Epidemiological Observations of Thyroid Cancer
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Cancer as a disease has been well recognized in India since Vedic times (41) but its magnitude and problems have only been identified since the beginning of the century. Paymaster (31) studied the pattern of cancer in India by scrutinizing the relative frequency data from cancer hospital in the country. Apart from cancers associated with tobacco chewing and smoking habits, an epidemiological study of Thyroid Cancer (TC) in India has not been carried out in detail. It is well known that TC is infrequent in many parts of the world and its etiology is yet to be known. An attempt has been made in this article to identify the epidemiological aspects of this cancer in India, its status in the world, current knowledge regarding the associated factors and high-risk population.

Clinical Epidemiology
At the Tata Memorial Hospital (TMH), Mumbai, TC has been recorded since the inception of this hospital in 1941.

Table 1 : The decade wise relative frequency of thyroid cancer at TMH - 1941-93

Year	Total Cancer Cases	Thyroid Cases	%	Histology Confirmed	%
1941-50	16,154	61	0.4	44	72
1951-60	34,018	123	0.4	96	78
1961-70	63,483	424	0.7	325	77
1971-80	88,104	770	0.9	703	91
1981-90	1,24,633	1,464	1.2	1,404	96
1991-93	46,538	606	1.3	592	98

In the Year 1941, six TC cases were recorded out of a total of 1,100 cancer cases diagnosed in the hospital. Ever since then the relative frequency of this cancer has increased from 0.5% in 1941 to 1.2% in 1993, Table 1. Ninety percent of the cases were microscopically confirmed. During the period 1941-93; 3,448 (0.9%) TC cases were diagnosed out of a total of 3,72,930 cancer cases. The microscopic confirmation was about 72% in 1941-50, which increased to over 98% in 1991-93. Advancement in diagnostic techniques and the introduction of Fine Needle Aspiration Cytology (FNAC) have greatly improved the percentage of microscopic confirmation of the disease. The gender ratio for TC is about 1:1.4 (M:F) in the predominance of females over males was seen in all

the years. The average ages for males and females based on hospital data were 45.2 years and 41.5 years respectively.

Table 2 : Decade wise histological classification of thyroid cancer – TMH

Decade	Papillary	Medullary	Follicular	Mixed	Anaplastic	Others@	Total
1941-50	3	-	-	-	-	59	62
1951-60	12	-	-	-	-	110	122
1961-70	92 (21.7)	5 (6.3)	115 (27.1)	2	8	202	424
1971-80	206 (27.0)	60 (7.9)	215 (28.2)	47 (6.2)	15(2.0)	219	762
1981-90	570 (38.9)	166 (11.3)	455 (31.1)	51 (3.5)	59(4.0)	163	1,464
Total	883 (31.2)	231 (8.2)	785 (27.7)	100 (3.5)	82(2.9)	753 (26.5)	2,834

@ includes undifferentiated carcinoma, carcinoma, NOS. malignant tumour and clinical cases.Figures ( ) shows percentages of total in that decade

Among 2,834 TC seen over last 50 years, Papillary Carcinoma (PC) was the predominant type (883 cases –31.2%) followed by Follicular Carcinoma (FC 785 cases – 27.7%) and Medullary Carcinoma (MC 231 Cases – 8.2%). In a 100 cases (3.5%) mixed classification of two major types namely the papillary and follicular variety was observed (Table 2). Medullary carcinoma type has been identified in our data in the late 60's.

The gender ratio and average age of patients with TC according to histological classification based on 1554 cases seen during the period 1984-82 are presented in Table 3, (9). The female predominance was evident only in the papillary and follicular variety whereas male predominance was observed among medullary type. Though the average age for males in three common histological types did not show much variation, the average age among females in the papillary and medullary type was lower than for males.

Table 3 : Histological type and average age according to sex in TMH data 1984-92

Histology	Number		Average		Sex ratio
	Males	Females	Males	Females	M : F
Papillary(n= 694)	287	407	43.1	37.4	1 : 1.4
Follicular(n= 505)	178	327	46.8	44.9	1 : 1.8
Medullary(n=183)	116	67	43.9	38.7	1.7 : 1
Others (n=172)	78	94	-	-	-
Total (n = 1,554)	659	895	45.2	41.5	1 : 1.3

Relative frequency - National scene

With the establishment of the National Cancer Registry Program (NCRP) by the Indian Council of Medical Research (ICMR), New Delhi, cancer registries in the three main cancer hospitals namely in Mumbai, Madras and Bangalore and three general hospitals in Chandigarh, Dibrugarh and Thiruvananthapuram were initiated in 1984. NCRP has collected data (Table 4) on over 1, 77,318 cancers in males and 1,61,198 cancers in females during the period 1984-93 from six cancer registries (27).

Table 4: Number and percentage of thyroid cancer in six Hospital cancer registries by sex 1984-93

Cancer Registry	Males No. (%)	Females No. (%)
Mumbai	724 (0.92)	1008 (1.64)
Bangalore	356 (1.14)	677 (1.87)
Madras	287 (1.17)	451 (1.57)
Thiruvananthapuram	554 (1.99)	1348 (5.71)
Chandigarh	56 (0.8)	99 (1.34)
Dibrugarh	30 (0.36)	34 (0.9)
Total	2007 (0.1)	3617 (0.2)
All sites	1,77,318	1,61,198

Over 5,614 TC cases were recorded which included 2,007 males and 3,617 females. The relative frequency of TC in males varied between 0.36% in Dibrugarh and 1.99% in Thiruvananthapuram whereas in females it varied between 0.9% in Dibrugarh and 5.71% in Thiruvananthapuram. An excess of females was seen in all the registries. In most of the registries the histological confirmation was found in 80-95% if cases. Among the registries, a high frequency of TC was observed in the Thiruvananthapuram registry, in both sexes. This phenomenon has been observed in all the years' data from this registry.

The histological distribution of TC among the hospital registries (27) by sex is shown in (Fig. 1). The percentage of papillary adenocarcinoma though separately reported has been included in PC type. The 'other' category includes other carcinoma type, carcinoma NOS and malignant tumors. The proportion of the 'other' category was found more in the Dibrugarh registry as compared to the other registries. The relative frequency of PC was the predominant type in all the registries except Dibrugarh where the FC was common in both sexes.
In the Dibrugarh, registry the relative frequency of undifferentiated carcinoma accounted for 10.7% in males and 11.8% in females. These percentages were higher than that reported in other registries.

Pediatric Cancer – Relative Frequency

The occurrence of TC among children (0-14 years) has been reported from hospitals in India. Though its relative frequency is infrequent there are variations among the cases seen from different hospitals in the country. At TMH, Mumbai, in an analysis of 7,057 childhood cancers seen during 1984-94, cancer of the thyroid accounted for 30 cases (0.4%) which included 11 males

and 19 females (10). Histological classification of childhood TC cases seen at the TMH showed the predominance of PC (males: 63.6% females: 89.5%) followed by FC (males: 36.3% females: 10.5%) in both sex (10). About 13,387 childhood cancers from six-hospital cancer registries over a ten-year period 1984-93 (27) were reported to the NCRP network which formed about 3.95% of all cancers. This percentage varied between 2% (Dibrugarh registry) to 7.5% (Chandigarh registry). For males and females it varied between 2.9% (Dibrugarh registry and 3.8% Thiruvananthapuram registry). Epithelial cancers in the pediatric group constituted about 2.9% among males and 4.4% among females. Twenty-four males (0.3%) and 39 females (0.8) were diagnosed as having TC among all the childhood cancers from the six registries (27).

Incidence – National Scene

A Mumbai population based cancer registry was established in 1961 and since then cancer incidence for the Mumbai population has been published. In 1964-66 the Age Standardized Rate (ASR) for TC were 0.5 and 0.9 per 100,000 for males and females respectively (16). The ASR in 1993 was 1.0 and 1.9 for males and females respectively (13). With the establishment of the NCRP, by the ICMR, New Delhi, there are at present five urban population based cancer registries in India and one rural registry at Barshi, Sholapur. The other registries mentioned in (Table 5); were either supported by a voluntary organization or by the institutions themselves. The ASR for TC reported from population based cancer registries in India for the year 1991 are shown in (Table 5).

Table 5 : **Age adjusted incidence rates per 100,000 of thyroid cancer in India in 1991**

	Males ASR	Females ASR	Population covered (in million)
Bangalore	1.4	3.2	4.09
Mumbai	1.0	1.8	9.81
Madras	0.8	2.2	3.80
Delhi	0.7	1.9	8.36
Ahmedabad	0.8	1.9	3.33
Bhopal	1.1	2.0	1.05
Pune	0.8	1.3	2.20
Nagpur	1.3	0.7	1.60
Barshi – rural	0.6	0.5	0.41
Aurangabad	0.6	1.1	0.57
Thiruvananthapuram*	1.8	3.9	1.06
Karunagapally – rural**	1.2	4.4	0.3
*1991-92; ** 1990-94; Refs: 9, 13, 20, 33.			

In most of the metropolitan registries the ASRs in females were two to three times higher than the

ASRs in males. For females the rates in Bangalore, Thiruvananthapuram and Karunagapally were higher than the rates for females in other registries.

Trend

The incidence rates of TC observed in the six registries (13) in India for a six year period from 1988-93 are shown in (Fig.2). Though it is too short a period to analyze the trend, there has been hardly any increase in the incidence over the years in India.

Incidence – International Scene

Cancer incidence in five continents has been reported by the International Agency for Research on Cancer (IARC) in six volumes from 1966 onwards. These reports give the incidence of cancer in several countries around the world for the last 30 years (3,14, 15,29,36,37). The ASR for TC collected from the six volumes for selected countries for males and females are presented in (Fig.3). Among the 60 odd countries reported, USA Hawaii, Hawaiian group (7) showed the highest rate for TC in both sexes. The rates in both sexes in India (Mumbai) though higher than that in the UK (Oxford) in males remained lower than the rates in most of the population groups. Further, the ASRs are higher in females than in males. The increasing incidence has been observed in males and females in the USA, Japan, Finland and Singaporean Chinese populations, whereas in India and the UK the rates remained almost steady. A high incidence of TC has been observed in Iceland and in native Alaskan women (21).

An analysis of incidence data from Connecticut, USA between 1935-39 and 1990-92 indicated that the increase in the incidence was due to cohort effect. The increase was observed in the cohort born between 1915 and 1945 for those born after 1945 the incidence declined. This was attributed to the practice of radiation treatment for benign childhood conditions (42).

Pediatric Cancer – The National and International Scene

Cancer of thyroid in children has been observed and reported from all over the world. Though its frequency is infrequent throughout the world, it has provided a base to study the etiology of this disease. Parkin et al (29) have collected data on children from both population based registries and from established hospitals throughout the world and published a book entitled “The international incidence of childhood cancer”. Over 50 countries had contributed data to this volume, which included regions from Africa, North America (USA and Canada), South American (Brazil, Columbia, Cuba, Jamaica, Puerto Rico), Asia (15 countries), Europe (22 countries) and Oceania (Australia, New Zealand and Fiji). The incidence rates of childhood cancer per million, from a selected population/ countries in the world and also the incidence rate of TC (epithelial) around the world are shown in (Table 6).

The highest ASR’s for TC in children among females were reported from Blacks in Los Angeles, USA with a rate of 2.8 per million and among males from the non Jewish population in Israel at 2.3 per million. Further the ASR’s were higher in females than in males. It was observed in 33 out of the 65 populations reported and the rate in females was about one to five times higher than that in males.

Table 6 : **ASR for all pediatric cancer and thyroid cancer for selected countries by sex**

Countries	ASR per million					
	All Sites (0-14 years)			Thyroid		
	Male	Female	Total	Male	Female	Total
Africa Nigeria Ibadan	198.5	111.7	155.6	-	-	-
America North Canada Western Province USA, New York (White), (Black) USA, Los Angels (White),(Black)	148.7 145.5 121.0 156.8 118.4	119.4 127.4 82.4 136.2 100.5	134.4 136.7 101.8 146.7 109.6	0.6 0.4 1.7 0.5 0.5	1.4 1.9 0.8 2.5 2.8	1.0 1.1 1.3 1.5 1.7
America Others Brazil Sao Paulo Costa Rica Puerto Rico	164.1 154.7 116.8	126.4 119.3 99.0	145.4 137.4 108.1	0.1 0.6 0.5	0.7 2.7 1.2	0.4 1.6 0.9
Asia China, Shanghai India, Bangalore Mumbai Japan, Osaka Israel, Jews Non Jews Singapore, Chinese	115.2 75.2 86.3 127.0 148.8 121.1	98.9 41.9 54.5 100.5 118.9 78.2 88.8	107.3 58.6 70.9 114.1 134.2 100.5 97.3	0.3 0.6 0.3 0.2 0.7 2.3 0.6	0.4 1.7 0.1 0.1 1.8 - 1.6	0.3 1.1 0.2 0.1 1.2 1.2 1.1
Europe UK, England & Wales 119.6 France, Bas Rhin German Democratic Republic	96.8 136.4 132.9	108.5 123.5 113.8	0.2 130.1 123.6	0.5 - 0.4	0.3 - 1.2	- 0.8
Oceania Australia, New South Wales New Zealand, Maori 173.9 Non Maori	153.0 111.5 140.7	122.2 143.2 121.6	138.0 - 131.4	0.2 - 0.9	0.8 - 0.9	0.5 - 0.9

Prediction For The Year 2001

The incidence of cancer for the whole country at present is not available due to the lack of countrywide cancer registration. Even existing population based cancer registries cover about 17% of the urban population and less than 1% of the rural population. With these limitations some authors have attempted to estimate the cancer load for the entire country in 2001 both for all sites and for specific sites. The population projection prepared by an expert committee for 2001 (24) indicates that there will be around 1004 million persons of which 30% will be living in urban areas and 70% in rural areas. The estimates of cancer load in India in 2001 (11,13,25,46) for all sites and some specific sites have been provided by some investigators (Table 7). The cancer load

would be between 0.566 million (46) and 0.924 million (11). The number of persons with TC in India in 2001 will be around 3,524 (0.6%) (46).

Table 7 : Projected number of incidence cases in India by sex in 2001 (in thousands)

Author	All Sites			Thyroid		
	Male	Female	Total	Male	Female	Total
Jain	393.0	111.7	806.0	2.358+	2.64+	4.998+
Murthy et al (25)	432.6	413.0	923.3	2.596+	3.140+	5.736+
ICMR (11)	476.3	490.6	924.8	2.858+	2.870+	5.728+
Yeole (46)	265.9	300.0	566.0	1.594(0.6%)	1.930(0.64%)	3.524(0.62%)

+ estimated using the relative frequency as per Yeole (46) estimate

Though other estimators did not include the thyroid as a site, it has been calculated by using the relative frequency of thyroid (%) from one estimate. The estimated range will be between 4,836 (13) and 5,548 incident cases (11). Sixty percent of these incidence cases would be diagnosed in rural areas of the country. In Mumbai there were 60 males and 118 females registered during the 5-year period from 1968 – 72 and it has been estimated that in 1998 – 2002 there would be 265 males and 320 females with TC. The increase in incidence rates will be in the order of 60% in males and 20% in females in Mumbai over a 30 – year period (46).

Multiple Primary

The occurrence of multiple cancers in a patient has been well documented. It has been observed that multiple cancers are known to occur simultaneously (synchronous) or at a later period (metachronus). The incidence of TC with second cancer or as a second cancer in the thyroid has been reported in the literature. In a study conducted at the TMH, Mumbai, Vyas et al (43) reported 177 multiple cancers recorded during the period 1942-81. Out of these 139 patients had a second cancer and 38 had synchronous multiple cancer. In this series one patient had a second cancer in the thyroid from 71 patients with the first primary in head and neck cancer. Among the synchronous lesions there were two cases of thyroid cancers (papillary adenocarcinoma) along with cancers in the head and neck region.

The occurrence of multiple primary cancers in the same individual was explored in 475,000 Norwegian cancer patients with a diagnosis after the age of 30 years between 1953 and 1993 (6). For each type of cancer the observed occurrence of smoking associated cancers in the patients was compared with the expected occurrence if the patients hadthe same risk as the general population. This study included a total of 4,996 TC patients. The results indicated that among smoking associated cancers the risk of getting TC was about 3-fold in males and about 8-fold among females. For TC patients the risk of occurrence of smoking associated cancer as second cancer was 1.7 times higher for males only. An international cohort study of 1,33,411 cancers was carried out to assess the risk of second malignancy after primary cancer in the testis, ovary and

Hodgkin's disease. The relative risk of TC was found to be two-fold for testicular cancer, 1.4 for ovarian cancer and about 2.8 for Hodgkin's disease,(18). Such studies throw light on the possible role of suspected factors in the population.

Religious Groups

Epidemiological studies carried out in Mumbai have highlighted the variation in incidence among major religious groups (17). Hindus, Muslims, Christians and Parsis are the major religious groups living in Mumbai. The ASR per 1,00,000 for the Greater Mumbai by religion and sex are shown in (Table 8). In all communities rates in females were higher than that in males. Parsis in Mumbai had higher rates for TC in both sexes as compared to other communities except that their rate in females was lower than that the females belonging to Christian religion. The differences observed between communities and sex need to be studied further for possible associated factors in terms of habits, dietary and cultural practice.

Table 8 : Age standardized rates per 1,00,000 for thyroid cancer among major religious communities, Mumbai 1973-78.

	Thyroid (1973-78)		All Cancer	
	Male	Female	Male	Female
Hindu	0.8	1.9	150.9	135.6
Muslim	0.5	2.0	161.3	145.0
Christian	0.8	4.3	147.0	128.9
Parsi	1.3	3.5	106.7	129.5
Buddhist	0.4	0.6	68.6	84.2
Jain	0.3	0.5	71.2	47.9
All religions	0.8	1.9	140.2	129.0

The religious and racial differences in the incidence of TC have been reported in the literature (3). In USA the rates in both sex amongst Whites were higher than that among Black's population. In Israel, all the Jewish population has higher rates for TC than the other religious groups and the differences remained irrespective of their place of birth. Singaporean Malays have a higher incidence rate of TC (males = 2.7, females = 5.0) than Singaporean Chinese (Males = 1.5, females = 4.3) and the Singaporean Indian population (males = 0.7, females = 1.1). There has been very little differences in the incidence of TC in the Japanese and Chinese who migrated to the USA, except for those who settled in Hawaii island, where there was an increase in the incidence of TC in both sex as compared to the population of the host country. Though many cancers are known to differ according to urban/rural status, there has not been any study to indicate this in the case of TC.

Associated Risk Factors

While the exact etiology remains unknown, certain factors are known to predispose to the development of TC in humans (Table 9). In general, the multistage theory of carcinogenesis also applies to TC. According to this theory, at least two processes are involved in neoplastic

transformation: initiation (irreversible), which set the second phase, promotion (reversible) which cause stimulation and proliferation of cells eventually resulting in neoplasia. While it is likely that there are many different agents operating as initiators or promoters, at present only a few are known in humans. The best known agent to play a role is radiation, which is thought to act as an initiator.

Table 9 : Associated risk factors with thyroid cancer

	Factor+	Risk
1.	Goiter / non toxic goiter	increases
2.	Toxic goiter	decreases
3.	Low iodine intake	increases *
4.	High iodine intake	increases **
5.	Ionizing radiation (atomic bomb explosives)	increases
6.	Radio active fall out	increases
7.	X-radiation	increases
8.	Gamma radiation (Monozitic sand)	increases
9.	Reproductive factors	increases
10.	Family history of cancer	increases ***
11.	History of still birth/miscarriage at first pregnancy	increases
12.	Occupational groups (fishing, ship officers and crew)	increases

*follicular carcinoma type., ** papillary carcinoma type., *** medullary carcinoma type + (2,4,32,35,44,45)

Patients who had previously undergone therapeutic head and neck radiation for diverse conditions such as thymic or tonsillar enlargement or acne, as well as populations exposed to radiation from fallout and atomic bomb survivors have an increased incidence of TC developing after a latent period of many years (1,540). Further, the effect of age at exposure has been found to be an important factor for radiation induced TC, the risk was estimated to be twice as large in children as in adults (12). The effect of radiation in inducing thyroid neoplasia has been confirmed experimentally in rats. Goitrogens, iodine deficient diets and chemical carcinogens also induce TC in experimental animals. The goitrogens and iodine deficient diets possibly induce neoplasia via the effect of elevated levels of Thyroid Stimulating Hormone (TSH), which probably act as a promoter. In humans, however elevated levels of TSH have not been detected in a consistent manner in patients with TC. It is known that the incidence of follicular and anaplastic carcinomas is slightly increased in endemic goiter areas and some of these patients are known to have increased TSH levels. Also, rare cases of follicular cancer have been reported in patients with familial goiters who have increased levels of TSH. At present, the influence of TSH in the genesis of human thyroid neoplasia remains unclear. Patients with nontoxic goiter and a history of treatment for hyperthyroidism are known to have a high risk for developing TC (30,41). Regarding medullary carcinomas, the etiology of the sporadic form is unknown. The familial form, being transmitted in an autosomal dominant manner, has a well-established genetic basis.

Goodman et al (8) showed that body size may be associated with the risk for TC among men and women. Hormones that are produced by the thyroid gland are important for regulation of human growth and development. It is interesting that a number of reproductive factors have been associated with TC including pregnancy (22,23,34,35,38,39) increased number of pregnancies (34,38), a history of miscarriage or still birth (19,34,38) use of fertility drugs (19), use of oral contraceptives (23,34) and menopausal estrogens (23). Some of these factors may be responsible for the excess risk observed in females all over the world.
Natural background radiation has been observed in the Karunagapally taluka of Quilon District in Karala, India. Cancer registry has been established in this area and the available data indicate a high incidence of TC in the area compared to other registries in India. The place is known for its monazite deposit, which emits gamma radiation. Even in Thiruvananthapuram, a 100 km away from Karunagappally taluka, the incidence of TC in both sexes shows higher rates than other areas in the country. The association between risk for cancer and geographic variations in natural background radiation remains equivocal (12).

Summary

Thyroid cancer in India is not a major health problem. Further secondary prevention through therapeutic intervention has been shown to produce favorable results. Screening of the population for thyroid cancer would be possible only for detecting familial medullary carcinoma type by carrying out special marker studies to identify the presence of Multiple Endocrine Neoplasia Type 2 Syndrome (MENIIa) (12). Though many high risk factors have been identified, the exact etiology of the disease still remains unknown.

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