounced for this type\(^{(46)}\). An independent and increasing risk (RR 6.3 for 4 or more pregnancies; \(p=0.03\)) was observed with an increase in the total number of pregnancies even after excluding women with prior thyroid disease and those whose first pregnancy ended in a miscarriage\(^{(48)}\). A 8% increase in risk (\(p=0.01\)) for each additional pregnancy was observed, with an OR of 2.2 (95% CI= 1.1-4.3) for women with eight or more pregnancies\(^{(38)}\). However, no clear association was observed with history of incomplete pregnancies by Galanti et al\(^{(49)}\). Age at first birth and last birth

Age at first birth has received more modest attention as a potential promoting factor. An early first childbirth (before 20 years of age, or less than 5 years after menarche) was associated with an increased risk of thyroid cancer\(^{(49)}\). In contrary, Franceschi et al\(^{(53)}\) observed late age (\(\geq 28\) years) at first birth had higher risk (RR 2.4) compared to less than or equal to 21 years and no association was observed by Rossing et al\(^{(50)}\) among women aged \(\geq 45\) years with age at first live birth. Furthermore, most of the studies did not find any significant effect of the age at entry into motherhood\(^{(46, 47, 48, 54)}\).

Age at last birth greater than or equal to 30 years had RR of 2.2 compared to less than 30 years among both the premenopausal and postmenopausal women\(^{(53)}\) and no association was observed among women aged \(\geq 45\) years\(^{(50)}\).

**Age at menarche**

Women who reported onset of menarche before age 12 years were at about 50% increased risk for papillary thyroid cancer\(^{(8)}\), however, the risk was associated also to later age at menarche (RR 2.8 for age \(\geq 14\) years)\(^{(53)}\) and no association was observed by Mack et al\(^{(52)}\). Yet, Sakoda et al\(^{(8)}\) noted differences in effects among subgroups of women. Asian women with later menarche were at increased risk of papillary thyroid cancer, whereas among white women, early age conferred some elevation in risk and the reasons for this difference are unclear. Furthermore, age at menarche (both early and late) seemed to be more important among older (more than 45 years) rather than younger women\(^{(8)}\). Another study from New Caledonia found late menarche (age 15 and above years) was strongly associated with thyroid cancer in European women (OR = 3.4; 95% CI= 1.0-12.0) and, to a lesser degree, in Melanesian women (OR = 1.5; 95% CI= 0.7-3.3), whereas an inverse association was observed for other ethnic groups, including Polynesian and Asian women (OR = 0.2; 95% CI= 0.1-0.7). It
Epidemiology of thyroid cancer, Al-Zahrani et al.

is possible that ethnic-specific risk factors for thyroid cancer also influencing age at menarche, such as dietary or genetic factors, explain the different odds ratios for the various ethnic groups. If late menarche increases the risk of thyroid cancer in Melanesian women, it may play a role in the elevated incidence observed in this group because menarche occurred noticeably later in Melanesian women than in other ethnic groups (age at menarche was 15 years for 46% of Melanesian and 13% of European controls) (38).

Menopause

There was an increased risk of thyroid cancer among women with a history of artificial menopause compared to those with a spontaneous menopause (OR 2.5; 95% CI= 1.0-6.6), which was more pronounced for the papillary carcinoma and after adjustment for age at menopause and use of replacement therapy (49). Also, a cohort study of hysterectomized women (55), two case control studies (50, 52) and a pooled analysis (even though whether hysterectomy or bilateral ovariectomy was not distinguished) (56) found an approximately two fold excess risk of thyroid cancer for hysterectomy. However, in another study (38), there was some evidence that hysterectomy but not ovariectomy was related, particularly when hysterectomy occurred at a young age. In contrast, Rossing et al (50) observed a risk only among women ≥ 45 years of age and among them also there was no clear relation found with duration since hysterectomy and age at which hysterectomy had occurred. Some authors have suggested that this association might reflect either increased detection of thyroid cancer at the time of hysterectomy or confounded by indication for hysterectomy or can be considered as an indicator of prolonged menstrual disorders and not as a cause of thyroid cancer (49, 50, 52).

Women who had never menstruated regularly had a RR of 1.7 (53), an OR of 3.6 (95% CI= 1.7-7.4) for women aged less than 45 years (38) and OR of 2.2 (95% CI= 0.9-6.1) for women aged less than 35 years (52).

A population-based case control study from Kuwait (4), the first such study from GCC states, suggested events such as age at menarche, pregnancy, menopausal status and age at menopause were not associated with thyroid cancer. Only age at last pregnancy and parity was associated with thyroid cancer risk. Women who had their last pregnancy at ages ≥ 30 years were at a significantly increased risk (OR 2.1; 95% CI= 1.2-3.8) and there was also a significant trend in risk with increasing age at last pregnancy; there was a modest increase in risk among women who had borne ≥ 5 children (OR 1.5; 95% CI= 0.9-2.5). In contrast to other studies, there was a significant decrease in risk (OR 0.1; 95% CI= 0.03-0.4) among women who had a miscarriage as outcome of first pregnancy and those who had experienced ≥ 3 miscarriages (OR 0.3; 95% CI= 0.1-0.8) was observed.

Hormonal factors

The generally higher incidence of thyroid cancer in women is not explained by childbearing. Childless women also run a much higher risk of developing a carcinoma in the thyroid gland than do men (46). Neither nulliparity nor infertility appeared to influence the occurrence of thyroid cancer (54). Use of Oral Contraceptives (OCs) has been found to give a slightly elevated risk (RR 1.6; 95% CI= 1.0-2.5) of thyroid cancer (57). From a pooled analysis of 13 case control studies, an increased risk of papillary thyroid cancer has been seen among current users of OCs (OR 1.6), whereas no such increase was evident among former users (58) and ever users of post menopausal estrogens had 1.4 times the risk of never users (95% CI= 0.9-2.3) (57). In contrary, a reduced risk (OR 0.7; 95% CI= 0.5-1.0) of papillary thyroid cancer was observed by Sakoda et al (8) for women who ever used OCs. However, Rossing et al (59) reported a decrease in risk (OR=0.6; 95% CI= 0.4-0.9) only among younger women (age < 45 years) and no association among older women. None of these studies, however, showed an association with duration of use or age at first use. Furthermore, several other studies observed no association between OC use and thyroid cancer (38, 49, 51, 52). The lack of trend with duration of use suggests that this association may not reflect an etiological effect but a possible confounding by yet unidentified characteristics of the women who did or did not
use OCs in these various studies (8). Moreover, the use of OCs might simply be a reflection of socio-economic status or lifestyle differences between cases and controls rather than an indicator of the impact of hormones on thyroid cancer risk (13).

Exogenous estrogen in the form of lactation suppressants has been found to give a slightly elevated risk of thyroid cancer. The parous women who had ever used a lactation suppressant had 1.7 times the risk of parous nonusers (95% CI= 1.1-2.8) (57). However, several others did not find any significant association of thyroid cancer with the use of lactation suppressants (51, 52) and hormone replacement therapy (38, 49, 58, 59).

Other Factors

Several studies which examined the relation of smoking and the risk of thyroid cancer identified female smokers were at a reduced risk (49, 60, 61). However, the risk observed for age started smoking, duration and quantity of smoked were not consistent even within these studies. In contrast to all these studies, a study found a RR of 7.1 (95% CI = 1.5-33.0) for smokers (62) and other could not find any association (39, 51, 63).

History of benign thyroid diseases, family history of thyroid cancer and obesity were associated with increased risk of thyroid cancer (39, 48, 51, 52, 54, 64).

Protection from thyroid carcinoma due to consumption of certain dietary factors was suggested by several studies (65) but the findings were relatively inconsistent. Consumption of fresh fruits, raw vegetables and both, led to a reduced risk associated with an OR of 0.7 for each factors with corresponding p=0.01, p=0.02 and 0.04 for all thyroid cancers (66). Similar risk were obtained for papillary thyroid cancers, however, none of these factors were significant for follicular carcinoma, may be due to less number of cases in follicular type.

Conclusion

All the descriptive epidemiological studies on thyroid cancer suggest a wide variation in incidence according to age, sex, region and ethnicity. All the study shows, consistently, thyroid cancer is far more frequent among women than in men and a substantially higher incidence rate was observed in women during the fertile period of their life compared with men of the same age. Papillary carcinoma is the most prevalent histological type, irrespective of gender and conditions like iodine level. Several studies have reported upward incidence trends especially of papillary thyroid cancer and several factors have been proposed as explanations, it is not clear whether these trends reflect a real increase in risk or an artifact. However, on the basis of available anecdotal information, we believe it is mainly due to changes in histological diagnostic criteria and, to a lesser extent, to increased diagnostic activity in addition to factors like iodine sufficiency.

Ionizing radiation, in particular radiotherapy to head and neck region is the most widely recited factor for the risk of thyroid cancer by several studies. Goiter may also predispose to thyroid cancer and we believe that the overall incidence of differentiated thyroid carcinoma is not influenced by iodine intake, rather the distribution of histological types is related to the intake of iodine.

The fact that the gender differences appearing greater during the fertile part of life speculates that sex hormones may play an important role in the etiology of thyroid cancer and several studies around the world among different population was conducted to reveal this fact. Although some of the characteristics of hormonal, menstrual and reproductive factors were more frequently present in thyroid cancer cases than controls in several studies, review of literature clearly shows that evidence relating to these characteristics and the risk of thyroid cancer is inconsistent so that conclusive judgment is not possible. However, miscarriage or abortion particularly in the first pregnancy is the most established reproductive risk factor for thyroid cancer in women and the impact of other characteristics on the incidence of thyroid cancer, if present at all, either often appears to be of small magnitude or insignificant.

According to studies, so far, lifestyle factors have only a small effect on the risk of thyroid cancer. Although many studies indicated a reduced
Epidemiology of thyroid cancer, Al-Zahrani et al.

risk for cigarette smoking, the dose-response with factors of smoking is not statistically significant in most of these studies suggesting smoking may be modifier of thyroid cancer risk. Even though it remains largely unclear how consumption of fruits and raw vegetables influence thyroid carcinogens, consumption of fruits and raw vegetables reduces the risk of thyroid cancer and this hypothesis needs further studies to clarify its role.

Further studies are necessary to investigate the remarkably high incidence of thyroid cancer seen in all the GCC states and to clarify the role of genetic, environmental and lifestyle factors on the risk of thyroid cancer. A country wide population based case control study is recommended to elucidate the potential relationship between menstrual, reproductive and hormonal factors with thyroid cancer in the GCC states. This is of particular interest since the reproductive health patterns of GCC states includes relatively high birth and total fertility rate, short birth intervals, older ages at last birth and high prevalence of consanguinity. Such a study is essential in the absence of any etiological studies on thyroid cancer from this region, except one from Kuwait, to the best of our knowledge.

Acknowledgement

We wish to acknowledge Ms. Batlah Al-Murshed for her support in preparing this manuscript.

References

17. dos Santos Silva I and Swerdlow AJ. Thyroid cancer epidemiology in England and Wales: time


Epidemiology of thyroid cancer, Al-Zahrani et al.


