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BACKGROUND

Malignancies of the thyroid gland are relatively rare worldwide, but incidence has steadily increased over the last few decades. Among US females, thyroid cancer accounts for about 3% of all cancers and is the eighth most common malignancy *[1]*. In contrast, in Kuwait, thyroid cancer ranks second, comprising 8% of all female cancers, and similar findings have been reported for other countries in the Gulf region *[2]*. Thyroid cancer is less common among males, with a female-to-male ratio ranging from 2:1 to 5:1 in most populations *[3]*. The age distribution of thyroid malignancies differs from most other malignancies, with thyroid tumors occurring at an earlier age *[4]*.

The majority of thyroid cancers are differentiated carcinomas of the papillary or follicular type, which typically have a good prognosis and 5-year survival rates close to or higher than 90% *[4]*. The major risk factor for differentiated papillary carcinoma is radiation exposure in childhood, as has been shown among children who had radiotherapy for benign or malignant conditions *[5]*, survivors of the Japanese atomic bombings *[6]*, and persons exposed to radiation from nuclear testing *[7,8]* or the Chernobyl disaster *[9]*. A history of benign thyroid conditions, most notably thyroid nodules and goiter, also appears to be a risk factor for both papillary and follicular thyroid cancer *[10]*. Other suggested etiologic factors include female hormonal and reproductive characteristics *[2,11,12]* and cruciferous vegetable intake (protective) *[13]*. Thyroid cancer incidence varies according to dietary iodine levels. Iodine deficiency and endemic goiter are related to increased risk of follicular thyroid cancer, whereas an iodine-rich diet is possibly associated with increased risk of papillary thyroid cancer *[14]*. In a large pooled analysis, fish intake was associated with decreased risk of thyroid cancer among iodine-deficient populations *[15]*. Smokers have a decreased risk of thyroid cancer, although the biologic mechanism of this finding is unclear *[16]*. Familial occurrences of papillary thyroid cancer have been described in rare instances *[17]*, as well as the joint occurrence of papillary thyroid cancer and colon cancer in families affected by familial adenomatous polyposis *[17]*. Follicular thyroid cancer and breast cancer occur in families with Cowden disease *[18]*.

Medullary thyroid cancers arise from the C-cells, and they account for 5%-10% of all thyroid cancers. Up to 25% of medullary cancers are thought to be genetically determined, as part of 3 family cancer syndromes: familial medullary thyroid cancer, multiple endocrine neoplasia (MEN) 2a, and MEN 2b, all of which have been related to specific mutations in the RET proto-oncogene *[19]*. Certain medical conditions, including thyroid nodules, were associated with increased risk of medullary thyroid cancer in a recent international pooled analysis *[20]*.

Anaplastic thyroid cancers are very rare (usually <15% of all thyroid cancers), aggressive, metastatic, and rapidly growing tumors that are among the most lethal human malignancies, with few patients surviving diagnosis beyond a year *[21]*. These cancers typically are diagnosed later in life than other thyroid malignancies, and a large proportion are thought to arise from untreated differentiated cancers. Due to the rarity of anaplastic thyroid cancers, few etiologic investigations have been conducted; nevertheless, radiation exposure and thyroid disorders have been reported as risk factors *[21]*.

RESULTS

Overall Incidence

Thyroid cancer age-standardized incidence rates (ASRs) vary considerably across the globe, as shown for selected countries in Figure 13.1. The overall incidence of thyroid cancer in the Middle

East Cancer Consortium (MECC) countries from the period 1996 to 2001 was distributed across the international spectrum, with high rates for Israeli Jews and low rates for Egyptians. Only Icelanders had higher rates than Israeli Jews (Figure 13.1).

As shown in Figure 13.1, thyroid cancer ASRs among females were lowest in Bombay, India (2.0). Rates among females in MECC countries were intermediate – 2.7 for Egyptians, 4.5 for Jordanians, 6.5 for Israeli Arabs, and 8.6 for Cypriots – except for the very high rates for Israeli Jews (11.2). On an additive scale, the rates among males had a tighter range, i.e., from 0.8 in Bombay to 4.3 in Iceland. From a multiplicative point of view, however, the difference was less pronounced: 6.3-fold and 5.7-fold for females and males, respectively. Level of medical care and surveillance practices are thought to contribute to international variation, because thyroid malignancies can remain indolent and undetected for many years. In all countries, the ASRs for females were at least twice as high as those for males, with ratios lower than 3 in Egypt and Jordan, and above 3 in Israel and Cyprus; these findings are similar to those from an earlier case series of Israeli Arabs *[22]*.

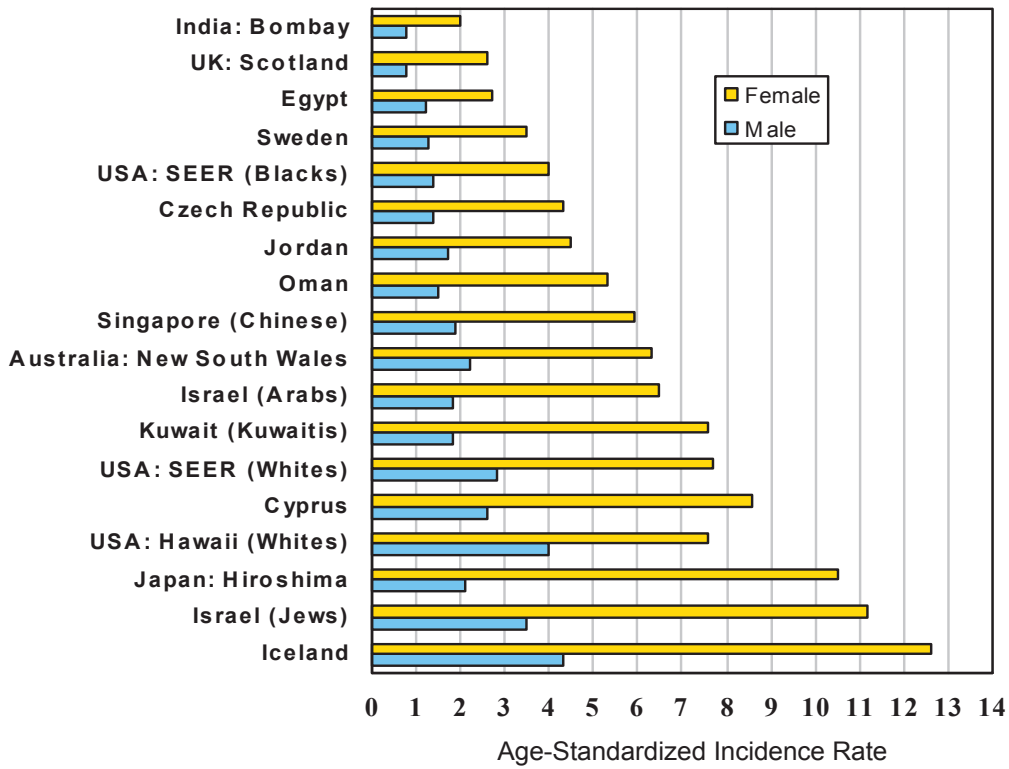
The especially high thyroid cancer ASRs observed among Israeli Jews is of interest because high rates also were observed in some *[23-25]*, though not all, epidemiologic studies *[26]* of Jewish communities in the United States. These findings may indicate a role for genetic factors, as has been seen for breast cancer *[27]*, although none have been identified so far. A possible effect of medical radiation exposure is discussed in more detail under "Age." McCredie et al. *[28]* compared Middle Eastern immigrants in Australia to native Australians and found higher rates of thyroid cancer, but lower rates of smoking-, alcohol-, and Western diet-related cancers among the immigrants. Although smokers usually have lower rates of thyroid cancer than nonsmokers *[16]*, the opposite was observed in a recent case-control study in Kuwait *[14]*.

Age

Thyroid cancer contributed a small proportion of all cancers diagnosed annually in the MECC populations, ranging from 1.5% in Egyptians to 3.8% in Israeli Arabs, although the proportion was almost always higher than in the US SEER registries (1.7%) (see Table 1.6). This pattern may be related to differences in the age structure of the populations. Although the burden of thyroid cancer relative to other malignancies was small in the MECC countries, there was considerable variation in incidence by age. Table 13.1 shows the proportion of cases by age for each country and in the United States. In all Middle Eastern countries as well as the United States, patients aged 30-49 years at diagnosis contributed a substantial proportion of thyroid cancers, ranging from more than 30% to nearly 50% of all cases. Over 70% of thyroid cancers among female Cypriots, Israeli Arabs, and Jordanians occurred among patients younger than 50 years, compared with approximately 50% among female Israeli Jews and Egyptians. Likewise, among males, patients younger than 50 years contributed approximately 70% of cases among Israeli Arabs and Jordanians. In Cypriots, Israeli Jews, and Egyptians, from 40% to a little more than 50% of the cases in males occurred before age 50 years.

These distributions partly reflect the typical younger age at diagnosis of thyroid cancer compared with other cancers, but also the age structure of the underlying populations. Approximately 90% of Jordanians, Egyptians, and Israeli Arabs were younger than 50 years of age in 1996-2001 (see Figure 1.1). However, the contribution of those under age 50 to the total thyroid cancer cases was lower for Egyptians compared with Jordanians and Israeli Arabs. Other case series have shown that thyroid cancer is, on average, diagnosed at a younger age in the Middle East compared with the average age of 45 years in the United States *[1]*; e.g., the mean ages were 32 years in Israeli Arabs *[22]*, 35 years in Kuwaitis *[2]*, and 38 years in Yemenites *[29]*. This variation in age at diagnosis could be entirely due to the much younger age structure of the populations in these countries, compared with the United States

Figure 13.1 Thyroid Cancer: Age-Standardized Incidence Rates* by Country†



*Rates are per 100,000 and are age-standardized to the World Standard Million.
†Data for most countries listed are for 1993-1997 and are from: Parkin DM, Whelan SL, Ferlay J, Teppo L, editors. Cancer incidence in five continents, volume VIII. IARC Scientific Publication No. 155. Lyon (France): International Agency for Research on Cancer; 2002. However, data for the following countries are taken from this monograph: Egypt (1999-2001); Israel (Arabs and Jews) and Jordan (1996-2001).

(see Figure 1.1). It is important to note that fewer than 200 thyroid cancer cases were observed in Egypt and in Cyprus, which can cause considerable imprecision in the incidence estimates, particularly when evaluating sex- and age-specific subgroups (Table 13.1).

Analyses of age-specific incidence rates, standardized to the world population, provided a better comparison across populations, irrespective of the age structure of the underlying populations (Table 13.1 and Figures 13.2 and 13.3). In most populations, the incidence of thyroid cancer rose with increasing age up to 45-55 years and then reached a plateau. There was some variation in this pattern across individual countries at ages 60 and older; e.g., there seemed to be a decrease in Cyprus, which may be due to the fine stratification and thus very small number of cases (only 28 cases in persons older than 60 years) available for that analysis. Among females, the most striking pattern appears for Israeli Jews, with incidence rates among younger individuals comparable to the US and Cypriot populations, but with the highest rate of any subgroup studied (24-27) for those

Table 13.1. Thyroid Cancer: Number of Cases, Age Distribution, and Age-Standardized Incidence Rates, by Age and Sex, in Cyprus, Israel (Jews and Arabs), Egypt, Jordan, and US SEER − 1996-2001*

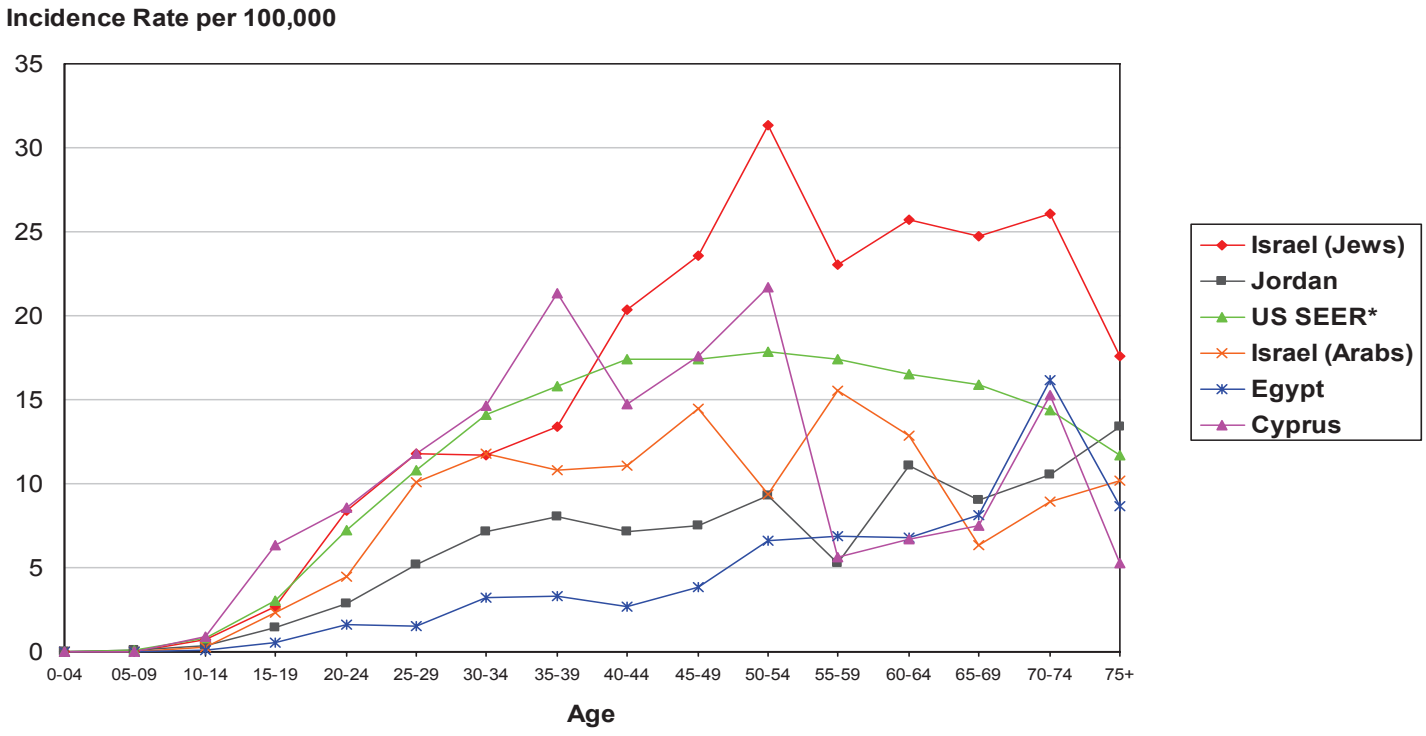
	Cyprus 1998-2001			Israel (Jews) 1996-2001			Israel (Arabs) 1996-2001			Egypt 1999-2001			Jordan 1996-2001			US SEER† 1999-2001		
	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female
Total cases	179	40	139	2,404	546	1,858	227	45	182	154	45	109	617	172	445	8,684	2,152	6,532
Age Groups (Distribution)																		
<20 y	*4.5%*	*0.0%*	*5.8%*	2.2%	*2.6%*	2.2%	*4.0%*	*0.0%*	*4.9%*	*4.5%*	*6.7%*	*3.7%*	7.1%	*7.6%*	7.0%	2.3%	1.9%	2.4%
20-29 y	15.1%	*15.0%*	15.1%	11.1%	7.5%	12.1%	25.1%	*26.7%*	24.7%	*9.1%*	-	*11.9%*	22.0%	19.2%	23.1%	10.9%	6.9%	12.2%
30-39 y	25.7%	*20.0%*	27.3%	12.1%	11.2%	12.4%	28.2%	*24.4%*	29.1%	18.8%	*11.1%*	22.0%	26.3%	24.4%	27.0%	20.2%	15.7%	21.7%
40-49 y	20.1%	*12.5%*	22.3%	21.8%	18.9%	22.7%	19.8%	*20.0%*	19.8%	20.8%	*33.3%*	15.6%	16.5%	19.2%	15.5%	23.7%	22.6%	24.1%
50-59 y	19.0%	*30.0%*	15.8%	20.2%	20.3%	20.2%	11.0%	*8.9%*	11.5%	20.1%	*22.2%*	19.3%	12.3%	14.0%	11.7%	19.3%	22.9%	18.1%
60+ y	15.6%	*22.5%*	13.7%	32.5%	39.6%	30.4%	11.9%	*20.0%*	*9.9%*	*26.6%*	*24.4%*	27.5%	15.7%	15.7%	15.7%	23.5%	30.0%	21.3%
Age Groups (Rates)‡																		
Total rate	5.6	2.6	8.6	7.5	3.5	11.2	4.1	1.8	6.5	2.0	1.2	2.7	3.0	1.7	4.5	6.2	3.2	9.2
<20 y	*0.8*	*0.0*	*1.6*	0.5	*0.3*	0.8	*0.3*	*0.0*	*0.6*	*0.1*	*0.1*	*0.1*	0.3	*0.2*	0.4	0.5	0.2	0.9
20-29 y	6.8	*3.1*	10.2	5.9	1.8	10.1	4.5	*1.9*	7.3	*0.8*	-	*1.5*	2.4	1.1	4.0	5.6	1.7	9.7
30-39 y	11.2	*4.0*	17.9	8.1	3.4	12.6	6.7	*2.3*	11.3	2.0	*0.7*	3.3	4.9	2.5	7.5	9.3	3.5	15.1
40-49 y	9.5	*2.7*	16.2	14.1	5.7	22.0	8.1	*3.4*	12.8	2.9	*2.7*	3.3	5.4	3.5	7.3	11.6	5.6	17.6
50-59 y	11.3	*8.0*	14.6	18.6	8.9	27.6	7.2	*2.3*	12.1	4.9	*3.2*	6.7	5.3	3.2	7.5	13.3	8.1	18.3
60+ y	6.7	*4.9*	8.2	18.1	10.9	24.0	7.9	*5.7*	9.9	6.6	*3.9*	9.2	7.4	4.0	10.8	12.5	8.9	15.4

The symbols "-" = 1-2 cases; and "[numeral]*" (italic) = 0 or 3-15 cases.

†SEER 13 Registries, Public Use Data Set, from data submitted November 2004.

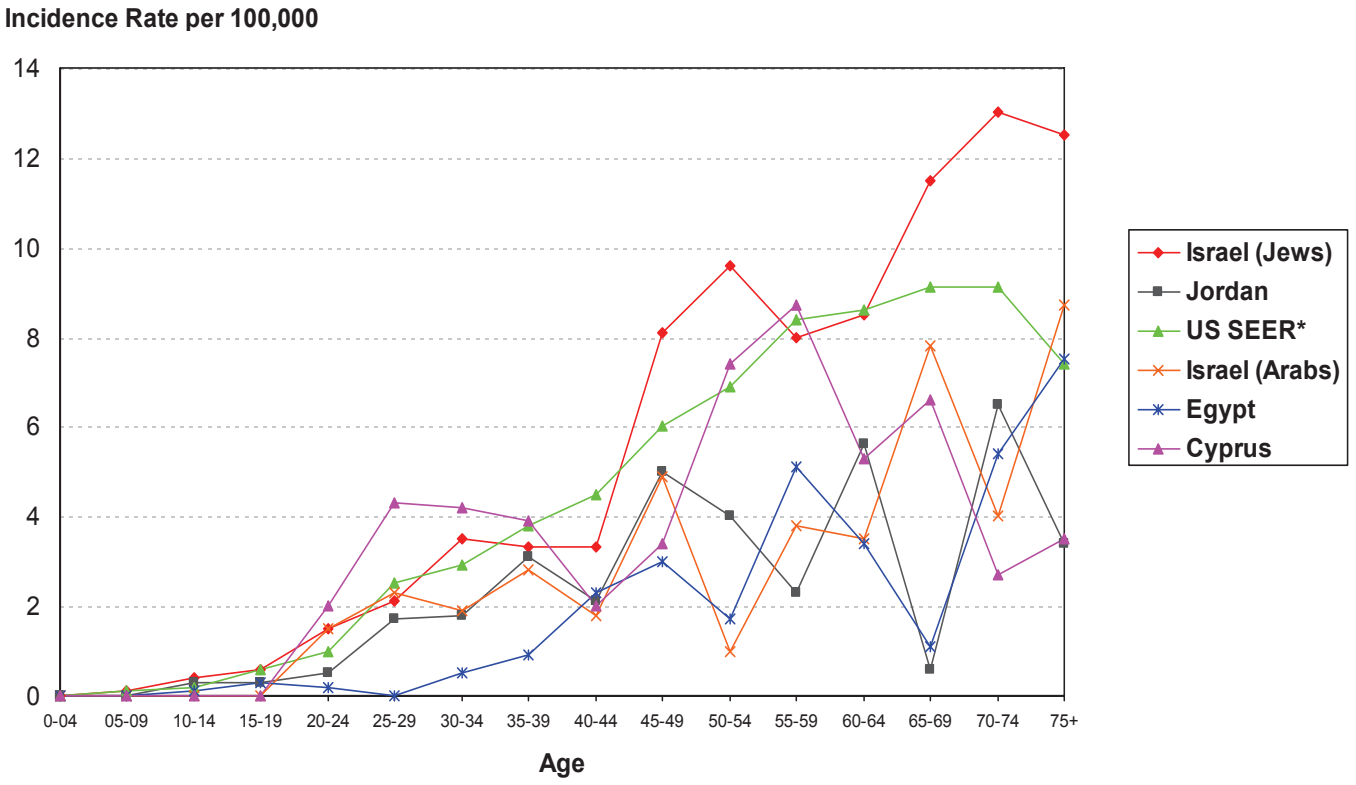
‡Rates are per 100,000 and are age-standardized to the World Standard Million.

Figure 13.2. Thyroid Cancer: Age-Specific Incidence Rates for Females in Cyprus, Israel (Jews and Arabs), Egypt, Jordan, and US SEER – 1996-2001



*SEER 13 Registries, Public Use Data Set, from data submitted November 2004.

Figure 13.3. Thyroid Cancer: Age-Specific Incidence Rates for Males in Cyprus, Israel (Jews and Arabs), Egypt, Jordan, and US SEER − 1996-2001



*SEER 13 Registries, Public Use Data Set, from data submitted November 2004.

older than 50 years (Table 13.1). This effect was slightly less pronounced among older Israeli Jewish males, although their rates also were higher than in most of the other countries.

The marked peak among 50-year-old Israeli Jews (Figure 13.3), compared with the smooth comparable age-specific curve from the US SEER registry, is thought provoking. This group of Israeli Jews includes those who received x-ray treatments for tinea capitis as children in the 1950s and are consequently known to be at substantially increased risk of thyroid cancer *[30]*. Although the number of exposed Israelis is estimated to be approximately 20,000, this number may be too small to have much influence on national rates. An increase in Israeli national rates of brain meningioma attributable to this radiation treatment was discernible, however *[31]*. In the future, Israeli thyroid cancer incidence patterns should be studied by country of origin because the large majority of irradiated individuals or their families immigrated to Israel from North Africa.

Histology

Microscopic confirmation for thyroid cancer was very high: over 99% in Cyprus, Jordan, and the United States, and between 93% and 95% in the other MECC countries (Table 13.2). These percentages represent a clear strength of the data presented in this chapter. Analyses limited to microscopically confirmed cases allowed for stratification by histologic type. Differentiated carcinoma (papillary and follicular subtypes) made up 90% to 94% of all thyroid cancers in Cyprus, Israel, Jordan, and the United States. The exception was Egypt, where only 73% of the thyroid cancers were differentiated. Some larger differences among countries emerged when more detailed histology was evaluated. Papillary carcinoma made up 80% or more of the thyroid cancers in Cypriots, Israeli Arabs and Jews, and the US population, whereas its contribution was considerably lower in Jordanians (77%) and Egyptians (62%). Medullary and anaplastic thyroid cancers were rare and contributed only 1% to 4%, except for Egypt, where 14% of all thyroid cancers were anaplastic.

Earlier case series in Middle Eastern countries reported lower proportions of papillary carcinoma – e.g., 66% among Israeli Arabs in Northern Israel in the 1990s *[22]*, and 58% in Kuwaitis in the 1970s *[32]*. These differences may be related to improved diagnostic tools and the change in the classification of the follicular variant of papillary carcinoma, which used to be classified as a separate entity, but is now considered papillary thyroid cancer *[33]*. Moreover, the earlier series were not population based and therefore were less reliable than current estimates. Historical comparisons for these MECC cancer registries were not possible because an earlier report did not include results for thyroid cancer *[34]*.

After appropriate adjustment for the age structure of the populations, the incidence rates for each histologic type of thyroid cancer were very low. Annual papillary cancer rates varied from 1.0 in Egyptians to 5.9 in Israeli Jews, whereas follicular cancer rates varied from 0.2 in Egyptians to 0.6 in Israeli Arabs and Jews, as well as in US SEER. The ratio of papillary to follicular thyroid cancers varied from around 5.0 among Israeli Arabs, Egyptians, and Jordanians, to 8.2 among Americans, 9.8 among Israeli Jews, and 12.2 among Cypriots. Countries with the lower ratio of papillary cancer to follicular cancer tended to be those with young populations and generally lower socioeconomic status, but it is difficult to draw conclusions because the small numbers of cases make the rates unstable. The female-to-male ratios were close to 3:1 for both types of cancer, except for follicular cancer among Israeli Arabs, which had a ratio of 10:1. In accordance with the high proportion of anaplastic cases mentioned earlier, the incidence rate of anaplastic thyroid cancer was much higher in Egypt (0.3) than in the other countries (0.0-0.1), which might reflect differences in access to medical care. Unpublished MECC data on disease stage have shown a pattern of more advanced stage at diagnosis in Egypt compared with other MECC countries for several other malignancies (Laurence Freedman, e-mail message to author, March 1, 2005), lending credibility to this hypothesis. Alternatively, the high incidence of anaplastic thyroid cancer in Egypt might be due to other, currently unknown factors. It is interesting to note that premenopausal breast

Table 13.2. Thyroid Cancer: Number of Cases, Proportions of Microscopic Confirmation and Histologic Type, and Age-Standardized Incidence Rates for Histologic Types, by Sex, in Cyprus, Israel (Jews and Arabs), Egypt, Jordan, and US SEER − 1996-2001*

	Cyprus 1998-2001			Israel (Jews) 1996-2001			Israel (Arabs) 1996-2001			Egypt 1999-2001			Jordan 1996-2001			US SEER† 1999-2001		
	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female
Microscopically confirmed	100.0%	100.0%	100.0%	93.8%	94.3%	93.6%	95.2%	97.8%	94.5%	92.9%	88.9%	94.5%	100.0%	100.0%	100.0%	99.5%	99.2%	99.6%
Total cases microscopically confirmed	179	40	139	2,254	515	1,739	216	44	172	143	40	103	617	172	445	8,642	2,134	6,508
Distribution of Microscopically Confirmed Cases																		
Histologic distribution	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
Carcinoma	98.9%	97.5%	99.3%	99.0%	99.0%	99.0%	99.5%	100.0%	99.4%	96.5%	97.5%	96.1%	99.0%	98.3%	99.3%	99.7%	99.6%	99.8%
Follicular carcinoma	*7.3%*	*7.5%*	*7.2%*	8.7%	10.3%	8.2%	12.5%	-	14.5%	11.2%	*12.5%*	*10.7%*	13.5%	10.5%	14.6%	9.5%	11.0%	9.0%
Papillary carcinoma	86.6%	85.0%	87.1%	82.7%	74.8%	85.0%	81.0%	88.6%	79.1%	62.2%	60.0%	63.1%	76.8%	74.4%	77.8%	83.4%	79.1%	84.8%
Medullary carcinoma	*1.7%*	-	-	3.1%	6.2%	2.2%	*4.2%*	*6.8%*	*3.5%*	*2.8%*	*7.5%*	-	*2.4%*	*4.7%*	*1.6%*	0.8%	1.4%	0.7%
Anaplastic carcinoma	*2.8%*	-	*2.9%*	2.0%	*2.7%*	1.8%	*0.0%*	*0.0%*	*0.0%*	14.0%	*12.5%*	*14.6%*	*1.8%*	-	*2.0%*	1.2%	1.6%	1.1%
Other specified carcinoma	-	*0.0%*	-	1.7%	3.3%	1.2%	-	*0.0%*	-	*5.6%*	-	*5.8%*	*1.6%*	*2.9%*	*1.1%*	4.0%	5.7%	3.5%
Unspecified carcinoma	*0.0%*	*0.0%*	*0.0%*	0.8%	*1.7%*	*0.6%*	-	*0.0%*	-	-	*0.0%*	-	2.9%	*4.7%*	*2.2%*	0.7%	0.8%	0.7%
Sarcoma	-	*0.0%*	-	-	-	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.2%*	*0.0%*
Unspecified cancer	-	-	*0%*	*0.9%*	*0.6%*	*1.0%*	-	*0.0%*	-	*3.5%*	-	*3.9%*	*1.0%*	*1.7%*	*0.7%*	*0.2%*	*0.1%*	*0.2%*
Rates‡																		
Total rate	5.6	2.6	8.6	7.0	3.3	10.5	4.0	1.8	6.2	1.8	1.0	2.5	3.0	1.7	4.5	6.2	3.1	9.2
Carcinomas	5.6	2.5	8.5	7.0	3.3	10.5	3.9	1.8	6.1	1.7	1.0	2.4	3.0	1.7	4.4	6.2	3.1	9.1
Follicular carcinoma	*0.4*	*0.2*	*0.6*	0.6	0.3	0.8	0.6	-	1.0	0.2	*0.1*	*0.3*	0.4	0.2	0.7	0.6	0.3	0.8
Papillary carcinoma	4.9	2.2	7.5	5.9	2.5	9.1	3.1	1.5	4.7	1.0	0.5	1.4	2.3	1.2	3.4	5.2	2.5	7.9
Medullary carcinoma	*0.1*	-	-	0.2	0.2	0.2	*0.2*	*0.2*	*0.2*	*0.0*	*0.1*	-	*0.1*	*0.1*	*0.1*	0.1	0.0	0.1
Anaplastic carcinoma	*0.1*	-	*0.2*	0.1	*0.1*	0.1	*0.0*	*0.0*	*0.0*	0.3	*0.2*	*0.5*	*0.1*	-	*0.1*	0.1	0.0	0.1
Other specified carcinoma	-	*0.0*	-	0.1	0.1	0.1	-	*0.0*	-	*0.1*	-	*0.2*	*0.1*	*0.1*	*0.1*	0.2	0.2	0.3
Unspecified carcinoma	*0.0*	*0.0*	*0.0*	0.0	*0.0*	*0.0*	-	*0.0*	-	-	*0.0*	-	0.1	*0.1*	*0.1*	0.0	0.0	0.1
Sarcoma	-	*0.0*	-	-	-	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*
Unspecified cancer	-	-	*0.0*	0.1	*0.0*	0.1	-	*0.0*	-	*0.1*	-	*0.1*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*

The symbols "-" = 1-2 cases; and "[numeral]*" (italic) = 0 or 3-15 cases.

†SEER 13 Registries, Public Use Data Set, from data submitted November 2004.

‡Rates are per 100,000 and are age-standardized to the World Standard Million.

cancer in Egypt has been found to be unusually aggressive compared with other countries *[35,36]*.

SUMMARY AND CONCLUSIONS

In this comparative analysis of patterns of thyroid cancer incidence, MECC countries shared many features, with a few notable exceptions. ASRs were distributed across the international spectrum, ranging from 2.0 for Egyptians to 7.5 for Israeli Jews. Thyroid cancer contributed 1.5% to 3.8% of all cancers diagnosed in the MECC countries annually, which was generally higher than the proportion in the United States (1.6%). In all these countries, the rates for females were at least twice as high as those for males, and patients 30-49 years of age at diagnosis contributed the largest proportion of cases, ranging from 30% to nearly 50% of all cases, depending on the age structure of the underlying population. In most countries, the incidence of thyroid cancer rose with increasing age up to ages 45-55 years, and then reached a plateau. ASRs among Israeli Jewish females older than 50 years of age were particularly high – approximately 50% higher than in the United States. The microscopic confirmation percentages for thyroid cancer were excellent, from 93% to over 99%. Finally, differentiated carcinoma accounted for 90%-94% of all thyroid cancers, with the exception of Egypt (73%). Also in Egypt, 14% of all thyroid cancers were anaplastic, compared with less than 3% in all other MECC countries and the United States.

Further research is indicated, including (1) an analysis of thyroid cancer rates by country of origin for Israeli Jews, to address the hypothesis that radiation treatment for tinea capitis among immigrants from North Africa contributed to the high rates among older Israeli Jews; and (2) an evaluation of possible explanations for the unfavorable stage distribution for thyroid and other malignancies in Egypt.

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