Peter D. Inskip, Elaine Ron

BACKGROUND

Brain and other central nervous system (CNS) cancers include a variety of histopathologic subtypes, but the most common, by far, are gliomas. These tumors, which arise from the glial cells that surround and support neurons, include astrocytoma, glioblastoma, oligodendroglioma, oligoastrocytoma, and ependymoma. Medulloblastoma, another neuroepithelial cancer, is relatively common in children but rare in adults. Brain cancers in children typically arise in the cerebellum, whereas brain cancers in adults are more likely to occur in the cerebral hemispheres *[1]*. In adults, older age at diagnosis of brain cancer is associated with higher tumor grade and poorer prognosis. Indeed, glioblastoma is among the most lethal of all cancers. Molecular studies of brain cancers reveal still greater heterogeneity of tumor types than is apparent based on histopathology, and efforts are underway to develop a molecular classification of brain cancer.

Very little is known about the etiology of brain and other CNS cancers *[2-4]*. These cancers occur in association with several rare familial cancer syndromes, such as neurofibromatosis type 1 and Li-Fraumeni syndrome *[5-8]*, but genetic predisposition related to such syndromes is unlikely to account for more than a few percent of brain cancers *[9]*. The only clearly established environmental risk factor is ionizing radiation, particularly for exposures to therapeutic doses during childhood *[10-15]*. Risks related to modern diagnostic radiography probably are very small. Unlike ionizing radiation, there is little evidence that non-ionizing radiation from electric power lines, appliances, or cellular telephones causes brain or other CNS cancers *[16,17]*.

Recorded brain cancer incidence rates increased over the past several decades in most developed countries, particularly in the elderly, but this is generally thought to be due more to improved diagnosis than to a real increase in incidence *[18,19]*. Incidence of glioma is positively associated with socioeconomic status *[20,21]*. In the United States, incidence is highest in Whites, intermediate for Blacks, and lowest for Asians; however, incidence rates for brain cancer exhibit less international variation than do most cancers, particularly when probable differences in completeness of diagnosis are taken into account *[2,22]*. Cancer of the brain and other CNS is more common in males than females *[23]*. A possible role of steroid sex hormones has been hypothesized, and a recent report noted reduced risk of glioma associated with early age at menarche and early age at first live birth *[24]*. Several studies have indicated a reduced risk of glioma among persons with a history of allergies or certain infections, possibly indicating a role for immune factors *[25-30]*. A recent report noted an inverse association between use of nonsteroidal anti-inflammatory drugs and glioblastoma *[31]*.

The blood-brain barrier is effective at keeping many potentially toxic agents in the bloodstream from reaching the glial cells that give rise to most brain cancers *[32]*. In studies with experimental animals, the most potent known chemical neurocarcinogens are nitrosamides, such as nitrosoureas, which can cross the blood-brain barrier *[33-36]*. Such compounds can be formed in the stomach from nitrites and amides in the diet. Whether they are important carcinogens in humans is an unresolved issue *[2,37,38]*. Experimental studies indicate that the developing nervous system is more susceptible to carcinogens than is the mature nervous system *[33,34,36]*. The suggestion of a higher radiation-related brain cancer risk for children compared with adults is consistent with this observation *[14,15]*.

RESULTS

Overall Incidence

The number of brain and other CNS cancers available for analysis in the Middle East Cancer Consortium (MECC) ranged from a low of 150 in Cypriots to a high of 1,690 in Israeli Jews (Table 12.1). Brain and other CNS cancers accounted for 4.8% of all cancers in Jordanians, 3.4% in Israeli Arabs, 3.1% in Egyptians, 2.4% in Cypriots, 1.6% in Israeli Jews, and 1.4% in US SEER (see Table 1.6). In each country, a large majority of cancers were located in the brain, but the proportion varied from 85.2% in Egyptians to 94.5% in Israeli Arabs. The rank order in age-standardized incidence rates (ASRs) for brain/CNS cancer for males and females combined was, in descending order, Israeli Jews, Cypriots, Jordanians, Israeli Arabs, and Egyptians. US SEER rates were similar to those for Israeli Jews (Table 12.1). The high incidence of brain and other CNS cancers in Israeli Jews is of note because an earlier analysis of data from the Israel Cancer Registry found a statistically significant increase in meningioma incidence rates among Israeli Jews born in either North Africa or the Middle East between 1940 and 1954. This observation is thought to be related to the considerable number of individuals in these 2 cohorts who received radiation therapy as children for treatment of tinea capitis *[39]*. While incidence rates for malignant brain tumors also increased among persons irradiated for tinea capitis, the risks were substantially smaller, and therefore the radiation exposure may not be a contributing factor in the high incidence of malignant brain tumors in Israeli Jews seen in Table 12.1.

The ASR for brain cancer was higher in males than females for each country, but the male-female incidence rate ratio varied from 1.08 in Cypriots and 1.10 in Egyptians to a high of 1.64 in Israeli Arabs. The rates of other CNS cancer were similar between sexes in most countries. Figure 12.1 extends the comparison of incidence rates to other countries in the region and worldwide. ASRs in the MECC countries were lower than those in the United States (Whites), northern Europe, and Australia, but higher than in Asia. Kuwait showed rates intermediate to those of MECC countries, whereas rates were decidedly lower in Oman, but this may be partly due to some under-ascertainment of cases *[23]*. Incidence among Blacks in the United States was more similar to that of populations in Arab countries than it was to Whites in the United States. The ranking of the countries by incidence in females is similar, but not identical, to that based on males.

Basis of Diagnosis

As shown in Table 12.2, the proportion of brain and other CNS cancers with microscopic confirmation was 94.7% in Jordanians, 87.5% in US SEER, 83.0% in Israeli Arabs, 80.0% in Cypriots, 79.1% in Israeli Jews, and 65.7% in Egyptians. In Cypriots, the proportion was higher in females than in males, whereas the reverse was true for the other populations (data not shown).

Subsites

Among brain cancers, the proportion coded to "Brain, not otherwise specified (NOS)" was far higher in the MECC countries than in the United States. This is reflected in the percentages in the category "Other/Unspecified" (shown in Table 12.1), which mostly consists of those cancers coded to "Brain, NOS." Whether this is related to the quality of medical records, less frequent use of MRI and CT, tumor registration practices, or other factors is unclear. Although the percentage of microscopically confirmed brain cancers was lower in Cypriots, Israeli Jews and Arabs, and Egyptians than in US SEER, this is not correlated with the proportion of brain cancers with unspecified location. MECC data showed that in Jordan, 94.7% of the brain cancers were microscopically confirmed, but 52% had unspecified location; in Egypt, although as few as 65.7% of the brain cancers were microscopically confirmed, only 33% had unspecified location. (Note that the percentage of the "Other/Unspecified" category shown in Table 12.1 is just over 50% for both Jordan and Egypt. However, whereas for Jordan almost all of this category

Table 12.1. Brain and Other Central Nervous System (CNS) Cancer: Number of Cases, Site Distribution, and Age-Standardized Incidence Rates, by Subsite and Sex, in Cyprus, Israel (Jews and Arabs), Egypt, and Jordan − 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	150	79	71	1,690	939	751	200	122	78	324	165	159	875	506	369	7,060	3,964	3,096
Primary Site (Distribution)																		
Brain/Other CNS combined‡	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%
Brain	87.3%	86.1%	88.7%	94.4%	95.4%	93.2%	94.5%	95.1%	93.6%	85.2%	86.1%	84.3%	92.3%	93.1%	91.3%	93.6%	94.9%	92.1%
Other CNS	12.7%	*13.9%*	*11.3%*	5.6%	4.6%	6.8%	*5.5%*	*4.9%*	*6.4%*	14.8%	13.9%	15.7%	7.7%	6.9%	8.7%	6.4%	5.1%	7.9%
Detailed Primary Site (Distribution)																		
Brain/Other CNS combined‡	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%
Cerebrum	34.0%	34.2%	33.8%	39.9%	40.4%	39.4%	29.0%	27.9%	30.8%	19.8%	21.2%	18.2%	24.0%	23.7%	24.4%	55.9%	57.8%	53.6%
Cerebellum	*4.7%*	*6.3%*	-	3.1%	3.4%	2.8%	*7.0%*	*6.6%*	*7.7%*	11.4%	11.5%	11.3%	12.2%	13.4%	10.6%	6.0%	6.4%	5.5%
Ventricles	*0.0%*	*0.0%*	*0.0%*	2.6%	2.7%	2.5%	*4.0%*	*5.7%*	-	*0.9%*	-	-	1.9%	*1.6%*	*2.4%*	2.1%	2.1%	2.0%
Brain stem	*2.0%*	*0.0%*	*4.2%*	2.5%	2.8%	2.1%	*5.0%*	*6.6%*	-	*4.0%*	*3.6%*	*4.4%*	3.1%	*2.8%*	*3.5%*	4.2%	3.7%	4.9%
Meninges	*2.0%*	-	-	2.4%	2.0%	2.9%	*2.0%*	-	-	-	*0.0%*	-	2.2%	*2.6%*	*1.6%*	1.8%	1.1%	2.6%
Spinal cord	*8.0%*	*7.6%*	*8.5%*	1.7%	1.8%	*1.5%*	*1.5%*	-	-	*4.0%*	*3.6%*	*4.4%*	2.4%	*1.8%*	*3.3%*	2.9%	2.5%	3.4%
Cranial nerves	-	-	*0.0%*	*0.7%*	-	*1.2%*	*0.0%*	*0.0%*	*0.0%*	-	-	-	*0.5%*	-	*0.8%*	0.9%	0.9%	1.0%
Other/Unspecified	48.0%	48.1%	47.9%	47.1%	46.8%	47.5%	51.5%	50.8%	52.6%	58.6%	58.8%	58.5%	53.7%	54.0%	53.4%	26.2%	25.6%	27.0%
Detailed Primary Site (Rates)§																		
Brain/Other CNS combined	4.9	5.2	4.6	5.2	6.1	4.3	3.9	4.8	3.0	3.7	3.8	3.5	4.0	4.4	3.6	5.2	6.2	4.4
Brain	4.1	4.3	4.0	4.9	5.8	4.0	3.6	4.6	2.8	3.2	3.3	3.0	3.7	4.1	3.3	4.9	5.8	4.0
Other CNS	0.8	*0.9*	*0.6*	0.3	0.3	0.3	*0.2*	*0.2*	*0.2*	0.5	0.5	0.5	0.3	0.3	0.3	0.4	0.3	0.4
Cerebrum	1.5	1.6	1.4	2.0	2.4	1.7	1.3	1.6	0.9	0.8	0.8	0.7	1.2	1.3	1.0	2.8	3.4	2.2
Cerebellum	*0.3*	*0.4*	-	0.2	0.2	0.2	*0.2*	*0.2*	*0.1*	0.3	0.3	0.3	0.3	0.4	0.3	0.4	0.5	0.4
Ventricles	*0.0*	*0.0*	*0.0*	0.2	0.2	0.1	*0.1*	*0.2*	-	*0.0*	-	-	0.1	*0.1*	*0.1*	0.1	0.2	0.1
Brain stem	*0.1*	*0.0*	*0.3*	0.2	0.2	0.1	*0.1*	*0.2*	-	*0.1*	*0.1*	*0.1*	0.1	*0.1*	*0.1*	0.3	0.3	0.3
Meninges	*0.1*	-	-	0.1	0.1	0.1	*0.1*	-	-	-	*0.0*	-	0.1	*0.1*	*0.1*	0.1	0.1	0.1
Spinal cord	*0.5*	*0.5*	*0.5*	0.1	0.1	*0.1*	*0.1*	-	-	*0.1*	*0.1*	*0.1*	0.1	*0.1*	*0.1*	0.2	0.2	0.2
Cranial nerves	-	-	*0.0*	*0.0*	-	*0.1*	*0.0*	*0.0*	*0.0*	-	-	-	*0.0*	-	*0.0*	0.1	0.1	0.1
Other/Unspecified	2.3	2.5	2.1	2.4	2.8	2.0	2.1	2.5	1.7	2.3	2.4	2.2	2.2	2.4	1.9	1.3	1.5	1.0

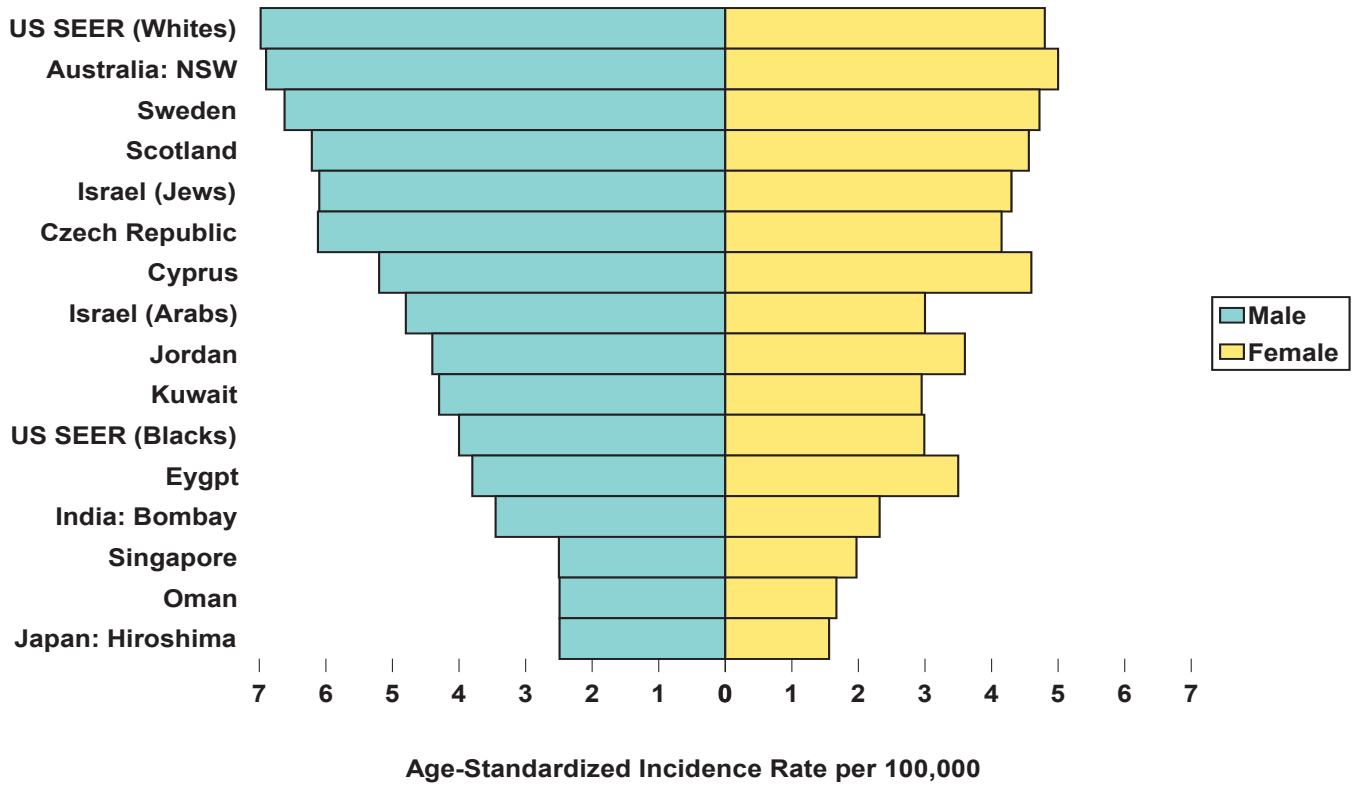
The symbols "-" = 1-2 cases; and "[numeral]*" (italic) = 0 or 3-15 cases.

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

‡Percentages should sum over a column to 100% (with some rounding). However, where a percentage has been suppressed because it is based on only 1 or 2 cases, the remaining percentages will not sum to 100%.

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

Figure 12.1. Brain and Central Nervous System Cancer: Age-Standardized Incidence Rates* by Country



*Rates are per 100,000 and are age-standardized to the World Standard Million.
Sources: Data for non-MECC populations are taken 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. Data for MECC populations are taken from the MECC database.

consisted of tumors of unspecified location, for Egypt about 40% of this category consisted of "overlapping lesions," the remaining having unspecified location.) The ratio of the number of tumors occurring in the cerebellum to the number occurring in the cerebrum was higher in Egypt and Jordan than in the other countries. This reflects the young age structures of populations in these countries (see Figure 1.1) and the tendency of pediatric brain cancers to occur in the cerebellum. Comparison of subsite-specific incidence rates must be made with caution in light of the variable proportions with unspecified location.

Age

Age-specific incidence rates in the different countries were quite similar through middle age, with the major differences emerging at older ages (Figure 12.2). Small peaks in incidence rates were apparent for young children in some, but not all, MECC countries. Rates typically were lowest in the second or third decade of life and increased markedly beginning in the 40s or early 50s. A leveling off or decrease in incidence at the oldest ages was seen in most countries. This might reflect differences in the completeness of diagnosis. The age distribution of cases varied dramatically among

Table 12.2. Brain and Other Central Nervous System Cancer: Number of Cases Microscopically Confirmed and Proportions of Microscopic Confirmation, by Histology and Sex, in Cyprus, Israel (Jews and Arabs), Egypt, and Jordan − 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 microscopically confirmed	120	61	59	1,337	759	578	166	105	61	213	109	104	829	485	344	6,175	3,556	2,619
Microscopically confirmed	80.0%	77.2%	83.1%	79.1%	80.8%	77.0%	83.0%	86.1%	78.2%	65.7%	66.1%	65.4%	94.7%	95.9%	93.2%	87.5%	89.7%	84.6%
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%
Tumours of neuroepithelial tissue	93.3%	91.8%	94.9%	93.6%	94.3%	92.7%	93.4%	91.4%	96.7%	94.4%	94.5%	94.2%	91.0%	91.3%	90.4%	95.5%	96.3%	94.5%
Gliomas	87.5%	86.9%	88.1%	87.7%	87.9%	87.5%	81.9%	80.0%	85.2%	81.7%	83.5%	79.8%	76.1%	74.0%	79.1%	90.3%	90.7%	89.8%
Astrocytic tumours	76.7%	78.7%	74.6%	70.7%	69.8%	71.8%	63.3%	63.8%	62.3%	67.6%	70.6%	64.4%	60.3%	59.6%	61.3%	69.8%	71.1%	68.0%
Oligodendroglial/Mixed gliomas	-	-	*0.0%*	11.1%	11.6%	10.6%	10.8%	*10.5%*	*11.5%*	*3.3%*	*2.8%*	*3.8%*	4.3%	3.7%	5.2%	13.1%	12.7%	13.7%
Ependymal tumours	*4.2%*	-	*5.1%*	3.3%	3.4%	3.1%	*6.6%*	*4.8%*	*9.8%*	8.0%	*6.4%*	*9.6%*	4.9%	3.9%	6.4%	4.4%	3.9%	5.1%
Gliomas of uncertain origin	*5.0%*	-	*8.5%*	2.6%	3.0%	*2.1%*	-	-	-	*2.8%*	*3.7%*	-	6.5%	6.8%	6.1%	3.0%	3.1%	2.9%
Embryonal tumours	*5.8%*	*4.9%*	*6.8%*	5.5%	6.1%	4.8%	10.8%	*10.5%*	*11.5%*	12.7%	*11.0%*	*14.4%*	14.7%	17.1%	11.3%	5.0%	5.3%	4.5%
Medulloblastoma	*2.5%*	-	-	4.3%	4.9%	3.5%	*9.0%*	*9.5%*	*8.2%*	10.3%	*9.2%*	*11.5%*	11.2%	13.4%	8.1%	3.4%	3.9%	2.8%
Other	*3.3%*	-	*5.1%*	1.3%	*1.2%*	*1.4%*	*1.8%*	-	-	*2.3%*	-	*2.9%*	3.5%	3.7%	*3.2%*	1.6%	1.5%	1.7%
Unspecified tumours	-	*0.0%*	-	*0.8%*	*0.4%*	*1.4%*	-	-	*0.0%*	*0.0%*	*0.0%*	*0.0%*	2.1%	*2.1%*	*2.0%*	0.6%	0.6%	0.7%
Other specified types	*5.8%*	*8.2%*	-	5.5%	5.3%	5.9%	*5.4%*	*6.7%*	-	*5.6%*	*5.5%*	*5.8%*	7.0%	6.6%	7.6%	3.8%	3.1%	4.9%

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.

‡The histologic types are included if they are higher than 1% in total in any of the MECC registries; percentages should sum over a column to 100% (with some rounding). Where a percentage has been suppressed because it is based on only 1 or 2 cases, the remaining percentages may not sum to 100%.

Figure 12.2. Malignant Brain and Other Central Nervous System Cancer: Age-Specific Incidence Rates by Country

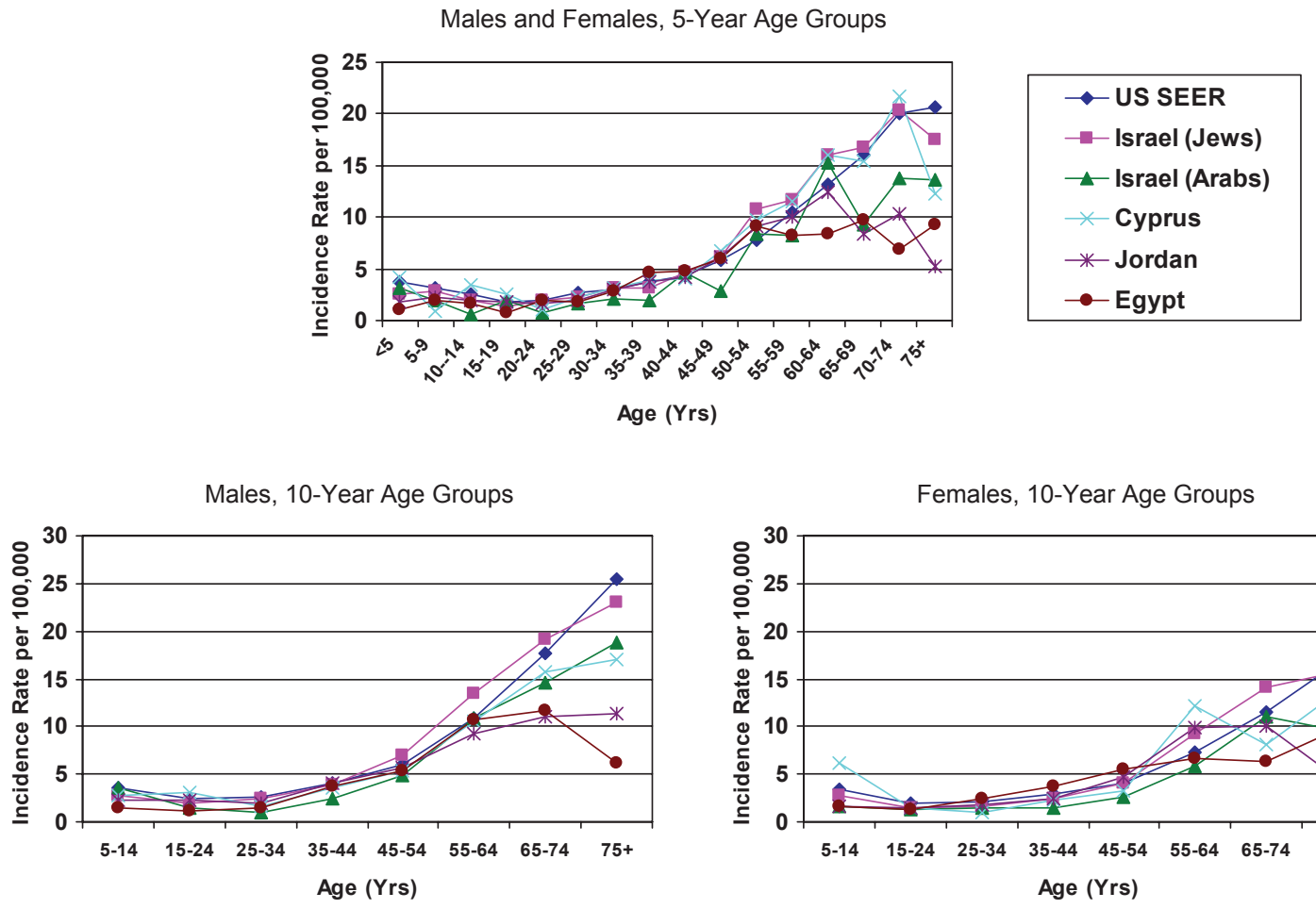


Table 12.3. Brain and Other Central Nervous System Cancer: Number of Cases, Age Distribution, and Age-Standardized Incidence Rates, by Age and Sex, in Cyprus, Israel (Jews and Arabs), Egypt, Jordan, and US SEER − 1996-2001*

	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	150	79	71	1,690	939	751	200	122	78	324	165	159	875	506	369	7,060	3,964	3,096
Age Groups (Distribution)																		
<20 y	17.3%	*15.2%*	*19.7%*	13.2%	12.7%	13.8%	35.5%	37.7%	32.1%	21.6%	20.0%	23.3%	33.7%	34.8%	32.2%	13.9%	13.6%	14.2%
20-49 y	22.0%	25.3%	*18.3%*	24.3%	26.9%	20.9%	28.0%	26.2%	30.8%	44.8%	41.2%	48.4%	35.9%	36.4%	35.2%	28.1%	28.9%	27.0%
50-69 y	40.0%	40.5%	39.4%	36.9%	36.5%	37.3%	27.5%	27.0%	28.2%	28.7%	35.2%	22.0%	26.3%	23.9%	29.5%	31.1%	33.0%	28.8%
70+ y	20.7%	*19.0%*	22.5%	25.7%	23.9%	28.0%	9.0%	*9.0%*	*9.0%*	4.9%	*3.6%*	*6.3%*	4.1%	4.9%	*3.0%*	26.9%	24.5%	29.9%
Age Groups (Rates)‡																		
Total rate	4.9	5.2	4.6	5.2	6.1	4.3	3.9	4.8	3.0	3.7	3.8	3.5	4.0	4.4	3.6	5.2	6.2	4.4
<20 y	3.4	*2.9*	*4.0*	2.3	2.3	2.2	2.0	2.5	1.5	1.4	1.3	1.5	1.9	2.3	1.6	3.0	3.2	2.8
20-49 y	2.7	3.3	*2.1*	3.4	4.3	2.6	2.2	2.6	1.8	3.5	3.3	3.7	3.3	3.7	2.9	3.6	4.1	3.0
50-69 y	11.5	12.8	10.4	13.4	15.9	11.3	10.2	12.5	8.1	8.8	11.1	6.6	10.1	10.1	10.0	11.2	14.0	8.7
70+ y	15.1	*17.0*	13.6	18.9	23.2	15.8	13.6	*18.8*	*9.5*	8.1	*6.1*	*9.7*	7.8	11.3	*4.5*	20.2	25.6	16.4

"[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.

countries (Table 12.3), again owing to the striking differences in age structures of the populations. Approximately two-thirds of cases in Jordanians, Egyptians, and Israeli Arabs occurred among persons younger than 50 years of age, and less than 10% occurred among persons 70 years or older among these populations. The majority of cases in Cypriots, Israeli Jews, and US SEER occurred among persons older than 50 years. The incidence rates in males relative to females varied by age, with a higher rate in females for ages less than 20 years in Cyprus and Egypt (Table 12.3). However the numbers of cases were small.

Histology

As seen in Table 12.2, astrocytic tumors were the most common type of brain and other CNS cancers in all MECC countries and in US SEER. Embryonal tumors (primarily medulloblastoma) accounted for higher proportions of all brain/CNS cancers in Jordanians, Egyptians, and Israeli Arabs than in the other populations. Oligodendroglioma and mixed glioma accounted for higher proportions of all CNS cancers among Israeli Jews and Arabs and in US SEER than in other countries.

SUMMARY AND CONCLUSIONS

Incidence rates in the MECC countries are in the mid-range of those represented in a worldwide sampling of cancer registries, with Israeli Jews closer to the high end and Egyptians, Israeli Arabs, and Jordanians toward the lower end *[23]*. Because so little is known about the etiology of brain/CNS cancer, it is difficult to interpret results in terms of known risk factors. One factor that may influence the incidence rate in these countries is the known trend for incidence to increase with increasing socioeconomic status. World Bank statistics indicate that Israel has a much higher GNP than either Jordan or Egypt (data for Cyprus were not available) and, within Israel, Jews have a higher socioeconomic status than Arabs *[40]*.

What is clear is that brain/CNS cancer affects different age groups in these Middle Eastern countries. In Jordanians, Egyptians, and Israeli Arabs, it is primarily a disease of children and young adults. In Cypriots and Israeli Jews, as in the US SEER population, it is more often a disease of middle or old age. This is overwhelmingly due to differences in population age structure, rather than to underlying incidence rates. Differences in tumor subsite and histology mirror the age differences, as childhood cancers are much more likely to be infratentorial and embryonal or ependymal. Other interesting epidemiologic patterns include variable male-to-female ratios in incidence by country and age, and the general similarity of age-specific incidence rates at young and middle ages. A surprising finding was the high proportion of brain cancers with unspecified subsite. Although there has been progress in treating some types of brain cancer, the fatality rate for most types is still high *[41]*. This analysis did not address differences in survival by country.

While these data are limited both by the relatively small number of cases and the short time period, they do provide new understanding about brain and other CNS tumors in the Middle East. Some of the patterns appear to be related to variation in the age distribution, and possibly access to medical care, of the 5 Middle Eastern populations. The heavy burden that brain cancers put on patients, their families, and society suggests that collection of additional data would be worthwhile.

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