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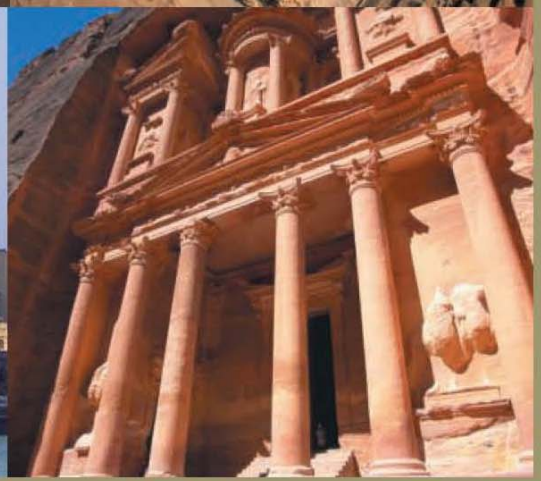
Cancer Incidence in Four Member Countries (Cyprus, Egypt, Israel, and Jordan) of the Middle East Cancer Consortium (MECC) Compared with US SEER



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Cancer Incidence in Four Member Countries (Cyprus, Egypt, Israel, and Jordan) of the Middle East Cancer Consortium (MECC) Compared with US SEER

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Front cover pictures (clockwise, beginning upper left):

Cyprus: 7th century Byzantine castle in Pathos, ruined by earthquake in 1222.
Egypt: Menkaure's Pyramid on Giza Plateau.
Israel: Jaffa Port, a seaport at least 3200 years old.
Jordan: Petra, an impressive facade carved into the rock more than 2000 years ago.

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Preface

In 1996, the Ministers of Health of Egypt, Israel, Jordan, Cyprus, and the Palestinian Authority (PA) signed an agreement to establish the Middle East Cancer Consortium (MECC). The U.S. Secretary of Health and Human Services witnessed the signature ceremony (Figure 1). Turkey joined the Consortium as a full member state in 2004. The main goal of the new Consortium was to develop regional cooperation and to lessen the burden of cancer in the Middle East. After continuous deliberations, it was decided that the development of a cancer registration network across borders would be the first feasible project. Prior to the agreement, most of the countries in the Consortium had only recently begun to establish population-based registries, starting with, in most cases, hospital-based registries. Hence, by accelerating and strengthening this process, the Joint Cancer Registration Project very quickly became the flagship of MECC's activities in the region.

MECC has either established or supported, along with the respective Ministries of Health, local centers for cancer registry covering the following populations: Jordan (registry situated in Amman); Gharbiah Region, Egypt (registry situated in Tanta); Israel (registry situated in Jerusalem); West Bank, PA (registry situated in Beit Jala, Bethlehem); Gaza Strip, PA (registry situated in Gaza City); Cyprus (registry situated in Nicosia); and Izmir, Turkey (registry situated in the city of Izmir). The major preliminary goal of educating and training a nucleus of registry staff in each country was achieved via courses in the region and in the United States, led by Dr. John Young of Emory University, Atlanta, Georgia. An additional important issue related to standardizing the coding and classification of the registration information and adopting one computer program that would enable comparative studies among the countries. With the support of the International Agency for Research on Cancer (IARC) in Lyon, France, the new MECC cancer registries began to use the CANREG program. This software was relatively easy to operate and had the constant backing of IARC staff (Drs. Andy Cook and

Figure 1. Ministers of Health, Geneva, 2000. From left to right: Mr. Frixos Savvides (Cyprus); Dr. Riad El-Zaanoun (Palestinian Authority); Dr. Donna Shalala, chair (United States); Dr. Ismail Salam (Egypt); and Mr. Shlomo Benizri (Israel). Not pictured: Dr. Faleh Al-Naser (Jordan), who was not present at that occasion.

Preface

Venkata Kumar) through electronic support and site visits to the Middle Eastern centers.

To coordinate the work of this international group, Professor Laurence Freedman was appointed as chairman of the Steering Committee for the Joint Cancer Registration Project. Professor Freedman's responsibilities were to provide overall supervision of the scientific direction of the project, maintain communications across borders, and organize the annual meetings of the Joint Cancer Registration Project, which initially rotated between the various capitals in the Middle East and IARC in Lyon. One person in each cancer registry center was appointed as principal investigator (PI), to serve on the Steering Committee and as the chairman's contact person for ongoing issues. These PIs are Dr. Charitini Komodiki (Cyprus), Professor Amal S. Ibrahim (Egypt), Dr. Khamis Najjar (Gaza Strip, PA), Dr. Micha Barchana (Israel), Dr. Samir Al-Kayed (Jordan), Dr. Sultan Eser (Turkey), and Dr. Abdel Razzaq Salhab (West Bank, PA). The coordination was often difficult, due to circumstances in the region, but by and large it yielded very positive results, including, ultimately, this monograph. The frequent interactions between the PIs and the cancer registry staff in the MECC countries also served to develop better understanding between the individuals involved, including physicians, nurses, secretaries, statisticians, and others.

The scientific aspects of the regional cancer registry program have been strongly supported by Dr. John Young; Dr. Elaine Ron of the Division of Cancer Epidemiology and Genetics, National Cancer Institute (NCI), Bethesda, Maryland; and Dr. Brenda Edwards, Associate Director, Division of Cancer Control and Population Sciences, NCI, and her dedicated staff. Drs. Young, Ron, and Edwards serve as members of the Steering Committee.

The policies associated with the present and future work of the registry project are set by the MECC Board of Governors (one representative from each member state): Dr. Samir Al-Kayed, chairman (Jordan); Professor Amal S. Ibrahim (Egypt); Dr. Charitini Komodiki (Cyprus); Dr. Khamis Najjar (Palestinian Authority); Professor Rami Rahamimoff (Israel); and Professor Murat Tuncer (Turkey); together with the NCI coordinator, Dr. Joe Harford (United States) (Figure 2). The Board of Governors bears the responsibility of approving the annual budget for each center, adding special allocations for new equipment, assigning the budget for the annual meetings, and discussing all other initiatives and proposals associated with the registry project. The greater part of MECC's annual budget is allocated to the registry project, and funds are channeled to MECC through NCI.

Because MECC is supported directly by the National Institutes of Health through NCI, which is a research institute, the expectations are always that the program will eventually yield a tangible scientific product. I believe that this monograph complies with the above expectations, and I do hope that it is only the first in a series of comprehensive publications related to cancer registration in the Middle East.

Michael Silbermann
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Figure 2. MECC Board of Governors

Executive Summary

Cancer Incidence in Four Member Countries (Cyprus, Egypt, Israel, and Jordan) of the Middle East Cancer Consortium (MECC) Compared with US SEER is the first comprehensive publication of the MECC Cancer Registration Project. This monograph presents information about cancer incidence for populations in Cyprus, Egypt (Gharbiah Region), Israel (Jews and Arabs), and Jordan for the period 1996-2001. The MECC findings are compared with those from the US Surveillance, Epidemiology, and End Results (SEER) Program.

For most of the cancers described in this monograph, incidence is expressed as age-standardized incidence rates (ASRs) per 100,000 population. The ASR is a summary measure that permits comparison of incidence rates across populations while adjusting for differences in age distributions. ASRs for childhood cancers are expressed per 1 million population.

MAJOR FINDINGS

- The **overall incidence of cancer** was substantially higher in the US SEER population and in Israeli Jews than in the other MECC populations. Cypriots, Israeli Arabs, and Egyptians had intermediate rates, while the Jordanian rates were the lowest. This pattern was seen for both males and females across the registries.
- Israeli Jews had the highest rate of **colorectal cancer** among the MECC populations, and their rate was higher than that of US SEER. The other MECC populations had rates less than half that of Israeli Jews.
- The incidence of **liver cancer** in Egyptians was more than 3 times that in US SEER and about 5 to 7 times that in the other MECC populations.
- Although overall **lung cancer** incidence in the MECC populations was much lower than in the US SEER population, younger Israeli Arab males (under 60 years of age) had rates comparable to those in US SEER.
- **Urinary bladder cancer** incidence was very high among Egyptians and Israeli Jews, surpassing rates in the US SEER population. Egypt's high rate is at least partly explained by the previously high prevalence of schistosomiasis, known to lead to squamous cell carcinoma of the urinary bladder. However, the currently high proportion of transitional cell carcinoma in Egypt may indicate a changing etiology of urinary bladder cancer in that population.
- **Non-Hodgkin lymphoma** incidence was very high in Israeli Jews and Egyptians – higher than in US SEER, which was considered to have one of the highest rates worldwide.
- **Childhood cancer** incidence (under age 15 years) was high among Cypriots and higher than in the US SEER population. The high rate among Cypriots was mainly due to high rates of childhood leukemia and central nervous system malignancies.
- The incidence of **childhood lymphoma** was particularly high among Egyptians, compared with the other populations studied.

MAIN FINDINGS BY CHAPTER

Chapter 1: Overview and Summary Data

- The age distributions of the populations varied widely. The populations of Egyptians, Israeli Arabs, and Jordanians had higher proportions of young people (younger than 20 years) and lower proportions of older people (older than 50 years) than the populations of Cypriots, Israeli Jews, and US SEER.
- In the populations studied, cancer of the digestive system accounted for about 20% of all cancers, and cancer of the breast, about 33% of female cancers – with relatively little variation across the populations.

- Cancer of the male genital system (mostly prostate) accounted for as little as 4%-10% of male cancers in Egyptians, Jordanians, and Israeli Arabs, compared with 19%-33% in Israeli Jews, Cypriots, and the US SEER population.
- The younger populations (Israeli Arabs, Jordanians, and Egyptians) had a greater proportion (16%-18%) of leukemias and lymphomas than the older populations (Cypriots, Israeli Jews, and US SEER) (7%-9%).
- Two populations, US SEER and Israeli Jews, had substantially higher ASRs overall (318.6 and 274.4, respectively), compared with the others. The Cypriot (164.2), Israeli Arab (149.8), and Egyptian (143.0) populations had intermediate rates, while the Jordanian rates (113.3) were the lowest. This same pattern was seen for both males and females.

Chapter 2: Esophageal Cancer

- The incidence of esophageal cancer in the MECC countries was among the lowest in the world, with ASRs ranging between 0.6 and 1.5, compared with 3.0 in US SEER. This may be related to the relatively low consumption of alcohol in the region. In contrast, there is a high prevalence of smoking in almost all of the MECC countries, which would tend to increase esophageal cancer rates. Further study seems warranted.

Chapter 3: Stomach Cancer

- Compared with the US SEER population (5.3), the ASR for stomach cancer was low among Egyptians (2.9); similar among Cypriots, Israeli Arabs, and Jordanians; and high among Israeli Jews (8.5).

Chapter 4: Colorectal Cancer

- The ASR for colorectal cancer was particularly high among Israeli Jews (36.9), and higher than in the US SEER population (32.0). Other MECC populations had rates less than half that among Israeli Jews. The gap in incidence between the Israeli Jewish and US SEER populations was even greater in the 70-and-older age group.

Chapter 5: Liver and Intrahepatic Bile Duct Cancer

- The incidence of liver and intrahepatic bile duct cancer in Egyptians (12.8) was more than 3 times that in the US SEER population (4.2) and 5 to 7 times that in the other MECC populations. The high rates in Egypt may be related to the prevalence of hepatitis B and hepatitis C in the population or to contamination of food by aflatoxins.

Chapter 6: Lung Cancer

- The incidence of lung cancer in the MECC populations (9.9-20.4) was lower than that in the US SEER population (39.2).
- Age-specific rates of lung cancer among Israeli Arab males aged 50 to 59 years (92.9) were comparable to those in the US SEER population (86.2). Israeli Arab men are known to have high tobacco consumption, and the high lung cancer rates at younger ages may reflect a cohort effect of rising rates in this population.
- The lung cancer ASR in Israeli Jews (19.0) was less than half that in the US SEER population (39.2). Yet, past records indicate higher rates of tobacco consumption among Israeli males than US males for the past 30 years. This possible anomaly calls for further study.

Executive Summary

Chapter 7: Laryngeal Cancer

- The incidence of laryngeal cancer in males in the MECC populations (1.6-3.1) was comparable to that in US SEER (2.7), although rates were somewhat higher in Israeli Arabs (3.1) and somewhat lower in Cypriots (1.6). This similarity between rates in MECC and US SEER merits further study.

Chapter 8: Breast Cancer

- The ASR of female breast cancer was high in Israeli Jews (93.1), comparable to that in the US SEER population (97.2). The other MECC populations had much lower rates (36.7-57.7).
- Age-specific rates of breast cancer among women under 55 years of age were higher in Israeli Jews than in the US SEER population. These high rates may be related to the genetic mutations in the *BRCA* genes known to be more prevalent among Ashkenazi women.

Chapter 9: Cervical and Corpus Uterine Cancer

- The incidence of cervical cancer was low in the MECC populations (2.5-5.3), substantially lower than in the US SEER population (7.0). This may be related to differences in sexual behavior between the populations.
- The incidence of corpus cancer and uterine cancer not otherwise specified was lower in the MECC populations (3.5-13.8) than in the US SEER population (17.6). Within MECC populations, the higher rates were found among Cypriots (11.8) and Israeli Jews (13.8). These results may be related to differences in the number of children born and the use of hormone replacement therapy in these populations.

Chapter 10: Ovarian Cancer

- The incidence of ovarian cancer in Israeli Jews (9.4) and Cypriots (7.7) was a little lower than that in the US SEER population (10.0). The rate was substantially lower in the other MECC populations (3.6-5.4). These differences may be related to differences in the number of children born in these populations.

Chapter 11: Urinary Bladder Cancer

- The incidence of urinary bladder cancer was very high in Egyptians (16.6) and Israeli Jews (15.1) – higher than the incidence in the US SEER population (12.2). The ASR was intermediate among Cypriots (11.2) and low among Israeli Arabs (8.6) and Jordanians (7.6).
- The high urinary bladder cancer rate in Egypt is at least partly explained by the previously high prevalence of schistosomiasis, known to lead to squamous cell carcinoma (SCC) of the urinary bladder. The proportion of SCC among all urinary bladder cancers was 26% in Egyptians, compared with 0%-2% in the other MECC populations and US SEER. Transitional cell carcinoma (TCC), the type of urinary bladder cancer found in most Western countries and associated with cigarette smoking, accounted for 63% of the urinary bladder cancers in Egypt and over 90% of the urinary bladder cancers in the other MECC populations and US SEER. That as much as 63% of the cancers in Egypt were TCC may indicate a changing etiology of urinary bladder cancer in that population. Further studies are indicated.
- The high rate of urinary bladder cancer in Israeli Jews may be related to high rates of cigarette smoking. This calls for further study.

Chapter 12: Brain and Other Central Nervous System Cancer

- The ASR of malignant brain tumors in Israeli Jews was identical to that in the US SEER population (4.9). The rates in the other MECC populations were somewhat lower (3.2-4.1). The higher rate in Israeli Jews may be related to the practice of head irradiation for tinea capitis, a treatment given to a substantial proportion of immigrant children entering Israel during the 1950s.

Chapter 13: Thyroid Cancer

- The ASR of thyroid cancer was higher in Israeli Jews (7.5) than in the US SEER population (6.2). The ASRs were moderate in Cypriots (5.6) and lower in Israeli Arabs, Egyptians, and Jordanians (2.0-4.1). The ASR in Israeli Jewish women (11.2) was second only to that among Icelandic women (13.1), and may be related to the head irradiation treatment for tinea capitis received by many children immigrating to Israel during the 1950s.

Chapter 14: Lymphoma and Leukemia

- The incidence rate of non-Hodgkin lymphoma was very high in Israeli Jews (15.2) and Egyptians (14.2) – higher than the rate in the US SEER population (12.9), which was considered one of the highest worldwide. The other MECC populations had lower rates (6.4-10.2). The reasons for the high rates in Israeli Jews and Egyptians are not well understood and require further study.
- The proportions of non-Hodgkin lymphomas that were extranodal did not differ widely across the populations studied (23%-36%).
- The ASR of Hodgkin lymphoma was somewhat higher in most of the MECC populations (2.1-3.4) than in the US SEER population (2.4). Rates were highest among Israeli Jews (3.4) and Cypriots (3.0).
- The ASR of leukemia in Israeli Jews (8.6) was similar to that in the US SEER population (8.8). The rates in the other MECC populations were lower (6.0-6.9).

Chapter 15: Childhood Cancer

- The ASR of childhood cancer (under age 15 years) was high among Cypriots (170.0 per million), compared with US SEER (153.3) and with the other MECC populations (114.8-133.3).
- Rates of childhood leukemia (under age 15) were highest among Cypriots (53.0) and the US SEER population (50.4). The rates in other MECC populations ranged from 29.4 to 39.2.
- The incidence of childhood lymphoma (under age 15) was particularly high among Egyptians (37.7), compared with the other populations studied, and was higher in MECC populations (15.7-24.2) than in the US SEER population (13.5).
- The incidence of childhood central nervous system malignancies (under age 15) was high in Cypriots (40.1) and higher than in the US SEER population (32.5). ASRs in other MECC populations were lower (16.5-24.2).
- Reasons for the high rates of childhood leukemia and CNS malignancies in Cypriots and the high rate of childhood lymphoma in Egyptians are not understood and call for investigation.

Overview and Summary Data

Chapter 1

Laurence Freedman, Brenda K. Edwards, Lynn A. G. Ries, Samir Al-Kayed, Micha Barchana, Amal Samy Ibrahim, Charitini Komodiki, John L. Young

BACKGROUND

Cancer Incidence in Four Member Countries (Cyprus, Egypt, Israel, and Jordan) presents information on cancer incidence over the period 1996-2001, drawn from data collected by 4 registries in the Middle East – situated in Cyprus, Egypt, Israel, and Jordan – as part of the Joint Cancer Registration Project of the Middle East Cancer Consortium (MECC). This chapter provides background information to help readers better understand the data, the populations they describe, the way the data were collected, and their strengths and limitations. Tables in the latter part of the chapter provide an overall summary of the cancer incidence rates in the populations covered by the MECC registries and, for comparison, the Surveillance, Epidemiology, and End Results (SEER) registry program in the United States. Each succeeding chapter covers a particular anatomical site or histological type of cancer in more detail.

Three other registries participate in the MECC Cancer Registration Project, covering the populations of Gaza and the West Bank in the Palestinian Authority (PA), and of Izmir in Turkey. A condition for inclusion in this monograph was that the registry data had been checked by audit. Unfortunately, these registries have not yet been audited – the PA registries due to difficulties of access, and the Izmir registry due to its very recent participation in the project. It is hoped that these registries can be audited in the near future and will be included in future MECC publications.

THE REGISTRIES

Cyprus National Cancer Registry

The Cyprus National Cancer Registry covers the population currently governed by the Government of the Republic of Cyprus (2001 population: 705,500), and not the Turkish-controlled part of the island.

Collection of data on cancer incidence from histopathological reports was initiated in Cyprus in 1990. The population-based cancer registry was established in 1998, after Cyprus joined the MECC. From that time, the data collection and coding operation was redefined and strengthened.

Since its establishment, the Cyprus National Cancer Registry has functioned in Nicosia as a unit of the Ministry of Health. It is staffed with 3 tumor registrars and comes under the direct responsibility of the Chief Health Officer of the Ministry of Health. Tumor registrars actively collect data by regularly visiting the hospitals and their oncology departments, and reviewing cytology and bone marrow registers and the histology reports.

Cancer is not yet a notifiable disease in Cyprus, and death certificates in Cyprus are not sufficiently detailed to be used as a source for cancer registration.

Gharbiah Regional Cancer Registry, Egypt

The Gharbiah Regional Cancer Registry, a population-based registry covering the Gharbiah Governorate, was established in 1998 within the context of the MECC Joint Cancer Registration Project. It is located in the Tanta Cancer Center of the Ministry of Health and Population. Tanta, the capital city of the Gharbiah Governorate, is situated in the middle of the Nile Delta, about 100 kilometers north of Egypt's capital city, Cairo. The registry is jointly sponsored by MECC and the Ministry of Health and Population, Cairo.

The registrar's principal investigator is Professor Amal Samy Ibrahim, professor of epidemiology and past vice dean of the

National Cancer Institute in Cairo. The current executive director is Professor Hany Hussein, professor of pediatric oncology in the National Cancer Institute in Cairo and director of the Tanta Cancer Center. The previous executive directors are Dr. Kadry Ismail and Dr. Ahmed Hablas, both surgery consultants and previous directors of the Tanta Cancer Center. They currently act as co-investigators in the registry and are responsible for field supervision. The data managers are Dr. Ibrahim Abdel Bar, a surgery consultant at Tanta Cancer Center, and Dr. Mohammed Ramadan, a chemotherapy specialist at Tanta Cancer Center. They also supervise the daily activities of the registry, and are helped by 5 technicians and secretaries.

Medical doctors of the Tanta Cancer Center actively collect data through regular visits to all governmental, non-governmental, and private centers and laboratories dealing with cancer patients. Data are also collected from death certificates. Centers outside Tanta that deal with cancer patients, mainly the National Cancer Institute in Cairo, are visited regularly to collect data on Gharbiah patients who might be treated there.

Registration began in 1999. The registry records all incident cancer cases among the approximately 3.4 million residents of Gharbiah diagnosed within and outside the Gharbiah Governorate. Although notification of cancer is not obligatory by law, a Ministerial decree that was issued to request collaboration with the registry has enhanced data collection efforts.

In the rest of this monograph, for convenience, we refer to Gharbiah as “Egypt.” The reader is to understand that this is merely a shorthand description, and that all results for Egypt in the monograph are derived from the Gharbiah subpopulation.

Israel National Cancer Registry

The Israel National Cancer Registry, established in 1960, is part of the Center for Disease Control at the Ministry of Health of Israel. The main goal of this population-based registry is to maintain an updated, complete database on cancer incidence in the Israeli population. The registry provides data regarding incidence, prevalence, and survival, and is the basis for medical research, health planning, and monitoring of malignancies.

Reporting to the registry, which was voluntary prior to 1982, is now mandatory, and all Israeli hospitals (and since the late 1980s, also the private pathology laboratories) report, usually by submitting a copy of the medical documentation. Thus, the method of data collection is mostly passive, but when needed, registry staff visit reporting sources to collect data actively.

Reporting sources include pathology, cytology, and hematology laboratories; hospital discharge forms; oncology institutes; death notification from district health offices; and the file of deaths from the Central Bureau of Statistics. Since 2000, through collaboration with the Israeli Hematology Society, all hematologists have been reporting the hematological malignancies that they see.

Several studies have been conducted to assess the registry’s completeness during its more than 40 years of operation. These studies began in the 1970s, with the latest one based on 1994 data. The method used for these studies was to actively search for cancer patients in a defined period in all (or major) hospitals, and to compare the resulting data with the file in the registry (record linkage). These studies resulted in estimated completeness rates of over 94% (usually 95% and more) for solid tumors. In the latest study, a completeness rate of only 85%-90% was noted for non-solid tumors, resulting in the above-mentioned initiative to collaborate with the Israeli Hematology Society. One problem in these studies was that the Israel National Cancer Registry registers only Israeli citizens, but hospitals also treat non-Israeli patients.

The work at the registry is simplified by the existence of a unique identification number that is given to all Israeli citizens (at birth or immigration). This number, used by Israelis in all their contacts

with the health system and other government departments, prevents duplication of data. Each year, the registry receives a file containing all deaths in the country, which it uses to update the vital status of those in the register.

The registry uses the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) coding system for sites and histologies. Other parameters (such as stage of disease) are coded in accordance with the SEER Program, thus bringing the registry in line with MECC standards, which are described later in this chapter.

Jordan Cancer Registry

The population-based Jordan Cancer Registry was established in 1996 under the umbrella of the Ministry of Health. Administration of the registry on a daily basis is the responsibility of the operations manager, under the supervision of His Excellency the Minister of Health. Much of the energy behind the establishment of the Registry was provided by Dr. Aref Bataynaha, the previous Minister of Health. Dr. Samir Al-Kayed (oncologist) and Dr. Bassam Al Hijawi (epidemiologist) pioneered the early work of the registry and set up its system of data collection.

The registry is located in Amman, capital city of Jordan, with 4 sub-offices: 1 located in Irbid in the Northern region, and 3 in large health institutions in Amman. The total number of staff in the registry is 11, of whom 3 are supported by a MECC grant. The remaining staff members are supported by the Ministry of Health. The staff members of the registry include an epidemiologist, a community health doctor, a statistician, data entry personnel, and a general secretary.

The registry covers the entire Jordanian population distributed over all 12 governorates, located in 3 regions. Amman includes approximately 38% of the total population.

Data for cancer registration are collected from all possible sources of information in the 4 health sectors: government, military, private, and university. Well-trained designated persons at each institution abstract cancer data from patients' files, complete the notification forms, and forward them to the registry. The data collection system may therefore be described as partly passive. However, there is also an active component, implemented by the central registry staff through regular site visits to the health institutions, the frequency of visits determined according to the size of the institutions' patient loads. Currently, 97 hospitals and 19 pathology laboratories notify cancer to the registry.

Since its establishment, the registry has been fully computerized and has produced regular annual statistical reports that contain information on cancer incidence by age, sex, and type of cancer, as well as cancer trends. The reports are circulated widely throughout Jordan. The registry also has served as a focus for clinical and epidemiological research, and is increasingly used in planning oncology services such as radiotherapy units, a breast cancer mass screening program, cancer prevention and control programs, hospices, and palliative care activities.

In 2003, the Ministry of Health declared by Public Health Law that cancer is a notifiable disease in Jordan, requiring all health institutions in all sectors to report cancer cases. Registry staff members are working in collaboration with the Civil Department to improve the quality of the national death certificate. It is hoped that this will help to collect better data on deaths where cancer is an underlying cause, and thereby on cancer mortality.

US Surveillance, Epidemiology, and End Results Program

The SEER Program of the National Cancer Institute (NCI) is an authoritative source of information on cancer incidence and survival in the United States (http://seer.cancer.gov). SEER currently collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 26% of

the US population. The SEER Program registries routinely collect data on patient demographics, primary tumor site, tumor morphology and stage at diagnosis, first course of treatment, and follow-up for vital status. The SEER Program is the only comprehensive source of population-based information in the United States that includes patient survival data.

SEER began collecting data on cancer cases in 1973 in the states of Connecticut, Iowa, New Mexico, Utah, and Hawaii, and the metropolitan areas of Detroit (Michigan) and San Francisco-Oakland (California). In 1974-1975, the metropolitan area of Atlanta (Georgia) and the 13-county Seattle-Puget Sound (Washington) area were added. In 1978, 10 predominantly Black rural counties in Georgia were added, followed in 1980 by the addition of American Indians residing in Arizona. Three additional geographic areas participated in the SEER program prior to 1990: New Orleans, Louisiana (1974-1977, rejoined 2001); New Jersey (1979-1989, rejoined 2001); and Puerto Rico (1973-1989). The NCI also funds a cancer registry that, with technical assistance from SEER, collects information on cancer cases among Alaska Native populations residing in Alaska. In 1992, the SEER Program was expanded to increase coverage of minority populations, especially Hispanics, by adding the state of California's Los Angeles County and 4 counties in the San Jose-Monterey area south of San Francisco. In 2001, the SEER Program expanded coverage to include Kentucky and the remaining counties in California (known as the Greater California registry); in addition, New Jersey and Louisiana once again became participants. For the expansion registries (Kentucky, Greater California, New Jersey, and Louisiana), NCI funds are combined with funding from the US Centers for Disease Control and Prevention (through the National Program of Cancer Registries) and with funding from the states.

For this report, the SEER Program utilized cancer incidence data submitted to the NCI in November 2004 for cancer cases diagnosed in 1999-2001 from 13 population-based cancer registries that cover approximately 14% of the US population: Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Utah, Los Angeles County, San Jose-Monterey, rural Georgia, and the Alaska Native Tumor Registry. Corresponding population data for these respective geographic areas come from the US Bureau of the Census.

The SEER Program is considered the standard for data quality around the world. Quality control has been an integral part of SEER Program activities since its inception. Currently, quality control studies of various types, including case finding, recoding, and reliability, are conducted every 1-2 years to evaluate the quality and completeness of the data being reported (SEER's standard for case ascertainment is 98%). In some studies, a sample of cases is reabstracted to evaluate the accuracy of each of the data elements collected from the medical records. In other studies, targeted information gathering is performed to address specific data quality needs. Computer edits also are used by registries to ensure accurate and consistent data.

THE REGISTRY POPULATIONS

Many of the tables in this chapter and in the remainder of this monograph present statistics for each population side by side in the same table. The populations are arranged from left to right in the following order: Cyprus, Israel (Jews), Israel (Arabs), Egypt, Jordan, and US SEER. This order originally arose from a desire to place together MECC populations with similar age structure. Thus Cyprus and Israel (Jews) are placed adjacent to one another, and similarly Israel (Arabs), Egypt, and Jordan. US SEER is placed last as a comparison population, even though the population structure of the SEER geographic areas is similar to those of Cyprus and Israel (Jews). The Israeli population is subdivided into Israeli Jews and Israeli Arabs for the purpose of comparing cancer rates in the 2 sectors within Israel, and also to allow comparisons between Israeli Arabs and the Arabs in neighboring countries.

Table 1.1 and Figure 1.1 present the number of persons in the 6 populations (MECC and US SEER) subdivided by sex and 5-year age groups, averaged over the reporting period.

The age distributions in these populations vary widely. The percentage of individuals under age 20 years is higher in Jordanians (52%), Egyptians (48%), and Israeli Arabs (50%) than in Cypriots (31%), Israeli Jews (35%), and the US SEER population (29%). Conversely the percentage over 50 years is lower in Jordanians (10%), Egyptians (12%), and Israeli Arabs (10%) than in Cypriots (26%), Israeli Jews (24%), and the US SEER population (25%). These profound differences in age distribution make it difficult to compare cancer incidence across the countries using crude incidence rates; therefore, this monograph uses age-standardized and age-specific incidence rates for purposes of comparison (see "Statistical Methods").

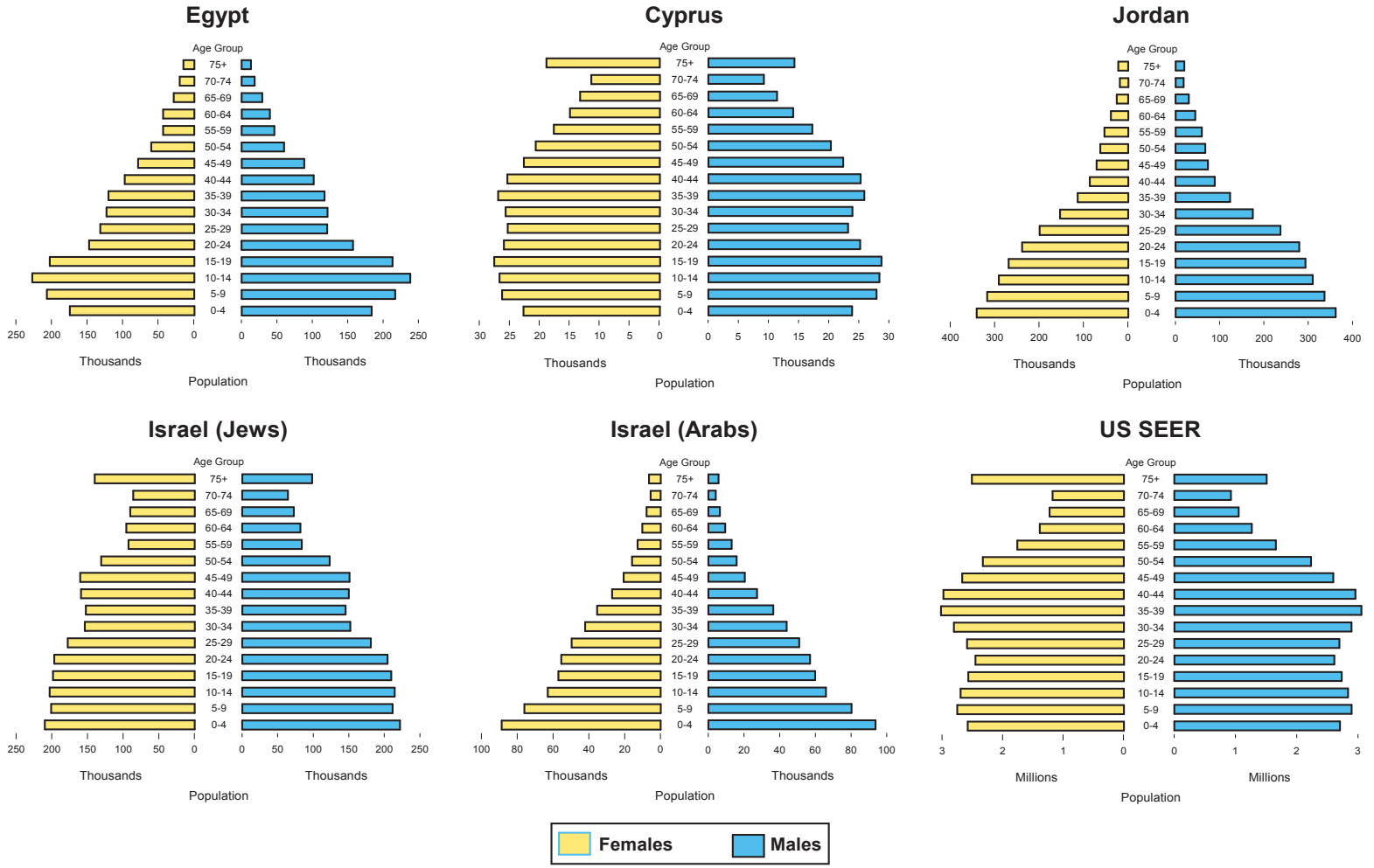
Table 1.1 also shows clear differences in the size of the populations covered by the registries. US SEER has the largest population; the Jordanian, Israeli Jewish, and Egyptian populations are intermediate; and the Israeli Arab and Cypriot populations are the smallest. The size of the population influences the total number of cancer cases registered, although other important factors also govern this number (see "Statistical Methods").

Table 1.1. Overview and Summary Data: Number of Persons by 5-Year Age Group and Sex, Averaged over the Reporting Period, 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		
Age Group	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female
Total cases	694,125	341,225	352,900	4,816,677	2,364,568	2,452,108	1,165,217	590,017	575,200	3,491,875	1,764,255	1,727,620	4,820,401	2,512,962	2,307,439	38,951,829	19,238,095	19,713,734
00-04 y	46,600	23,850	22,750	432,017	221,867	210,150	182,467	93,667	88,800	358,727	183,535	175,192	702,411	361,218	341,194	2,778,108	1,422,556	1,355,553
05-09 y	54,275	27,925	26,350	412,600	211,433	201,167	156,350	80,200	76,150	424,112	216,918	207,195	654,115	336,252	317,863	2,934,003	1,501,781	1,432,221
10-14 y	55,150	28,400	26,750	417,885	214,502	203,383	128,917	65,883	63,033	465,851	238,011	227,839	601,175	309,485	291,690	2,846,936	1,457,808	1,389,128
15-19 y	56,400	28,725	27,675	408,217	209,550	198,667	116,900	59,800	57,100	416,429	213,149	203,280	562,932	293,450	269,482	2,728,754	1,404,392	1,324,362
20-24 y	51,250	25,200	26,050	401,183	204,267	196,917	112,517	56,983	55,533	305,313	157,392	147,921	518,330	279,362	238,968	2,674,846	1,369,046	1,305,800
25-29 y	48,550	23,175	25,375	358,983	180,900	178,083	100,600	50,883	49,717	252,762	120,569	132,194	436,268	236,598	199,669	2,898,812	1,475,844	1,422,968
30-34 y	49,650	23,900	25,750	306,225	152,067	154,158	86,100	43,867	42,233	244,766	121,259	123,507	327,785	174,187	153,598	3,096,528	1,575,017	1,521,512
35-39 y	52,875	25,875	27,000	297,883	145,267	152,617	71,883	36,350	35,533	237,593	117,030	120,563	236,953	122,967	113,986	3,222,935	1,624,420	1,598,516
40-44 y	50,700	25,250	25,450	309,200	149,883	159,317	54,383	27,250	27,133	199,395	101,518	97,877	175,426	88,730	86,697	3,131,515	1,561,457	1,570,058
45-49 y	45,050	22,375	22,675	311,583	150,950	160,633	41,083	20,417	20,667	167,462	88,347	79,114	144,402	72,981	71,422	2,790,328	1,374,232	1,416,096
50-54 y	41,050	20,325	20,725	254,250	122,917	131,333	31,883	15,883	16,000	120,391	59,942	60,449	129,809	67,031	62,777	2,410,692	1,176,959	1,233,733
55-59 y	34,950	17,250	17,700	176,483	83,767	92,717	25,967	13,067	12,900	89,939	46,160	43,779	112,773	58,985	53,788	1,789,482	869,731	919,751
60-64 y	29,075	14,075	15,000	178,017	81,983	96,033	19,733	9,433	10,300	83,634	39,724	43,910	83,348	44,264	39,084	1,363,376	650,187	713,189
65-69 y	24,725	11,400	13,325	162,967	72,550	90,417	14,367	6,450	7,917	57,952	29,075	28,877	55,796	29,991	25,805	1,153,046	530,666	622,379
70-74 y	20,650	9,225	11,425	150,617	64,350	86,267	9,767	4,150	5,617	38,898	18,363	20,535	36,986	17,901	19,085	1,065,058	468,173	596,885
75+ y	33,175	14,275	18,900	238,567	98,317	140,250	12,300	5,733	6,567	28,652	13,264	15,388	41,894	19,561	22,333	2,067,409	775,826	1,291,583

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

Figure 1.1. Overview and Summary Data: Age Distributions in Cyprus, Israel (Jews and Arabs), Egypt, Jordan, and US SEER - 1996 - 2001



DATA COLLECTED BY THE MECC REGISTRIES

Data Items

The collection of data by the MECC registries is guided by the *Manual of Standards for Cancer Registration [1]*. The manual specifies that certain data items are required for registration, while others are optional. The list of required items includes the following: identification number, sequence number, age at diagnosis, date of birth, sex, residential status, date of diagnosis, basis of diagnosis, primary site code (ICD-O-3), histologic type, behavior and grade, and summary stage.

Inclusion Criteria

For the purposes of this monograph, only those diseases that carry an ICD-O-3 behavior code 3 – i.e., those defined as malignant, with one exception noted below – are counted as cancer. Within this rubric, certain cancers are excluded, namely, basal or squamous cell carcinomas of the skin (which are very numerous in certain populations but almost always nonlethal). Note that, because of the behavior code exclusion, cervical intra-epithelial neoplasia and various carcinomas in situ are not counted here, even though they are recorded at MECC registries. Furthermore, some MECC registries record cases of benign brain tumors, but these too are not counted in this monograph. The one exception to the rule of including only behavior code 3 is the inclusion of in situ bladder carcinomas.

Cancer registries use special rules to decide whether to separately count multiple tumors developing in the same person. Although all the MECC countries follow the rules for counting multiple primary tumors suggested by the International Association of Cancer Registries (IACR), US SEER follows slightly different rules. The major differences are that the SEER Program considers each segment of the colon and rectum a separate primary site, each skin site a separate primary site, and, in general, each breast a separate organ/primary site. Therefore, the rates for colorectal cancers, melanomas, and breast cancers may be slightly higher for SEER than for those registries utilizing the IACR rules.

Data Quality

MECC has regularly conducted exercises to check the quality and standardization of coding across the registries. These exercises have indicated that although some data items are already reliably recorded, others still have some way to go toward achieving the required quality. Specifically, age at diagnosis, major anatomical site (the 3-digit code where the leading “C” is counted as one of the digits – e.g., C34 for Bronchus and Lung), and major histological type are reliably recorded; summary stage is not. For this reason, summary stage information is not included in this monograph.

Equally important to a successful and meaningful population-based registry program is the completeness of coverage of the population; that is, a high proportion of the cancers diagnosed in the population need to be registered. MECC has instituted an external audit program that checks this important issue. The registries participating in this monograph have all been checked by audit and have shown rates of coverage above 90% for the populations concerned.

The quality of data in a population-based cancer registry can be judged by various statistical measures. One measure, the proportion of cases identified solely by death certificate, cannot be applied universally across the MECC registries because death certificates in Cyprus do not carry sufficient information to be used as a source for registration. Another such measure, the proportion of cases that are microscopically verified, is shown in Table 1.2 for the various populations and for the major sites and subsites of cancer. Generally speaking, a high proportion is considered to indicate high quality, but proper interpretation should take into account the level of diagnostic facilities available to and used by the population, and the clinical conventions used for diagnosing cancer. For example, a population with an extensive screening program for prostate cancer

using prostate-specific antigen may include individuals whose cancer diagnosis and treatment are based solely on the results of a clinical test, thus leading to a higher proportion of clinically diagnosed prostate cancers. Similarly, in some populations, diagnosis of lung cancer by radiological imaging might be deemed sufficient for diagnosis in some fairly common clinical situations (e.g., advanced tumors in the elderly). In such a population, a very high proportion of histologically or cytologically diagnosed cases would be an indication that clinically diagnosed cases are being missed.

The data in Table 1.2 indicate generally higher rates of microscopic confirmation in Cyprus, Jordan, and the US SEER populations than in Israel and Egypt. The most likely explanation for the lower rate of microscopic confirmation in Egypt is that the medical facilities afforded to that population rely less on histology or cytology and more on clinical investigations for diagnosing malignancy than in other MECC populations. The most likely explanation for the lower rate of microscopic confirmation at the Israel registry is that the full details of the medical record are not always provided by the hospital to the registry. For some cancers in Israel, where the diagnosis may have been made by histology or cytology and the abstractor is not sure which, an unknown category is coded – the same code used for cases where the basis of diagnosis is completely unknown. Because these cases become indistinguishable from cases with diagnoses of unknown origin, they are therefore counted as "not microscopically confirmed." Now that this problem has been revealed, future coding practice will be revised to avoid this confusion.

Conversely, in some registries and for some cancers, percentages of microscopic confirmation are unrealistically high, which might indicate clinical cases that are missed because persons did not attend hospital or for other reasons.

These observations demonstrate that although the MECC data included in this monograph have reached accepted standards, they still need to be interpreted with an understanding of their potential weaknesses and idiosyncrasies.

REGISTRATION PERIOD

In this report, the period covered by each registry differs, in large part due to the age of the registry. The Israel and Jordan registries cover the 1996-2001 period, the Cyprus registry covers 1998-2001, and the Egypt and US SEER registries cover 1999-2001. MECC has determined that these between-registry differences in the reporting period do not cause serious bias in the comparisons of incidence rates in its populations. Such bias could occur only if there were dramatic changes in incidence rates over the short span of 6 years (1996-2001), and there is no such indication.

STATISTICAL METHODS

The simplest measure of cancer incidence, the *annual crude incidence rate*, is equal to the number of incident cases divided by the person years at risk. However, this measure is greatly influenced by the age distribution of the population, and as explained earlier under "The Registry Populations," the age distributions in the MECC populations vary widely. Two other statistical methods allow a fair comparison of the incidence rates in different populations when the age distributions differ: (1) annual age-specific incidence rates and (2) annual age-standardized incidence rates.

The definition of the *annual age-specific incidence rate* is simply the annual crude incidence rate within a narrowly defined (usually 5-year) specific age group. When these rates are provided, population incidence rates may be compared within age groups. Comparisons done in this fashion are often informative, but a comparison over the 16 age groups (from 0-4 years to 75+ years) is often cumbersome and arduous.

Table 1.2. Overview and Summary Data: Proportions of Microscopic Confirmation, by Site 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		
Site	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female
All sites	96.2%	95.5%	96.9%	85.3%	83.5%	87.0%	86.3%	86.0%	86.7%	81.6%	78.4%	84.9%	98.5%	98.4%	98.7%	95.1%	95.2%	95.0%
Oral cavity and pharynx	97.8%	100.0%	94.3%	93.8%	93.6%	94.0%	95.1%	95.8%	93.8%	96.4%	97.7%	94.8%	98.4%	97.6%	100.0%	98.7%	98.8%	98.3%
Lip	100.0%	100.0%	-	96.1%	95.4%	96.9%	95.3%	96.4%	93.3%	80.0%	100.0%	-	98.3%	97.7%	100.0%	99.6%	99.5%	100.0%
Tongue	100.0%	100.0%	100.0%	94.3%	95.5%	93.2%	100.0%	100.0%	100.0%	96.8%	97.4%	95.8%	98.2%	97.1%	100.0%	98.9%	99.0%	98.7%
Salivary gland	94.4%	100.0%	90.9%	90.6%	91.1%	90.1%	81.8%	84.6%	77.8%	96.4%	96.4%	96.4%	100.0%	100.0%	100.0%	99.0%	99.2%	98.7%
Floor of mouth	100.0%	100.0%	0.0%	97.0%	100.0%	91.7%	-	-	0.0%	100.0%	-	-	92.9%	88.9%	100.0%	99.4%	99.4%	99.2%
Gum and other mouth	100.0%	100.0%	100.0%	93.0%	94.3%	91.6%	95.0%	92.3%	100.0%	98.8%	100.0%	97.7%	100.0%	100.0%	100.0%	98.3%	98.4%	98.1%
Nasopharynx	91.7%	100.0%	80.0%	90.6%	90.8%	90.1%	100.0%	100.0%	100.0%	97.2%	100.0%	90.9%	98.2%	97.5%	100.0%	97.9%	99.0%	95.6%
Tonsil	100.0%	100.0%	-	93.9%	91.7%	100.0%	100.0%	100.0%	0.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	99.6%	99.7%	99.3%
Oropharynx	-	-	0.0%	90.7%	92.0%	88.9%	100.0%	-	-	100.0%	-	100.0%	100.0%	100.0%	-	97.6%	98.0%	96.8%
Hypopharynx	100.0%	-	-	91.7%	88.6%	100.0%	100.0%	100.0%	-	96.4%	100.0%	91.9%	92.9%	88.9%	100.0%	99.0%	98.9%	99.5%
Other oral cavity and pharynx	100.0%	-	-	80.8%	76.5%	88.9%	100.0%	-	-	75.0%	57.1%	100.0%	-	-	-	89.1%	89.0%	89.4%
Digestive system	95.5%	96.4%	94.5%	84.2%	85.2%	83.1%	86.0%	85.1%	87.2%	59.7%	58.2%	62.7%	98.5%	98.7%	98.4%	92.9%	93.5%	92.3%
Esophagus	100.0%	100.0%	100.0%	85.4%	86.7%	83.6%	95.0%	100.0%	83.3%	88.3%	93.1%	80.6%	97.9%	97.0%	100.0%	96.1%	96.8%	94.3%
Stomach	99.0%	98.2%	100.0%	89.9%	90.5%	88.9%	93.2%	95.4%	89.9%	79.6%	81.0%	77.5%	98.8%	98.8%	98.8%	96.8%	97.8%	95.2%
Small intestine	100.0%	100.0%	-	94.1%	95.9%	91.6%	88.5%	86.7%	90.9%	82.1%	75.0%	91.7%	100.0%	100.0%	100.0%	98.1%	98.6%	97.5%
Colon and rectum	99.0%	99.7%	98.2%	91.4%	91.9%	90.9%	91.5%	92.0%	90.9%	84.6%	84.7%	84.5%	99.0%	99.5%	98.5%	97.5%	98.0%	97.0%
Colon excluding rectum	98.7%	99.6%	97.9%	90.5%	91.2%	89.9%	90.8%	90.9%	90.7%	78.3%	78.7%	77.8%	98.9%	99.3%	98.4%	97.1%	97.6%	96.7%
Cecum	98.6%	100.0%	97.4%	94.8%	94.5%	95.1%	95.8%	92.3%	100.0%	96.0%	92.9%	100.0%	100.0%	100.0%	100.0%	98.8%	99.1%	98.6%
Appendix	100.0%	100.0%	-	98.3%	100.0%	97.4%	75.0%	-	-	-	0.0%	-	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
Ascending colon	100.0%	100.0%	100.0%	96.5%	96.3%	96.6%	100.0%	100.0%	100.0%	94.1%	100.0%	83.3%	100.0%	100.0%	100.0%	98.7%	98.9%	98.6%
Hepatic flexure	100.0%	100.0%	100.0%	95.7%	97.3%	94.4%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	93.8%	100.0%	83.3%	99.3%	99.7%	98.9%
Transverse colon	100.0%	100.0%	100.0%	95.9%	97.0%	94.8%	93.3%	100.0%	88.9%	85.7%	72.7%	100.0%	98.0%	95.8%	100.0%	98.9%	99.1%	98.8%
Splenic flexure	100.0%	100.0%	100.0%	95.2%	96.8%	93.7%	85.7%	66.7%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	98.6%	98.9%	98.2%
Descending colon	100.0%	100.0%	100.0%	96.1%	96.3%	95.9%	96.2%	93.8%	100.0%	82.6%	78.6%	88.9%	100.0%	100.0%	100.0%	98.8%	99.2%	98.3%
Sigmoid colon	99.4%	100.0%	98.8%	95.4%	95.7%	95.1%	97.3%	96.1%	98.3%	96.1%	93.5%	100.0%	99.6%	100.0%	99.3%	99.0%	99.1%	98.9%
Colon, NOS‡	97.4%	98.8%	96.1%	75.4%	77.1%	73.7%	75.0%	77.1%	73.1%	60.0%	62.7%	56.7%	98.5%	99.1%	97.9%	63.1%	68.2%	58.7%
Rectum and junction	99.6%	100.0%	99.0%	93.9%	93.8%	94.0%	92.7%	93.8%	91.4%	96.8%	96.6%	97.1%	99.3%	100.0%	98.6%	98.6%	98.9%	98.1%
Rectosigmoid junction	97.8%	100.0%	94.4%	95.2%	95.6%	94.7%	92.3%	95.5%	88.2%	95.6%	96.6%	93.8%	99.4%	100.0%	98.6%	98.9%	99.2%	98.5%
Rectum	100.0%	100.0%	100.0%	93.5%	93.1%	93.8%	92.9%	93.3%	92.2%	97.3%	96.6%	98.1%	99.3%	100.0%	98.6%	98.4%	98.8%	97.9%
Anus, anal canal, and anorectum	100.0%	100.0%	100.0%	96.0%	96.4%	95.5%	100.0%	100.0%	100.0%	93.5%	86.7%	100.0%	100.0%	100.0%	100.0%	99.5%	99.7%	99.3%
Liver and intrahepatic bile duct	89.9%	94.2%	76.5%	56.4%	59.4%	52.3%	73.4%	68.8%	87.5%	40.7%	42.3%	34.5%	97.9%	97.9%	97.8%	71.8%	72.6%	70.2%
Liver	90.0%	93.2%	81.3%	60.8%	63.3%	57.1%	72.6%	68.1%	86.7%	40.5%	42.1%	34.3%	98.0%	97.7%	98.6%	72.0%	72.7%	70.2%
Intrahepatic bile duct	88.9%	100.0%	-	21.2%	19.6%	22.6%	-	-	-	50.0%	50.0%	-	96.4%	100.0%	94.1%	70.9%	71.6%	70.1%
Gallbladder	97.6%	100.0%	96.2%	79.3%	74.3%	80.5%	89.7%	75.0%	93.5%	68.8%	62.5%	75.0%	99.5%	98.2%	100.0%	92.4%	88.8%	93.7%
Other biliary	100.0%	100.0%	100.0%	70.2%	74.2%	66.1%	54.8%	52.6%	58.3%	52.9%	51.7%	54.5%	98.0%	96.7%	100.0%	87.5%	90.9%	83.7%
Pancreas	67.5%	74.3%	56.8%	43.8%	45.6%	41.9%	58.4%	61.0%	52.8%	30.2%	31.7%	28.2%	92.9%	94.5%	90.0%	77.1%	80.1%	74.2%
Retroperitoneum	100.0%	-	-	83.7%	81.8%	85.7%	100.0%	100.0%	100.0%	91.2%	86.7%	94.7%	100.0%	100.0%	100.0%	98.7%	98.8%	98.6%
Peritoneum, omentum, and mesentery	100.0%	0.0%	100.0%	89.2%	95.3%	87.2%	100.0%	-	100.0%	100.0%	0.0%	100.0%	96.8%	93.3%	100.0%	99.0%	100.0%	98.9%

Table 1.2 continued

Site	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
Other digestive organs	-	-	0.0%	80.2%	91.2%	67.2%	81.8%	66.7%	100.0%	80.0%	84.6%	73.1%	100.0%	100.0%	0.0%	82.2%	86.8%	78.0%
Respiratory system	92.0%	91.5%	94.4%	81.8%	82.7%	80.0%	85.5%	87.0%	76.1%	81.7%	82.9%	78.1%	97.6%	97.4%	98.2%	90.5%	91.4%	89.4%
Nose, nasal cavity, and middle ear	100.0%	100.0%	100.0%	93.2%	94.6%	91.5%	90.0%	83.3%	100.0%	96.7%	100.0%	94.1%	100.0%	100.0%	100.0%	98.3%	98.7%	97.8%
Larynx	98.3%	100.0%	83.3%	90.2%	91.5%	82.3%	92.0%	93.2%	77.8%	91.0%	93.2%	66.7%	98.6%	98.5%	100.0%	98.4%	98.6%	97.7%
Lung and bronchus	90.9%	90.1%	94.5%	80.2%	80.7%	79.1%	84.1%	85.6%	74.7%	77.2%	77.8%	75.4%	97.2%	97.1%	97.6%	89.9%	90.6%	89.0%
Pleura	100.0%	100.0%	-	93.6%	94.2%	92.6%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	95.4%	95.4%	95.2%
Trachea, mediastinum, and other respiratory organs	100.0%	100.0%	100.0%	85.6%	86.3%	84.4%	87.5%	100.0%	60.0%	83.3%	85.7%	80.0%	95.2%	92.9%	100.0%	92.6%	92.8%	92.2%
Bones and joints	92.7%	92.9%	92.3%	87.6%	88.9%	85.7%	88.6%	92.0%	84.2%	79.5%	83.0%	75.0%	97.6%	98.2%	96.6%	97.4%	97.6%	97.2%
Soft tissue including heart	93.0%	95.8%	89.5%	91.0%	92.6%	89.0%	89.2%	87.7%	91.1%	94.9%	98.3%	91.6%	99.1%	99.2%	99.0%	98.3%	98.5%	98.0%
Skin excluding basal and squamous	97.3%	100.0%	95.1%	93.1%	93.4%	92.7%	96.7%	96.2%	97.4%	100.0%	100.0%	100.0%	98.3%	98.1%	98.5%	99.0%	98.7%	99.5%
Melanoma of the skin	97.9%	100.0%	96.4%	93.3%	93.4%	93.2%	97.7%	96.2%	100.0%	100.0%	100.0%	100.0%	97.7%	95.7%	100.0%	99.6%	99.5%	99.6%
Other non-epithelial skin	93.3%	100.0%	83.3%	92.3%	93.3%	90.5%	95.7%	96.3%	95.0%	100.0%	100.0%	100.0%	98.9%	100.0%	96.2%	95.4%	93.9%	98.6%
Breast	98.7%	100.0%	98.7%	91.9%	83.3%	92.0%	92.9%	90.9%	92.9%	93.5%	88.5%	93.5%	99.4%	100.0%	99.4%	98.9%	99.6%	98.9%
Female genital system	98.5%	0.0%	98.5%	91.6%	0.0%	91.6%	88.9%	0.0%	88.9%	88.7%	0.0%	88.7%	99.2%	0.0%	99.2%	97.3%	0.0%	97.3%
Cervix uteri	98.6%	0.0%	98.6%	92.6%	0.0%	92.6%	87.0%	0.0%	87.0%	99.0%	0.0%	99.0%	99.5%	0.0%	99.5%	98.8%	0.0%	98.8%
Corpus and uterus, NOS‡	99.6%	0.0%	99.6%	94.7%	0.0%	94.7%	94.4%	0.0%	94.4%	83.1%	0.0%	83.1%	99.0%	0.0%	99.0%	98.9%	0.0%	98.9%
Corpus uteri	99.5%	0.0%	99.5%	97.4%	0.0%	97.4%	98.6%	0.0%	98.6%	98.1%	0.0%	98.1%	99.1%	0.0%	99.1%	99.4%	0.0%	99.4%
Uterus, NOS‡	100.0%	0.0%	100.0%	80.4%	0.0%	80.4%	69.6%	0.0%	69.6%	71.4%	0.0%	71.4%	98.9%	0.0%	98.9%	73.2%	0.0%	73.2%
Ovary	96.5%	0.0%	96.5%	86.4%	0.0%	86.4%	77.3%	0.0%	77.3%	85.7%	0.0%	85.7%	99.2%	0.0%	99.2%	93.6%	0.0%	93.6%
Vagina	100.0%	0.0%	100.0%	96.5%	0.0%	96.5%	100.0%	0.0%	100.0%	100.0%	0.0%	100.0%	100.0%	0.0%	100.0%	98.3%	0.0%	98.3%
Vulva	100.0%	0.0%	100.0%	91.7%	0.0%	91.7%	83.3%	0.0%	83.3%	100.0%	0.0%	100.0%	100.0%	0.0%	100.0%	98.9%	0.0%	98.9%
Other female genital organs	0.0%	0.0%	0.0%	87.4%	0.0%	87.4%	100.0%	0.0%	100.0%	90.0%	0.0%	90.0%	100.0%	0.0%	100.0%	91.5%	0.0%	91.5%
Male genital system	96.0%	96.0%	0.0%	73.2%	73.2%	0.0%	73.8%	73.8%	0.0%	73.3%	73.3%	0.0%	98.6%	98.6%	0.0%	97.6%	97.6%	0.0%
Prostate	95.7%	95.7%	0.0%	72.3%	72.3%	0.0%	71.4%	71.4%	0.0%	70.6%	70.6%	0.0%	98.6%	98.6%	0.0%	97.5%	97.5%	0.0%
Testis	98.2%	98.2%	0.0%	87.7%	87.7%	0.0%	86.0%	86.0%	0.0%	95.2%	95.2%	0.0%	98.5%	98.5%	0.0%	99.6%	99.6%	0.0%
Penis	100.0%	100.0%	0.0%	76.5%	76.5%	0.0%	80.0%	80.0%	0.0%	-	-	0.0%	-	-	0.0%	98.6%	98.6%	0.0%
Other male genital organs	-	-	0.0%	100.0%	100.0%	0.0%	0.0%	0.0%	0.0%	-	-	0.0%	100.0%	100.0%	0.0%	98.3%	98.3%	0.0%
Urinary system	98.3%	98.3%	98.3%	91.7%	92.2%	90.2%	91.7%	94.3%	81.4%	88.3%	88.8%	86.4%	99.5%	99.6%	99.3%	95.9%	96.7%	94.0%
Urinary bladder	99.3%	99.2%	100.0%	94.5%	94.5%	94.3%	95.7%	96.2%	92.1%	88.7%	89.2%	86.8%	99.9%	100.0%	99.2%	98.7%	98.9%	98.2%
Kidney and renal pelvis	94.4%	93.6%	95.7%	85.9%	85.8%	86.0%	82.0%	87.7%	72.3%	85.4%	85.7%	84.8%	98.6%	98.1%	99.4%	90.8%	92.0%	88.9%
Ureter	-	-	-	100.0%	100.0%	100.0%	100.0%	100.0%	0.0%	100.0%	100.0%	-	100.0%	100.0%	-	98.1%	99.0%	96.8%
Other urinary organs	-	-	-	92.6%	97.6%	81.1%	100.0%	-	-	80.0%	80.0%	0.0%	100.0%	100.0%	0.0%	98.8%	99.1%	97.9%
Eye and orbit	80.0%	66.7%	100.0%	67.8%	66.7%	69.1%	83.3%	90.0%	75.0%	90.9%	85.7%	100.0%	97.8%	97.6%	97.9%	73.1%	73.4%	72.8%
Brain and other nervous system	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%
Brain	80.2%	76.5%	84.1%	78.9%	80.4%	77.1%	83.6%	85.3%	80.8%	62.3%	63.4%	61.2%	94.9%	96.0%	93.5%	87.6%	89.9%	84.6%
Cranial nerves and other nervous system	78.9%	81.8%	75.0%	81.9%	90.7%	74.5%	72.7%	100.0%	40.0%	85.4%	82.6%	88.0%	92.5%	94.3%	90.6%	84.9%	85.7%	84.1%

Table 1.2 continued

Site	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
Endocrine system	100.0%	100.0%	100.0%	92.3%	91.0%	92.8%	91.8%	90.6%	92.2%	89.5%	82.7%	94.1%	99.7%	100.0%	99.6%	99.2%	98.7%	99.4%
Thyroid	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%
Other endocrine including thymus	100.0%	100.0%	100.0%	76.2%	75.2%	77.2%	66.7%	73.7%	54.5%	78.3%	75.0%	90.0%	97.7%	100.0%	95.3%	95.2%	96.0%	94.2%
Lymphoma	98.3%	98.5%	98.2%	91.6%	91.7%	91.4%	92.2%	91.9%	92.6%	93.1%	93.8%	91.9%	99.0%	99.3%	98.6%	97.9%	97.9%	97.9%
Hodgkin lymphoma	96.4%	94.6%	97.8%	92.9%	92.9%	92.9%	93.4%	91.9%	95.5%	99.1%	98.7%	100.0%	99.2%	99.5%	98.8%	99.2%	99.1%	99.4%
Hodgkin - Nodal	97.5%	94.4%	100.0%	93.0%	93.0%	93.0%	93.8%	91.8%	96.9%	99.0%	98.6%	100.0%	99.2%	99.4%	98.8%	99.2%	99.1%	99.3%
Hodgkin - Extranodal	75.0%	-	66.7%	87.5%	90.0%	83.3%	75.0%	-	66.7%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	98.6%	97.7%	100.0%
Non-Hodgkin lymphoma	98.9%	99.4%	98.3%	91.3%	91.5%	91.2%	91.8%	91.9%	91.6%	91.9%	92.7%	90.7%	98.9%	99.2%	98.4%	97.7%	97.7%	97.7%
NHL - Nodal	99.0%	99.1%	98.7%	89.9%	89.7%	90.0%	90.4%	90.7%	89.9%	89.7%	91.0%	87.7%	98.7%	99.2%	97.9%	97.3%	97.5%	97.0%
NHL - Extranodal	98.8%	100.0%	97.5%	96.6%	97.0%	96.0%	96.3%	96.2%	96.3%	99.2%	98.6%	100.0%	99.6%	99.4%	100.0%	98.4%	98.0%	98.9%
Myeloma	98.3%	97.0%	100.0%	73.5%	74.8%	71.9%	70.7%	73.3%	68.1%	100.0%	100.0%	100.0%	99.3%	100.0%	98.4%	91.4%	93.1%	89.4%
Leukemia	99.1%	99.3%	98.9%	69.1%	71.5%	66.1%	70.2%	75.5%	62.4%	85.4%	85.5%	85.3%	99.7%	99.6%	99.8%	93.7%	94.7%	92.3%
Lymphocytic leukemia	99.2%	98.7%	100.0%	70.8%	74.0%	66.3%	75.2%	83.3%	61.2%	100.0%	100.0%	100.0%	99.8%	99.8%	100.0%	94.4%	95.5%	92.8%
Acute lymphocytic leukemia	97.9%	96.4%	100.0%	75.5%	80.3%	68.7%	74.0%	82.0%	59.3%	100.0%	100.0%	100.0%	99.8%	99.7%	100.0%	98.4%	98.4%	98.3%
Chronic lymphocytic leukemia	100.0%	100.0%	100.0%	68.2%	70.6%	65.2%	76.1%	88.0%	61.9%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	92.2%	93.9%	89.7%
Other lymphocytic leukemia	100.0%	100.0%	-	81.8%	83.9%	75.0%	80.0%	77.8%	-	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	97.1%	98.0%	95.3%
Myeloid and monocytic leukemia	98.9%	100.0%	97.5%	71.5%	72.5%	70.4%	70.4%	70.8%	69.8%	99.5%	100.0%	99.1%	99.8%	100.0%	99.6%	96.0%	96.6%	95.2%
Acute myeloid leukemia	98.3%	100.0%	96.0%	70.6%	70.8%	70.4%	64.7%	63.5%	66.7%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	96.3%	97.0%	95.4%
Acute monocytic leukemia	-	-	0.0%	67.9%	72.2%	60.0%	100.0%	100.0%	-	-	0.0%	-	100.0%	100.0%	100.0%	98.6%	98.3%	99.2%
Chronic myeloid leukemia	100.0%	100.0%	100.0%	75.5%	76.8%	73.8%	80.0%	86.4%	73.9%	99.0%	100.0%	98.3%	99.5%	100.0%	99.0%	95.2%	95.7%	94.4%
Other myeloid/ monocytic leukemia	100.0%	100.0%	-	62.8%	72.2%	56.0%	-	-	0.0%	-	-	-	100.0%	100.0%	100.0%	93.7%	93.8%	93.5%
Other leukemia	100.0%	100.0%	0.0%	46.4%	49.0%	43.2%	52.5%	63.2%	42.9%	21.3%	28.1%	10.8%	98.6%	97.8%	100.0%	70.6%	72.2%	68.9%
Other acute leukemia	100.0%	100.0%	0.0%	52.8%	54.2%	50.7%	59.1%	60.0%	58.3%	68.8%	76.9%	33.3%	97.8%	96.7%	100.0%	79.9%	82.0%	78.0%
Aleukemic, subleukemic, and NOS‡	-	-	0.0%	36.0%	38.8%	33.3%	44.4%	66.7%	22.2%	11.5%	13.6%	8.8%	100.0%	100.0%	100.0%	61.6%	63.8%	59.1%
Miscellaneous	87.1%	87.1%	87.1%	69.8%	72.0%	67.8%	76.4%	82.0%	68.8%	57.5%	59.6%	54.7%	94.4%	94.3%	94.4%	77.5%	79.9%	75.3%

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.

‡NOS indicates "not otherwise specified."

The annual *age-standardized incidence rate (ASR)* combines these age-specific rates into one summary measure, providing a simpler method of comparing the incidence rates in different populations while adjusting for differences in the age distributions. The 2 main methods for calculating the ASR are the *direct* and the *indirect* method. This monograph follows the tradition established by the *Cancer Incidence in Five Continents* publications and uses the direct method. In order to calculate the ASR, one needs to define a standard population age distribution to which the other populations are referred. The standard population age distribution chosen for this monograph is known as the World Standard, and is shown in Table 1.3.

Also shown in Table 1.3 is a sample calculation of the ASR using data on female breast cancer from the Jordan cancer registry. Although the ASR is a very useful summary measure, it does have limitations. For example, a population with an unusually high rate of breast cancer in pre-menopausal women, but a moderate post-menopausal rate, will not usually display a high ASR because post-menopausal rates tend to dominate the value of the age-standardized rate. Therefore, examination of both age-standardized and age-specific rates is advised.

As shown earlier, the MECC registry populations (aside from US SEER) are not very large; consequently, the numbers of cancer cases also are not very large. After subdivision into type of cancer and sex, the numbers of cases in each 5-year age group are in many cases small. Therefore, for each type of cancer, MECC has chosen age groups broader than 5 years to present the age-specific incidence rates. However, when choosing a wider range – e.g., 0-30 years – the problem of age distribution differences between the populations re-emerges. Therefore, the direct age-standardization method has been applied to these broader age groups as well, to ensure comparability of rates across the populations. This method is illustrated in Table 1.4. Although the resulting rates are thus also "age-standardized," they are called age-specific rates in this monograph because they refer to the incidence rates in a particular age interval.

ASRs are presented throughout this monograph as annual rates per 100,000 persons, with one exception: In Chapter 15, childhood cancer annual rates are per million, to conform to most other publications on childhood cancer incidence rates.

To caution against drawing strong conclusions on the basis of small numbers, MECC adopted the following conventions for tables of rates or percentages: Rates or percentages based on 0 or 3-15 cases

Table 1.3. Overview and Summary Data: Sample Calculation of Age-Standardized Incidence Rate* in Jordan, Using the Standard World Distribution

Age (y)	World Population	Jordan Breast Cancer Incidence Rate per 100,000 Women	Expected Cases in World Population
X	W_x	R_x	$E_x=W_xR_x/10^5$
0-4 y	120,000	0	0
5-9 y	100,000	0	0
10-14 y	90,000	0	0
15-19 y	90,000	0.1	0.1
20-24 y	80,000	0.8	0.6
25-29 y	80,000	5.7	4.6
30-34 y	60,000	20.8	12.5
35-39 y	60,000	47.1	28.3
40-44 y	60,000	73.6	44.2
45-49 y	60,000	82.6	49.6
50-54 y	50,000	129.3	64.6
55-59 y	40,000	114.6	45.8
60-64 y	40,000	134.8	53.9
65-69 y	30,000	131.1	39.3
70-74 y	20,000	103.0	20.6
75+ y	20,000	77.6	15.5
All ages	1,000,000	21.2	379.6

*Age-standardized rate = $\sum E_x / \sum W_x$ = 379.6/ 1,000,000 = 38.0 per 100,000.

are italicized, and those based on 1-2 cases are omitted (indicated by a hyphen).

The standard error of an ASR is an expression of the uncertainty of the estimated rate due to sampling variation. It is calculated assuming that the number of cases diagnosed in each year has a Poisson distribution. The standard errors given in this monograph were calculated using the SEER*Stat package (http://seer.cancer.gov/seerstat/) *[2]*.

Table 1.4. Overview and Summary Data: Calculation of Age-Standardized Incidence Rates for Selected Age Ranges, Using the Standard World Distribution

Age	World Population	Jordan Breast Cancer Incidence Rate per 100,000	Expected Cases in World Population	Age-Standardized Rate in the Age Range
X	W_x	R_x	$E_x=W_xR_x/10^5$	$E_x/(W_x/10^5)$
0-4 y	120,000	0.0	0.0	
5-9 y	100,000	0.0	0.0	
10-14 y	90,000	0.0	0.0	
15-19 y	90,000	0.1	0.1	
20-24 y	80,000	0.8	0.6	
25-29 y	80,000	5.7	4.6	
30-34 y	60,000	20.8	12.5	
35-39 y	60,000	47.1	28.3	
0-39 y	680,000*	-	47.1*	6.9
40-44 y	60,000	73.6	44.2	
45-49 y	60,000	82.6	49.6	
40-49 y	120,000*	-	93.8*	78.2
50-54 y	50,000	129.3	64.6	
55-59 y	40,000	114.6	45.8	
50-59 y	90,000*	-	110.4*	122.7
60-64 y	40,000	134.8	53.9	
65-69 y	30,000	131.1	39.3	
60-69 y	70,000*		93.2*	133.1
70-74 y	20,000	103.0	20.6	
75+ y	20,000	77.6	15.5	
70+ y	40,000*	-	36.1*	90.2

* Obtained by summing over the 5-year age groups within the given age range.

SUMMARY TABLES

Table 1.5 displays the numbers of cases registered at each registry over the period covered. Note that the numbers are particularly influenced by the length of the reporting period for each registry. To obtain average annual numbers of cases, the reader is required to divide the numbers for Israel and Jordan by 6, the numbers for Cyprus by 4, and the numbers for Egypt and SEER by 3.

The average annual total numbers of cases in the MECC populations were approximately: US SEER, 325,000; Israeli Jews, 17,500; Egyptians, 3,500; Jordanians, 3,000; Cypriots, 1,500; and Israeli Arabs, 1,000. These numbers are influenced principally by the size of the populations (see Table 1.1). Age distribution is also a strong factor. Thus, although the Cypriot population is fewer in number than the Israeli Arab population, it had more cases of cancer, mainly because it is an older population.

Table 1.6 shows the proportions of all cancer cases that are due to a particular cancer type. This is useful for gaining impressions of the distribution of cancers in different populations, but cannot be used for comparing incidence rates. The table shows similarities and differences. Cancer of the digestive system accounted for about 20% of all cancers; and cancer of the breast, about 33% of female cancers – with relatively little variation across the populations. However, cancer of the male genital system (mostly prostate) accounted for as little as 4% of male cancers in Egypt, compared with 33% in US SEER. As might be expected, the younger populations (Israeli Arabs, Jordanians, and Egyptians) had a greater proportion of leukemias and lymphomas than the older populations (Cypriots, Israeli Jews, and US SEER).

Table 1.5. Overview and Summary Data: Number of Cases, by Site 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		
Site	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female
All Sites	6,152	3,139	3,013	104,913	49,952	54,961	5,961	3,210	2,751	10,455	5,284	5,171	18,261	9,242	9,019	501,182	257,009	244,173
Oral cavity and pharynx	91	56	35	2,116	1,179	937	143	95	48	391	219	172	441	287	154	11,194	7,447	3,747
Lip	8	7	1	904	481	423	43	28	15	5	3	2	58	44	14	975	751	224
Tongue	19	11	8	265	133	132	11	8	3	62	38	24	55	34	21	2,773	1,828	945
Salivary gland	18	7	11	299	168	131	22	13	9	56	28	28	75	38	37	1,300	743	557
Floor of mouth	4	4	0	33	21	12	2	2	0	3	2	1	14	9	5	774	523	251
Gum and other mouth	18	11	7	242	123	119	20	13	7	82	38	44	39	26	13	1,788	941	847
Nasopharynx	12	7	5	223	152	71	31	22	9	72	50	22	169	118	51	759	508	251
Tonsil	4	3	1	33	24	9	3	3	0	11	5	6	10	4	6	1,412	1,113	299
Oropharynx	2	2	0	43	25	18	3	1	2	4	1	3	5	4	1	339	244	95
Hypopharynx	3	2	1	48	35	13	5	3	2	84	47	37	14	9	5	807	614	193
Other oral cavity and pharynx	3	2	1	26	17	9	3	2	1	12	7	5	2	1	1	267	182	85
Digestive system	1,224	661	563	24,992	12,886	12,106	1,053	591	462	2,036	1,358	678	3,356	1,868	1,488	95,525	50,563	44,962
Esophagus	23	19	4	665	390	275	20	14	6	94	58	36	144	99	45	4,826	3,616	1,210
Stomach	198	112	86	3,605	2,169	1,436	177	108	69	206	126	80	687	434	253	9,235	5,541	3,694
Small Intestine	12	10	2	288	169	119	26	15	11	28	16	12	86	56	30	1,823	954	869
Colon and rectum	697	355	342	15,533	7,805	7,728	550	287	263	455	261	194	1,654	845	809	55,480	27,892	27,588
Colon excluding rectum	475	237	238	11,463	5,627	5,836	357	175	182	300	174	126	1,061	546	515	40,008	19,161	20,847
Cecum	73	34	39	1,179	542	637	24	13	11	25	14	11	41	22	19	9,260	3,995	5,265
Appendix	6	5	1	60	21	39	4	2	2	2	0	2	8	5	3	531	249	282
Ascending colon	28	12	16	1,795	871	924	60	32	28	17	11	6	44	27	17	6,603	2,971	3,632
Hepatic flexure	9	4	5	327	148	179	11	4	7	16	13	3	16	10	6	2,284	1,088	1,196
Transverse colon	18	10	8	607	297	310	15	6	9	21	11	10	49	24	25	3,682	1,670	2,012
Splenic flexure	10	5	5	313	154	159	7	3	4	10	5	5	20	10	10	1,477	793	684
Descending colon	20	12	8	922	459	463	26	16	10	23	14	9	30	16	14	2,345	1,217	1,128
Sigmoid colon	155	75	80	3,350	1,713	1,637	110	51	59	51	31	20	253	111	142	11,831	6,256	5,575
Colon, NOS†	156	80	76	2,910	1,422	1,488	100	48	52	135	75	60	600	321	279	1,995	922	1,073
Rectum and junction	222	118	104	4,070	2,178	1,892	193	112	81	155	87	68	593	299	294	15,472	8,731	6,741
Rectosigmoid junction	46	28	18	977	546	431	39	22	17	45	29	16	161	87	74	4,543	2,487	2,056
Rectum	176	90	86	3,093	1,632	1,461	154	90	64	110	58	52	432	212	220	10,929	6,244	4,685
Anus, anal canal, and anorectum	8	4	4	224	112	112	8	5	3	31	15	16	52	36	16	1,487	643	844
Liver and intrahepatic bile duct	69	52	17	900	525	375	64	48	16	848	671	177	233	143	90	6,581	4,463	2,118
Liver	60	44	16	801	479	322	62	47	15	830	655	175	205	132	73	5,736	4,013	1,723
Intrahepatic bile duct	9	8	1	99	46	53	2	1	1	18	16	2	28	11	17	845	450	395
Gallbladder	84	32	52	363	70	293	39	8	31	16	8	8	182	55	127	1,281	330	951
Other biliary	9	5	4	325	163	162	31	19	12	51	29	22	49	30	19	1,665	878	787
Pancreas	114	70	44	2,658	1,306	1,352	113	77	36	205	120	85	197	127	70	11,440	5,647	5,793
Retroperitoneum	3	1	2	129	66	63	8	3	5	34	15	19	35	22	13	466	248	218

Table 1.5 continued

	Cyprus 1998-2001			Israel (Jews) 1996-2001			Israel (Arabs) 1996-2001			Egypt 1999-2001			Jordan 1996-2001			US SEER* 1999-2001		
Site	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female
Peritoneum, omentum, and mesentery	6	0	6	176	43	133	6	1	5	3	0	3	31	15	16	723	101	622
Other digestive organs	1	1	0	126	68	58	11	6	5	65	39	26	6	6	0	518	250	268
Respiratory system	600	493	107	8,797	5,966	2,831	855	738	117	706	537	169	1,797	1,518	279	69,363	39,393	29,970
Nose, nasal cavity, and middle ear	9	6	3	133	74	59	10	6	4	30	13	17	42	22	20	712	399	313
Larynx	59	53	6	886	756	130	112	103	9	145	133	12	365	335	30	3,927	3,107	820
Lung and bronchus	514	423	91	7,402	4,892	2,510	706	611	95	496	370	126	1,336	1,128	208	63,559	34,973	28,586
Pleura	8	6	2	188	120	68	11	7	4	23	14	9	33	19	14	949	762	187
Trachea, mediastinum, and other respiratory organs	10	5	5	188	124	64	16	11	5	12	7	5	21	14	7	216	152	64
Bones and joints	41	28	13	403	235	168	44	25	19	156	88	68	287	171	116	955	534	421
Soft tissue including heart	43	24	19	910	510	400	102	57	45	236	117	119	228	131	97	3,236	1,830	1,406
Skin excluding basal and squamous	110	49	61	4,808	2,578	2,230	91	53	38	49	31	18	175	108	67	22,112	12,761	9,351
Melanoma of the skin	95	40	55	3,698	1,845	1,853	44	26	18	22	11	11	87	46	41	19,235	10,810	8,425
Other non-epithelial skin	15	9	6	1,110	733	377	47	27	20	27	20	7	88	62	26	2,877	1,951	926
Breast	1,076	10	1,066	17,528	203	17,325	773	11	762	1,971	26	1,945	2,975	45	2,930	79,368	566	78,802
Female genital system	469	0	469	5,783	0	5,783	305	0	305	470	0	470	1,028	0	1,028	29,838	0	29,838
Cervix uteri	70	0	70	922	0	922	54	0	54	96	0	96	194	0	194	5,284	0	5,284
Corpus and uterus, NOS†	225	0	225	2,645	0	2,645	161	0	161	124	0	124	405	0	405	14,129	0	14,129
Corpus uteri	218	0	218	2,227	0	2,227	138	0	138	54	0	54	217	0	217	13,849	0	13,849
Uterus, NOS†	7	0	7	418	0	418	23	0	23	70	0	70	188	0	188	280	0	280
Ovary	143	0	143	1,749	0	1,749	75	0	75	210	0	210	372	0	372	8,233	0	8,233
Vagina	6	0	6	86	0	86	5	0	5	6	0	6	14	0	14	419	0	419
Vulva	25	0	25	254	0	254	6	0	6	24	0	24	23	0	23	1,351	0	1,351
Other female genital organs	0	0	0	127	0	127	4	0	4	10	0	10	20	0	20	422	0	422
Male genital system	799	799	0	9,321	9,321	0	324	324	0	217	217	0	896	896	0	84,094	84,094	0
Prostate	727	727	0	8,735	8,735	0	269	269	0	194	194	0	693	693	0	80,331	80,331	0
Testis	55	55	0	554	554	0	50	50	0	21	21	0	194	194	0	3,224	3,224	0
Penis	15	15	0	17	17	0	5	5	0	1	1	0	1	1	0	367	367	0
Other male genital organs	2	2	0	15	15	0	0	0	0	1	1	0	8	8	0	172	172	0
Urinary system	588	467	121	9,596	7,114	2,482	434	348	86	1,239	967	272	1,467	1,187	280	34,619	24,080	10,539
Urinary bladder	460	387	73	6,215	4,991	1,224	299	261	38	1,057	852	205	1,038	915	123	21,355	15,893	5,462
Kidney and renal pelvis	124	78	46	3,152	1,967	1,185	128	81	47	171	105	66	418	262	156	12,409	7,650	4,759
Ureter	2	1	1	108	72	36	4	4	0	6	5	1	8	7	1	529	308	221
Other urinary organs	2	1	1	121	84	37	3	2	1	5	5	0	3	3	0	326	229	97
Eye and orbit	10	6	4	143	75	68	18	10	8	22	14	8	89	41	48	811	447	364

Table 1.5 continued

Site	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
Brain and other nervous system	150	79	71	1,690	939	751	200	122	78	324	165	159	875	506	369	7,060	3,964	3,096
Brain	131	68	63	1,596	896	700	189	116	73	276	142	134	808	471	337	6,611	3,761	2,850
Cranial nerves and other nervous system	19	11	8	94	43	51	11	6	5	48	23	25	67	35	32	449	203	246
Endocrine system	189	44	145	2,618	659	1,959	257	64	193	200	81	119	705	217	488	9,371	2,527	6,844
Thyroid	179	40	139	2,404	546	1,858	227	45	182	154	45	109	617	172	445	8,684	2,152	6,532
Other endocrine including thymus	10	4	6	214	113	101	30	19	11	46	36	10	88	45	43	687	375	312
Lymphoma	357	194	163	6,638	3,371	3,267	615	346	269	1,316	820	496	1,733	1,042	691	23,698	12,913	10,785
Hodgkin lymphoma	83	37	46	1,030	521	509	166	99	67	218	151	67	639	383	256	3,099	1,706	1,393
Hodgkin - Nodal	79	36	43	1,014	511	503	162	98	64	210	147	63	605	359	246	3,027	1,663	1,364
Hodgkin - Extranodal	4	1	3	16	10	6	4	1	3	8	4	4	34	24	10	72	43	29
Non-Hodgkin lymphoma	274	157	117	5,608	2,850	2,758	449	247	202	1,098	669	429	1,094	659	435	20,599	11,207	9,392
NHL - Nodal	191	114	77	4,385	2,155	2,230	342	194	148	848	523	325	829	496	333	13,712	7,494	6,218
NHL - Extranodal	83	43	40	1,223	695	528	107	53	54	250	146	104	265	163	102	6,887	3,713	3,174
Myeloma	58	33	25	1,338	711	627	92	45	47	68	47	21	268	143	125	5,849	3,125	2,724
Leukemia	223	134	89	3,220	1,790	1,430	325	192	133	515	283	232	1,354	782	572	13,178	7,528	5,650
Lymphocytic leukemia	127	78	49	1,728	1,001	727	133	84	49	218	131	87	662	403	259	5,981	3,570	2,411
Acute lymphocytic leukemia	48	28	20	322	188	134	77	50	27	122	69	53	486	294	192	1,721	945	776
Chronic lymphocytic leukemia	68	41	27	1,252	695	557	46	25	21	87	56	31	144	89	55	3,769	2,283	1,486
Other lymphocytic leukemia	11	9	2	154	118	36	10	9	1	9	6	3	32	20	12	491	342	149
Myeloid and monocytic leukemia	92	52	40	1,229	644	585	152	89	63	203	95	108	553	290	263	6,382	3,545	2,837
Acute myeloid leukemia	60	35	25	840	431	409	102	63	39	98	52	46	308	169	139	4,139	2,242	1,897
Acute monocytic leukemia	1	1	0	28	18	10	4	3	1	2	0	2	29	15	14	290	172	118
Chronic myeloid leukemia	26	12	14	318	177	141	45	22	23	101	42	59	194	95	99	1,795	1,050	745
Other myeloid/ monocytic leukemia	5	4	1	43	18	25	1	1	0	2	1	1	22	11	11	158	81	77
Other leukemia	4	4	0	263	145	118	40	19	21	94	57	37	139	89	50	815	413	402
Other acute leukemia	3	3	0	163	96	67	22	10	12	16	13	3	92	60	32	398	189	209
Aleukemic, subleukemic, and NOS†	1	1	0	100	49	51	18	9	9	78	44	34	47	29	18	417	224	193
Miscellaneous	124	62	62	5,012	2,415	2,597	330	189	141	539	314	225	587	300	287	10,911	5,237	5,674

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

†NOS indicates "not otherwise specified."

Table 1.6. Overview and Summary Data: Number and Proportions of Cases, by Site 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		
Site	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female
Total cases	6,152	3,139	3,013	104,913	49,952	54,961	5,961	3,210	2,751	10,455	5,284	5,171	18,261	9,242	9,019	501,182	257,009	244,173
Oral cavity and pharynx	1.5%	1.8%	1.2%	2.0%	2.4%	1.7%	2.4%	3.0%	1.7%	3.7%	4.1%	3.3%	2.4%	3.1%	1.7%	2.2%	2.9%	1.5%
Lip	0.1%	0.2%	-	0.9%	1.0%	0.8%	0.7%	0.9%	0.5%	0.0%	0.1%	-	0.3%	0.5%	0.2%	0.2%	0.3%	0.1%
Tongue	0.3%	0.4%	0.3%	0.3%	0.3%	0.2%	0.2%	0.3%	0.1%	0.6%	0.7%	0.5%	0.3%	0.4%	0.2%	0.6%	0.7%	0.4%
Salivary gland	0.3%	0.2%	0.4%	0.3%	0.3%	0.2%	0.4%	0.4%	0.3%	0.5%	0.5%	0.5%	0.4%	0.4%	0.4%	0.3%	0.3%	0.2%
Floor of mouth	0.1%	0.1%	0.0%	0.0%	0.0%	0.0%	-	-	0.0%	0.0%	-	-	0.1%	0.1%	0.1%	0.2%	0.2%	0.1%
Gum and other mouth	0.3%	0.4%	0.2%	0.2%	0.2%	0.2%	0.3%	0.4%	0.3%	0.8%	0.7%	0.9%	0.2%	0.3%	0.1%	0.4%	0.4%	0.3%
Nasopharynx	0.2%	0.2%	0.2%	0.2%	0.3%	0.1%	0.5%	0.7%	0.3%	0.7%	0.9%	0.4%	0.9%	1.3%	0.6%	0.2%	0.2%	0.1%
Tonsil	0.1%	0.1%	-	0.0%	0.0%	0.0%	0.1%	0.1%	0.0%	0.1%	0.1%	0.1%	0.1%	0.0%	0.1%	0.3%	0.4%	0.1%
Oropharynx	-	-	0.0%	0.0%	0.1%	0.0%	0.1%	-	-	0.0%	-	0.1%	0.0%	0.0%	-	0.1%	0.1%	0.0%
Hypopharynx	0.0%	-	-	0.0%	0.1%	0.0%	0.1%	0.1%	-	0.8%	0.9%	0.7%	0.1%	0.1%	0.1%	0.2%	0.2%	0.1%
Other oral cavity and pharynx	0.0%	-	-	0.0%	0.0%	0.0%	0.1%	-	-	0.1%	0.1%	0.1%	-	-	-	0.1%	0.1%	0.0%
Digestive system	19.9%	21.1%	18.7%	23.8%	25.8%	22.0%	17.7%	18.4%	16.8%	19.5%	25.7%	13.1%	18.4%	20.2%	16.5%	19.1%	19.7%	18.4%
Esophagus	0.4%	0.6%	0.1%	0.6%	0.8%	0.5%	0.3%	0.4%	0.2%	0.9%	1.1%	0.7%	0.8%	1.1%	0.5%	1.0%	1.4%	0.5%
Stomach	3.2%	3.6%	2.9%	3.4%	4.3%	2.6%	3.0%	3.4%	2.5%	2.0%	2.4%	1.5%	3.8%	4.7%	2.8%	1.8%	2.2%	1.5%
Small intestine	0.2%	0.3%	-	0.3%	0.3%	0.2%	0.4%	0.5%	0.4%	0.3%	0.3%	0.2%	0.5%	0.6%	0.3%	0.4%	0.4%	0.4%
Colon and rectum	11.3%	11.3%	11.4%	14.8%	15.6%	14.1%	9.2%	8.9%	9.6%	4.4%	4.9%	3.8%	9.1%	9.1%	9.0%	11.1%	10.9%	11.3%
Colon excluding rectum	7.7%	7.6%	7.9%	10.9%	11.3%	10.6%	6.0%	5.5%	6.6%	2.9%	3.3%	2.4%	5.8%	5.9%	5.7%	8.0%	7.5%	8.5%
Cecum	1.2%	1.1%	1.3%	1.1%	1.1%	1.2%	0.4%	0.4%	0.4%	0.2%	0.3%	0.2%	0.2%	0.2%	0.2%	1.8%	1.6%	2.2%
Appendix	0.1%	0.2%	-	0.1%	0.0%	0.1%	0.1%	-	-	-	0.0%	-	0.0%	0.1%	0.0%	0.1%	0.1%	0.1%
Ascending colon	0.5%	0.4%	0.5%	1.7%	1.7%	1.7%	1.0%	1.0%	1.0%	0.2%	0.2%	0.1%	0.2%	0.3%	0.2%	1.3%	1.2%	1.5%
Hepatic flexure	0.1%	0.1%	0.2%	0.3%	0.3%	0.3%	0.2%	0.1%	0.3%	0.2%	0.2%	0.1%	0.1%	0.1%	0.1%	0.5%	0.4%	0.5%
Transverse colon	0.3%	0.3%	0.3%	0.6%	0.6%	0.6%	0.3%	0.2%	0.3%	0.2%	0.2%	0.2%	0.3%	0.3%	0.3%	0.7%	0.7%	0.8%
Splenic flexure	0.2%	0.2%	0.2%	0.3%	0.3%	0.3%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.3%	0.3%	0.3%
Descending colon	0.3%	0.4%	0.3%	0.9%	0.9%	0.8%	0.4%	0.5%	0.4%	0.2%	0.3%	0.2%	0.2%	0.2%	0.2%	0.5%	0.5%	0.5%
Sigmoid colon	2.5%	2.4%	2.7%	3.2%	3.4%	3.0%	1.8%	1.6%	2.1%	0.5%	0.6%	0.4%	1.4%	1.2%	1.6%	2.4%	2.4%	2.3%
Colon, NOS‡	2.5%	2.5%	2.5%	2.8%	2.8%	2.7%	1.7%	1.5%	1.9%	1.3%	1.4%	1.2%	3.3%	3.5%	3.1%	0.4%	0.4%	0.4%
Rectum and junction	3.6%	3.8%	3.5%	3.9%	4.4%	3.4%	3.2%	3.5%	2.9%	1.5%	1.6%	1.3%	3.2%	3.2%	3.3%	3.1%	3.4%	2.8%
Rectosigmoid junction	0.7%	0.9%	0.6%	0.9%	1.1%	0.8%	0.7%	0.7%	0.6%	0.4%	0.5%	0.3%	0.9%	0.9%	0.8%	0.9%	1.0%	0.8%
Rectum	2.9%	2.9%	2.9%	2.9%	3.3%	2.7%	2.6%	2.8%	2.3%	1.1%	1.1%	1.0%	2.4%	2.3%	2.4%	2.2%	2.4%	1.9%
Anus, anal canal, and anorectum	0.1%	0.1%	0.1%	0.2%	0.2%	0.2%	0.1%	0.2%	0.1%	0.3%	0.3%	0.3%	0.3%	0.4%	0.2%	0.3%	0.3%	0.3%
Liver and intrahepatic bile duct	1.1%	1.7%	0.6%	0.9%	1.1%	0.7%	1.1%	1.5%	0.6%	8.1%	12.7%	3.4%	1.3%	1.5%	1.0%	1.3%	1.7%	0.9%
Liver	1.0%	1.4%	0.5%	0.8%	1.0%	0.6%	1.0%	1.5%	0.5%	7.9%	12.4%	3.4%	1.1%	1.4%	0.8%	1.1%	1.6%	0.7%
Intrahepatic bile duct	0.1%	0.3%	-	0.1%	0.1%	0.1%	-	-	-	0.2%	0.3%	-	0.2%	0.1%	0.2%	0.2%	0.2%	0.2%
Gallbladder	1.4%	1.0%	1.7%	0.3%	0.1%	0.5%	0.7%	0.3%	1.1%	0.2%	0.2%	0.2%	1.0%	0.6%	1.4%	0.3%	0.1%	0.4%
Other biliary	0.1%	0.2%	0.1%	0.3%	0.3%	0.3%	0.5%	0.6%	0.4%	0.5%	0.5%	0.4%	0.3%	0.3%	0.2%	0.3%	0.3%	0.3%
Pancreas	1.9%	2.2%	1.5%	2.5%	2.6%	2.5%	1.9%	2.4%	1.3%	2.0%	2.3%	1.6%	1.1%	1.4%	0.8%	2.3%	2.2%	2.4%
Retroperitoneum	0.0%	-	-	0.1%	0.1%	0.1%	0.1%	0.1%	0.2%	0.3%	0.3%	0.4%	0.2%	0.2%	0.1%	0.1%	0.1%	0.1%
Peritoneum, omentum, and mesentery	0.1%	0.0%	0.2%	0.2%	0.1%	0.2%	0.1%	-	0.2%	0.0%	0.0%	0.1%	0.2%	0.2%	0.2%	0.1%	0.0%	0.3%
Other digestive organs	-	-	0.0%	0.1%	0.1%	0.1%	0.2%	0.2%	0.2%	0.6%	0.7%	0.5%	0.0%	0.1%	0.0%	0.1%	0.1%	0.1%

Table 1.6. continued

Site	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
Respiratory system	9.8%	15.7%	3.6%	8.4%	11.9%	5.2%	14.3%	23.0%	4.3%	6.8%	10.2%	3.3%	9.8%	16.4%	3.1%	13.8%	15.3%	12.3%
Nose, nasal cavity, and middle ear	0.1%	0.2%	0.1%	0.1%	0.1%	0.1%	0.2%	0.2%	0.1%	0.3%	0.2%	0.3%	0.2%	0.2%	0.2%	0.1%	0.2%	0.1%
Larynx	1.0%	1.7%	0.2%	0.8%	1.5%	0.2%	1.9%	3.2%	0.3%	1.4%	2.5%	0.2%	2.0%	3.6%	0.3%	0.8%	1.2%	0.3%
Lung and bronchus	8.4%	13.5%	3.0%	7.1%	9.8%	4.6%	11.8%	19.0%	3.5%	4.7%	7.0%	2.4%	7.3%	12.2%	2.3%	12.7%	13.6%	11.7%
Pleura	0.1%	0.2%	-	0.2%	0.2%	0.1%	0.2%	0.2%	0.1%	0.2%	0.3%	0.2%	0.2%	0.2%	0.2%	0.2%	0.3%	0.1%
Trachea, mediastinum, and other respiratory organs	0.2%	0.2%	0.2%	0.2%	0.2%	0.1%	0.3%	0.3%	0.2%	0.1%	0.1%	0.1%	0.1%	0.2%	0.1%	0.0%	0.1%	0.0%
Bones and joints	0.7%	0.9%	0.4%	0.4%	0.5%	0.3%	0.7%	0.8%	0.7%	1.5%	1.7%	1.3%	1.6%	1.9%	1.3%	0.2%	0.2%	0.2%
Soft tissue including heart	0.7%	0.8%	0.6%	0.9%	1.0%	0.7%	1.7%	1.8%	1.6%	2.3%	2.2%	2.3%	1.2%	1.4%	1.1%	0.6%	0.7%	0.6%
Skin excluding basal and squamous	1.8%	1.6%	2.0%	4.6%	5.2%	4.1%	1.5%	1.7%	1.4%	0.5%	0.6%	0.3%	1.0%	1.2%	0.7%	4.4%	5.0%	3.8%
Melanoma of the skin	1.5%	1.3%	1.8%	3.5%	3.7%	3.4%	0.7%	0.8%	0.7%	0.2%	0.2%	0.2%	0.5%	0.5%	0.5%	3.8%	4.2%	3.5%
Other non-epithelial skin	0.2%	0.3%	0.2%	1.1%	1.5%	0.7%	0.8%	0.8%	0.7%	0.3%	0.4%	0.1%	0.5%	0.7%	0.3%	0.6%	0.8%	0.4%
Breast	17.5%	0.3%	35.4%	16.7%	0.4%	31.5%	13.0%	0.3%	27.7%	18.9%	0.5%	37.6%	16.3%	0.5%	32.5%	15.8%	0.2%	32.3%
Female genital system	7.6%	0.0%	15.6%	5.5%	0.0%	10.5%	5.1%	0.0%	11.1%	4.5%	0.0%	9.1%	5.6%	0.0%	11.4%	6.0%	0.0%	12.2%
Cervix uteri	1.1%	0.0%	2.3%	0.9%	0.0%	1.7%	0.9%	0.0%	2.0%	0.9%	0.0%	1.9%	1.1%	0.0%	2.2%	1.1%	0.0%	2.2%
Corpus and uterus, NOS‡	3.7%	0.0%	7.5%	2.5%	0.0%	4.8%	2.7%	0.0%	5.9%	1.2%	0.0%	2.4%	2.2%	0.0%	4.5%	2.8%	0.0%	5.8%
Corpus uteri	3.5%	0.0%	7.2%	2.1%	0.0%	4.1%	2.3%	0.0%	5.0%	0.5%	0.0%	1.0%	1.2%	0.0%	2.4%	2.8%	0.0%	5.7%
Uterus, NOS‡	0.1%	0.0%	0.2%	0.4%	0.0%	0.8%	0.4%	0.0%	0.8%	0.7%	0.0%	1.4%	1.0%	0.0%	2.1%	0.1%	0.0%	0.1%
Ovary	2.3%	0.0%	4.7%	1.7%	0.0%	3.2%	1.3%	0.0%	2.7%	2.0%	0.0%	4.1%	2.0%	0.0%	4.1%	1.6%	0.0%	3.4%
Vagina	0.1%	0.0%	0.2%	0.1%	0.0%	0.2%	0.1%	0.0%	0.2%	0.1%	0.0%	0.1%	0.1%	0.0%	0.2%	0.1%	0.0%	0.2%
Vulva	0.4%	0.0%	0.8%	0.2%	0.0%	0.5%	0.1%	0.0%	0.2%	0.2%	0.0%	0.5%	0.1%	0.0%	0.3%	0.3%	0.0%	0.6%
Other female genital organs	0.0%	0.0%	0.0%	0.1%	0.0%	0.2%	0.1%	0.0%	0.1%	0.1%	0.0%	0.2%	0.1%	0.0%	0.2%	0.1%	0.0%	0.2%
Male genital system	13.0%	25.5%	0.0%	8.9%	18.7%	0.0%	5.4%	10.1%	0.0%	2.1%	4.1%	0.0%	4.9%	9.7%	0.0%	16.8%	32.7%	0.0%
Prostate	11.8%	23.2%	0.0%	8.3%	17.5%	0.0%	4.5%	8.4%	0.0%	1.9%	3.7%	0.0%	3.8%	7.5%	0.0%	16.0%	31.3%	0.0%
Testis	0.9%	1.8%	0.0%	0.5%	1.1%	0.0%	0.8%	1.6%	0.0%	0.2%	0.4%	0.0%	1.1%	2.1%	0.0%	0.6%	1.3%	0.0%
Penis	0.2%	0.5%	0.0%	0.0%	0.0%	0.0%	0.1%	0.2%	0.0%	-	-	0.0%	-	-	0.0%	0.1%	0.1%	0.0%
Other male genital organs	-	-	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	-	-	0.0%	0.0%	0.1%	0.0%	0.0%	0.1%	0.0%
Urinary system	9.6%	14.9%	4.0%	9.1%	14.2%	4.5%	7.3%	10.8%	3.1%	11.9%	18.3%	5.3%	8.0%	12.8%	3.1%	6.9%	9.4%	4.3%
Urinary bladder	7.5%	12.3%	2.4%	5.9%	10.0%	2.2%	5.0%	8.1%	1.4%	10.1%	16.1%	4.0%	5.7%	9.9%	1.4%	4.3%	6.2%	2.2%
Kidney and renal pelvis	2.0%	2.5%	1.5%	3.0%	3.9%	2.2%	2.1%	2.5%	1.7%	1.6%	2.0%	1.3%	2.3%	2.8%	1.7%	2.5%	3.0%	2.0%
Ureter	-	-	-	0.1%	0.1%	0.1%	0.1%	0.1%	0.0%	0.1%	0.1%	-	0.0%	0.1%	-	0.1%	0.1%	0.1%
Other urinary organs	-	-	-	0.1%	0.2%	0.1%	0.1%	-	-	0.0%	0.1%	0.0%	0.0%	0.0%	0.0%	0.1%	0.1%	0.0%
Eye and orbit	0.2%	0.2%	0.1%	0.1%	0.2%	0.1%	0.3%	0.3%	0.3%	0.2%	0.3%	0.2%	0.5%	0.4%	0.5%	0.2%	0.2%	0.2%
Brain and other nervous system	2.4%	2.5%	2.4%	1.6%	1.9%	1.4%	3.4%	3.8%	2.8%	3.1%	3.1%	3.1%	4.8%	5.5%	4.1%	1.4%	1.5%	1.3%
Brain	2.1%	2.2%	2.1%	1.5%	1.8%	1.3%	3.2%	3.6%	2.7%	2.6%	2.7%	2.6%	4.4%	5.1%	3.7%	1.3%	1.5%	1.2%
Cranial nerves and other nervous system	0.3%	0.4%	0.3%	0.1%	0.1%	0.1%	0.2%	0.2%	0.2%	0.5%	0.4%	0.5%	0.4%	0.4%	0.4%	0.1%	0.1%	0.1%

Table 1.6. continued

Site	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
Endocrine system	3.1%	1.4%	4.8%	2.5%	1.3%	3.6%	4.3%	2.0%	7.0%	1.9%	1.5%	2.3%	3.9%	2.3%	5.4%	1.9%	1.0%	2.8%
Thyroid	2.9%	1.3%	4.6%	2.3%	1.1%	3.4%	3.8%	1.4%	6.6%	1.5%	0.9%	2.1%	3.4%	1.9%	4.9%	1.7%	0.8%	2.7%
Other endocrine including thymus	*0.2%*	*0.1%*	*0.2%*	0.2%	0.2%	0.2%	0.5%	0.6%	*0.4%*	0.4%	0.7%	*0.2%*	0.5%	0.5%	0.5%	0.1%	0.1%	0.1%
Lymphoma	5.8%	6.2%	5.4%	6.3%	6.7%	5.9%	10.3%	10.8%	9.8%	12.6%	15.5%	9.6%	9.5%	11.3%	7.7%	4.7%	5.0%	4.4%
Hodgkin lymphoma	1.4%	1.2%	1.5%	1.0%	1.0%	0.9%	2.8%	3.1%	2.4%	2.1%	2.9%	1.3%	3.5%	4.1%	2.8%	0.6%	0.7%	0.6%
Hodgkin - Nodal	1.3%	1.1%	1.4%	1.0%	1.0%	0.9%	2.7%	3.1%	2.3%	2.0%	2.8%	1.2%	3.3%	3.9%	2.7%	0.6%	0.6%	0.6%
Hodgkin - Extranodal	*0.1%*	-	*0.1%*	0.0%	*0.0%*	*0.0%*	*0.1%*	-	*0.1%*	*0.1%*	*0.1%*	*0.1%*	0.2%	0.3%	*0.1%*	0.0%	0.0%	0.0%
Non-Hodgkin lymphoma	4.5%	5.0%	3.9%	5.3%	5.7%	5.0%	7.5%	7.7%	7.3%	10.5%	12.7%	8.3%	6.0%	7.1%	4.8%	4.1%	4.4%	3.8%
NHL - Nodal	3.1%	3.6%	2.6%	4.2%	4.3%	4.1%	5.7%	6.0%	5.4%	8.1%	9.9%	6.3%	4.5%	5.4%	3.7%	2.7%	2.9%	2.5%
NHL - Extranodal	1.4%	1.4%	1.3%	1.2%	1.4%	1.0%	1.8%	1.7%	2.0%	2.4%	2.8%	2.0%	1.5%	1.8%	1.1%	1.4%	1.4%	1.3%
Myeloma	0.9%	1.1%	0.8%	1.3%	1.4%	1.1%	1.5%	1.4%	1.7%	0.7%	0.9%	0.4%	1.5%	1.5%	1.4%	1.2%	1.2%	1.1%
Leukemia	3.6%	4.3%	3.0%	3.1%	3.6%	2.6%	5.5%	6.0%	4.8%	4.9%	5.4%	4.5%	7.4%	8.5%	6.3%	2.6%	2.9%	2.3%
Lymphocytic leukemia	2.1%	2.5%	1.6%	1.6%	2.0%	1.3%	2.2%	2.6%	1.8%	2.1%	2.5%	1.7%	3.6%	4.4%	2.9%	1.2%	1.4%	1.0%
Acute lymphocytic leukemia	0.8%	0.9%	0.7%	0.3%	0.4%	0.2%	1.3%	1.6%	1.0%	1.2%	1.3%	1.0%	2.7%	3.2%	2.1%	0.3%	0.4%	0.3%
Chronic lymphocytic leukemia	1.1%	1.3%	0.9%	1.2%	1.4%	1.0%	0.8%	0.8%	0.8%	0.8%	1.1%	0.6%	0.8%	1.0%	0.6%	0.8%	0.9%	0.6%
Other lymphocytic leukemia	*0.2%*	*0.3%*	-	0.1%	0.2%	0.1%	*0.2%*	*0.3%*	-	*0.1%*	*0.1%*	*0.1%*	0.2%	0.2%	*0.1%*	0.1%	0.1%	0.1%
Myeloid and monocytic leukemia	1.5%	1.7%	1.3%	1.2%	1.3%	1.1%	2.6%	2.8%	2.3%	1.9%	1.8%	2.1%	3.0%	3.1%	2.9%	1.3%	1.4%	1.2%
Acute myeloid Leukemia	1.0%	1.1%	0.8%	0.8%	0.9%	0.7%	1.7%	2.0%	1.4%	0.9%	1.0%	0.9%	1.7%	1.8%	1.5%	0.8%	0.9%	0.8%
Acute monocytic leukemia	-	-	*0.0%*	0.0%	0.0%	*0.0%*	*0.1%*	*0.1%*	-	-	*0.0%*	-	0.2%	*0.2%*	*0.2%*	0.1%	0.1%	0.0%
Chronic myeloid leukemia	0.4%	*0.4%*	*0.5%*	0.3%	0.4%	0.3%	0.8%	0.7%	0.8%	1.0%	0.8%	1.1%	1.1%	1.0%	1.1%	0.4%	0.4%	0.3%
Other myeloid/ monocytic leukemia	*0.1%*	*0.1%*	-	0.0%	0.0%	0.0%	-	-	*0.0%*	-	-	-	0.1%	*0.1%*	*0.1%*	0.0%	0.0%	0.0%
Other leukemia	*0.1%*	*0.1%*	*0.0%*	0.3%	0.3%	0.2%	0.7%	0.6%	0.8%	0.9%	1.1%	0.7%	0.8%	1.0%	0.6%	0.2%	0.2%	0.2%
Other acute leukemia	*0.0%*	*0.1%*	*0.0%*	0.2%	0.2%	0.1%	0.4%	*0.3%*	*0.4%*	0.2%	*0.2%*	*0.1%*	0.5%	0.7%	0.4%	0.1%	0.1%	0.1%
Aleukemic, Subleukemic, and NOS‡	-	-	*0.0%*	0.1%	0.1%	0.1%	0.3%	*0.3%*	*0.3%*	0.7%	0.8%	0.7%	0.3%	0.3%	0.2%	0.1%	0.1%	0.1%
Miscellaneous	2.0%	2.0%	2.1%	4.8%	4.8%	4.7%	5.5%	5.9%	5.1%	5.2%	5.9%	4.4%	3.2%	3.2%	3.2%	2.2%	2.0%	2.3%

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

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

‡NOS indicates "not otherwise specified."

Table 1.7 shows the ASRs for different cancer types. Two populations, US SEER (318.6) and Israeli Jews (274.4), had substantially higher rates overall, compared with the others. The Cypriot (164.2), Israeli Arab (149.8), and Egyptian (143.0) populations had intermediate rates, while the Jordanian rates (113.3) were the lowest. This same pattern is seen for both males and females.

Comparison of the ASRs across populations for different cancers does not always conform to the overall pattern seen for "all sites." The results for specific sites and types of cancer are reviewed in detail in the remainder of this monograph.

Table 1.8 presents the standard errors of the estimated rates that are shown in Table 1.7. These standard errors may be used to judge the limits of uncertainty in an estimated rate. For example, Table 1.7 shows that the ASR of cancer of the oral cavity and pharynx among females in Cyprus is 1.9, and Table 1.8 shows that its standard error is 0.3. Approximate 95% confidence limits for this rate are therefore given by $1.9 \pm 2x0.3 = (1.3, 2.5)$. In other words, the true rate is very likely to lie between 1.3 and 2.5. As the numbers of cases underlying the estimated rate increase, the standard error becomes smaller relative to the rate. Thus the ASR of breast cancer among Israeli Jewish females is 93.1, and its standard error is 0.7 (less than 1% of the estimate), so that the 95% confidence limits are approximately (91.7, 94.5), meaning that the rate is quite precisely estimated.

The main source of the data presented in the following chapters is the MECC Joint Cancer Registration Project. Other sources that are used for comparative purposes are *Cancer Incidence in Five Continents [3]* and GLOBOCAN *[4]*. The data from the former publication are derived from well-established population-based registries and include a wide range of countries, but are not available for all the world's populations. Data from the latter publication are based on a variety of sources, including population-based registries, hospital-based registries, and population-based mortality records. Although GLOBOCAN's data provide wider coverage than *Cancer Incidence in Five Continents*, they are necessarily less reliable than data based on population-based registry data alone.

Table 1.7. Overview and Summary Data: Age-Standardized Incidence Rates,* by Site 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		
Site	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female
All Sites	164.2	173.3	159.4	274.4	282.6	272.1	149.8	175.7	128.7	143.0	152.6	135.0	113.3	115.2	112.2	318.6	363.8	285.9
Oral cavity and pharynx	2.5	3.1	1.9	5.5	6.9	4.3	3.5	4.8	2.3	5.5	6.4	4.6	2.7	3.5	1.8	7.4	10.9	4.3
Lip	0.2	0.4	-	2.3	2.7	2.0	1.1	1.5	0.7	0.1	0.1	-	0.4	0.6	0.2	0.6	1.0	0.2
Tongue	0.5	0.6	0.4	0.7	0.8	0.6	0.3	0.4	0.1	0.9	1.1	0.7	0.4	0.5	0.3	1.8	2.7	1.1
Salivary gland	0.5	0.3	0.6	0.7	0.9	0.6	0.5	0.6	0.4	0.8	0.8	0.8	0.4	0.5	0.4	0.8	1.0	0.7
Floor of mouth	0.1	0.3	0.0	0.1	0.1	0.1	-	-	0.0	0.0	-	-	0.1	0.1	0.1	0.5	0.8	0.3
Gum and other mouth	0.5	0.6	0.3	0.6	0.8	0.5	0.5	0.7	0.3	1.2	1.2	1.2	0.2	0.3	0.2	1.1	1.4	0.9
Nasopharynx	0.4	0.4	0.3	0.7	1.0	0.4	0.7	1.0	0.5	0.9	1.4	0.5	0.9	1.2	0.5	0.5	0.8	0.3
Tonsil	0.1	0.2	-	0.1	0.1	0.1	0.1	0.2	0.0	0.1	0.1	0.2	0.1	0.0	0.1	1.0	1.7	0.4
Oropharynx	-	-	0.0	0.1	0.2	0.1	0.1	-	-	0.0	-	0.1	0.0	0.1	-	0.2	0.4	0.1
Hypopharynx	0.1	-	-	0.1	0.2	0.1	0.1	0.2	-	1.2	1.4	1.0	0.1	0.1	0.1	0.6	0.9	0.2
Other oral cavity and pharynx	0.1	-	-	0.1	0.1	0.0	0.1	-	-	0.2	0.2	0.1	-	-	-	0.2	0.3	0.1
Digestive system	30.1	35.1	25.8	59.2	69.4	51.3	28.9	34.9	23.6	29.4	40.1	18.9	23.3	25.7	20.9	56.1	69.1	45.4
Esophagus	0.6	1.0	0.2	1.5	2.1	1.0	0.6	0.9	0.3	1.4	1.7	1.0	1.1	1.5	0.7	3.0	5.1	1.2
Stomach	4.9	5.9	4.1	8.5	11.7	6.0	4.6	6.0	3.4	2.9	3.6	2.2	4.8	6.0	3.5	5.3	7.4	3.6
Small intestine	0.3	0.5	-	0.7	1.0	0.5	0.7	0.8	0.6	0.4	0.5	0.3	0.6	0.8	0.4	1.2	1.3	1.0
Colon and rectum	17.3	19.0	16.0	36.9	41.7	33.3	15.2	17.3	13.6	6.0	6.9	5.1	11.3	11.5	11.2	32.0	37.7	27.4
Colon excluding rectum	11.9	12.7	11.2	26.7	29.6	24.7	9.9	10.5	9.4	3.9	4.6	3.3	7.4	7.6	7.2	22.5	25.5	20.0
Cecum	1.8	1.8	1.9	2.6	2.7	2.4	0.7	0.8	0.6	0.3	0.4	0.3	0.3	0.3	0.3	5.0	5.2	4.8
Appendix	0.2	0.3	-	0.2	0.1	0.2	0.1	-	-	-	0.0	-	0.0	0.1	0.0	0.4	0.4	0.4
Ascending colon	0.6	0.6	0.6	4.0	4.4	3.8	1.7	1.8	1.5	0.2	0.3	0.2	0.3	0.4	0.2	3.5	3.8	3.3
Hepatic flexure	0.2	0.2	0.3	0.8	0.8	0.7	0.3	0.3	0.4	0.2	0.3	0.1	0.1	0.1	0.1	1.2	1.4	1.1
Transverse colon	0.5	0.5	0.4	1.4	1.6	1.3	0.4	0.3	0.5	0.3	0.3	0.2	0.3	0.3	0.3	2.0	2.2	1.8
Splenic flexure	0.2	0.3	0.2	0.8	0.8	0.7	0.2	0.2	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.9	1.1	0.7
Descending colon	0.5	0.7	0.4	2.2	2.5	2.0	0.7	1.0	0.5	0.3	0.3	0.2	0.2	0.2	0.2	1.4	1.7	1.2
Sigmoid colon	3.9	4.1	3.8	8.1	9.2	7.3	3.0	3.2	2.9	0.6	0.7	0.5	1.8	1.6	2.0	7.1	8.7	5.9
Colon, NOS§	3.9	4.3	3.6	6.7	7.4	6.2	2.7	2.8	2.6	1.9	2.1	1.6	4.1	4.5	3.8	1.0	1.2	0.9
Rectum and junction	5.4	6.3	4.8	10.1	12.1	8.6	5.4	6.8	4.2	2.0	2.3	1.8	3.9	3.9	4.0	9.6	12.3	7.3
Rectosigmoid junction	1.2	1.6	0.8	2.4	3.0	2.0	1.1	1.4	0.8	0.6	0.7	0.4	1.1	1.1	1.0	2.8	3.5	2.2
Rectum	4.3	4.7	4.0	7.7	9.1	6.6	4.3	5.4	3.4	1.5	1.6	1.4	2.9	2.8	3.0	6.8	8.8	5.1
Anus, anal canal, and anorectum	0.2	0.2	0.2	0.6	0.6	0.5	0.2	0.2	0.1	0.4	0.4	0.5	0.4	0.5	0.2	1.0	0.9	1.0
Liver and intrahepatic bile duct	1.7	2.8	0.8	2.2	3.0	1.6	1.6	2.7	0.6	12.8	20.6	5.2	1.6	1.9	1.3	4.2	6.4	2.4
Liver	1.5	2.4	0.8	2.0	2.7	1.4	1.5	2.6	0.6	12.5	20.1	5.2	1.4	1.7	1.0	3.8	5.8	2.0
Intrahepatic bile duct	0.2	0.4	-	0.2	0.2	0.2	-	-	-	0.3	0.5	-	0.2	0.1	0.3	0.5	0.6	0.4
Gallbladder	1.8	1.5	2.2	0.8	0.4	1.2	1.2	0.6	1.8	0.2	0.2	0.2	1.4	0.8	1.9	0.7	0.4	1.0
Other biliary	0.2	0.3	0.2	0.8	0.9	0.7	0.9	1.2	0.7	0.8	1.0	0.6	0.3	0.4	0.3	0.9	1.2	0.8
Pancreas	2.7	3.8	1.7	6.1	7.1	5.3	3.3	4.8	1.9	3.2	3.7	2.5	1.5	1.8	1.0	6.6	7.7	5.7
Retroperitoneum	0.1	-	-	0.4	0.4	0.3	0.1	0.1	0.1	0.4	0.4	0.4	0.2	0.3	0.1	0.3	0.4	0.3
Peritoneum, omentum, and mesentery	0.1	0.0	0.3	0.5	0.3	0.7	0.2	-	0.2	0.0	0.0	0.1	0.2	0.2	0.2	0.5	0.2	0.8
Other digestive organs	-	-	0.0	0.3	0.4	0.2	0.3	0.3	0.2	0.9	1.1	0.7	0.0	0.1	0.0	0.3	0.3	0.2

Table 1.7. continued

Site	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
Respiratory system	15.8	27.6	5.4	22.8	34.9	13.0	24.4	45.4	5.9	10.8	17.0	4.9	13.1	21.9	4.0	43.1	55.0	33.6
Nose, nasal cavity, and middle ear	0.2	0.3	0.2	0.3	0.4	0.3	0.3	0.3	0.2	0.4	0.3	0.5	0.3	0.3	0.2	0.5	0.6	0.4
Larynx	1.6	3.0	0.2	2.4	4.6	0.6	3.1	6.0	0.5	2.2	4.2	0.3	2.7	4.8	0.4	2.7	4.6	1.0
Lung and bronchus	13.4	23.4	4.7	19.0	28.4	11.4	20.4	38.0	4.8	7.7	11.9	3.7	9.9	16.4	3.1	39.2	48.6	31.9
Pleura	0.2	0.4	-	0.5	0.7	0.3	0.3	0.5	0.2	0.3	0.4	0.3	0.2	0.2	0.2	0.5	1.0	0.2
Trachea, mediastinum, and other respiratory organs	0.4	0.4	0.3	0.6	0.8	0.4	0.4	0.6	0.2	0.1	0.2	0.1	0.1	0.2	0.1	0.2	0.3	0.1
Bones and joints	1.4	2.0	0.8	1.3	1.6	1.0	0.8	0.9	0.7	1.5	1.7	1.4	1.1	1.2	0.9	0.8	0.9	0.7
Soft tissue including heart	1.3	1.4	1.2	2.7	3.2	2.2	2.0	2.3	1.7	2.8	3.0	2.7	1.1	1.3	1.0	2.3	2.8	1.9
Skin excluding basal and squamous	2.9	2.8	3.0	13.4	15.4	11.8	2.1	2.8	1.6	0.7	0.9	0.4	1.1	1.3	0.9	14.5	17.8	11.9
Melanoma of the skin	2.6	2.4	2.7	10.8	11.6	10.2	1.0	1.3	0.8	0.3	0.3	0.3	0.5	0.6	0.5	12.7	15.2	10.9
Other non-epithelial skin	0.4	0.5	0.3	2.6	3.9	1.7	1.1	1.6	0.8	0.4	0.7	0.2	0.5	0.8	0.3	1.8	2.6	1.0
Breast	30.2	0.6	57.7	50.3	1.1	93.1	19.2	0.6	36.7	25.1	0.8	49.6	18.7	0.6	38.0	51.9	0.8	97.2
Female genital system	12.9	0.0	24.6	16.4	0.0	30.5	8.1	0.0	15.5	6.4	0.0	12.7	6.6	0.0	13.7	19.6	0.0	37.1
Cervix uteri	1.9	0.0	3.7	2.8	0.0	5.3	1.3	0.0	2.5	1.3	0.0	2.7	1.3	0.0	2.6	3.6	0.0	7.0
Corpus and uterus, NOS§	6.2	0.0	11.8	7.4	0.0	13.8	4.5	0.0	8.7	1.8	0.0	3.5	2.8	0.0	5.8	9.4	0.0	17.6
Corpus uteri	6.0	0.0	11.5	6.3	0.0	11.6	4.0	0.0	7.5	0.8	0.0	1.6	1.5	0.0	3.1	9.2	0.0	17.3
Uterus, NOS§	0.2	0.0	0.4	1.2	0.0	2.2	0.6	0.0	1.1	1.0	0.0	1.9	1.3	0.0	2.6	0.2	0.0	0.3
Ovary	4.0	0.0	7.7	5.0	0.0	9.4	1.9	0.0	3.6	2.7	0.0	5.4	2.2	0.0	4.6	5.3	0.0	10.0
Vagina	0.2	0.0	0.3	0.2	0.0	0.4	0.1	0.0	0.2	0.1	0.0	0.2	0.1	0.0	0.2	0.3	0.0	0.5
Vulva	0.6	0.0	1.1	0.6	0.0	1.0	0.2	0.0	0.3	0.4	0.0	0.8	0.2	0.0	0.4	0.8	0.0	1.4
Other female genital organs	0.0	0.0	0.0	0.3	0.0	0.6	0.1	0.0	0.2	0.1	0.0	0.2	0.1	0.0	0.3	0.3	0.0	0.5
Male genital system	18.7	40.9	0.0	22.7	51.0	0.0	9.2	20.1	0.0	3.8	8.0	0.0	6.4	12.7	0.0	55.7	122.6	0.0
Prostate	16.4	36.1	0.0	20.7	47.1	0.0	8.4	18.4	0.0	3.6	7.5	0.0	5.6	11.2	0.0	52.9	116.9	0.0
Testis	1.9	3.9	0.0	1.9	3.8	0.0	0.7	1.4	0.0	0.2	0.5	0.0	0.7	1.4	0.0	2.5	4.9	0.0
Penis	0.3	0.7	0.0	0.0	0.1	0.0	0.1	0.3	0.0	-	-	0.0	-	-	0.0	0.2	0.5	0.0
Other male genital organs	-	-	0.0	0.0	0.1	0.0	0.0	0.0	0.0	-	-	0.0	0.0	0.1	0.0	0.1	0.2	0.0
Urinary system	14.9	25.2	6.2	24.1	40.1	11.2	11.9	20.7	4.3	19.2	30.8	8.0	10.4	16.7	3.8	20.9	32.7	11.5
Urinary bladder	11.2	20.5	3.3	15.1	27.5	5.1	8.6	16.0	2.1	16.6	27.5	6.3	7.6	13.2	1.8	12.2	20.9	5.5
Kidney and renal pelvis	3.6	4.6	2.8	8.5	11.8	5.8	3.1	4.3	2.2	2.4	3.0	1.7	2.7	3.4	1.9	8.2	11.1	5.7
Ureter	-	-	-	0.3	0.4	0.2	0.1	0.2	0.0	0.1	0.2	-	0.1	0.1	-	0.3	0.4	0.2
Other urinary organs	-	-	-	0.3	0.4	0.2	0.1	-	-	0.1	0.2	0.0	0.0	0.1	0.0	0.2	0.3	0.1
Eye and orbit	0.3	0.3	0.2	0.4	0.5	0.4	0.3	0.4	0.3	0.3	0.4	0.2	0.4	0.3	0.4	0.6	0.7	0.5
Brain and other nervous system	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
Cranial nerves and other nervous system	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

Table 1.7. continued

Site	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
Endocrine system	6.1	2.9	9.1	8.2	4.2	11.8	4.6	2.4	6.8	2.5	2.0	2.9	3.4	2.1	4.8	6.8	3.8	9.7
Thyroid	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
Other endocrine including thymus	0.4	0.4	0.5	0.7	0.8	0.7	0.5	0.6	0.3	0.5	0.9	0.2	0.4	0.4	0.4	0.6	0.7	0.5
Lymphoma	10.6	12.1	9.3	18.6	20.6	16.9	12.9	14.4	11.4	16.3	20.0	12.6	8.9	10.3	7.4	15.3	18.3	12.6
Hodgkin lymphoma	3.0	2.7	3.3	3.4	3.5	3.3	2.7	3.0	2.3	2.1	2.9	1.4	2.5	3.0	2.0	2.4	2.7	2.2
Hodgkin - Nodal	2.9	2.6	3.1	3.4	3.5	3.3	2.6	3.0	2.2	2.1	2.8	1.3	2.4	2.8	1.9	2.3	2.6	2.1
Hodgkin - Extranodal	0.1	-	0.2	0.1	0.1	0.0	0.1	-	0.1	0.1	0.1	0.1	0.2	0.2	0.1	0.0	0.1	0.0
Non-Hodgkin lymphoma	7.6	9.4	6.0	15.2	17.1	13.6	10.2	11.4	9.1	14.2	17.1	11.3	6.4	7.3	5.4	12.9	15.7	10.5
NHL - Nodal	5.3	6.8	4.0	11.8	12.8	10.9	7.9	8.8	6.9	11.0	13.4	8.5	4.8	5.5	4.1	8.6	10.5	6.9
NHL - Extranodal	2.3	2.6	1.9	3.4	4.2	2.7	2.4	2.6	2.2	3.2	3.7	2.7	1.6	1.8	1.3	4.3	5.2	3.6
Myeloma	1.6	2.0	1.3	3.3	4.0	2.8	2.7	2.7	2.6	1.0	1.4	0.6	2.0	2.0	1.9	3.5	4.3	2.9
Leukemia	6.9	8.5	5.5	8.6	10.5	6.9	6.4	7.8	5.1	6.0	6.7	5.3	6.3	7.1	5.5	8.8	11.0	6.9
Lymphocytic leukemia	4.1	5.1	3.2	4.6	5.9	3.4	2.6	3.3	1.9	2.6	3.2	2.0	2.9	3.4	2.2	4.3	5.5	3.2
Acute lymphocytic leukemia	2.0	2.1	1.9	1.2	1.4	1.0	1.0	1.3	0.7	1.1	1.3	1.0	1.6	1.9	1.3	1.8	2.0	1.6
Chronic lymphocytic leukemia	1.8	2.4	1.2	3.0	3.8	2.3	1.3	1.5	1.2	1.3	1.7	0.9	1.1	1.3	0.8	2.2	3.1	1.4
Other lymphocytic leukemia	0.3	0.6	-	0.4	0.7	0.2	0.3	0.5	-	0.1	0.2	0.1	0.2	0.2	0.1	0.3	0.5	0.2
Myeloid and monocytic leukemia	2.7	3.1	2.3	3.4	3.8	3.0	3.1	3.8	2.5	2.3	2.2	2.4	2.7	2.8	2.7	4.1	5.0	3.3
Acute myeloid leukemia	1.8	2.1	1.5	2.3	2.5	2.1	2.1	2.7	1.5	1.1	1.1	1.0	1.4	1.5	1.3	2.7	3.2	2.2
Acute monocytic leukemia	-	-	0.0	0.1	0.1	0.1	0.1	0.2	-	-	0.0	-	0.1	0.1	0.2	0.2	0.2	0.2
Chronic myeloid leukemia	0.7	0.6	0.7	0.9	1.0	0.8	0.9	0.9	0.9	1.2	1.0	1.3	1.1	1.1	1.1	1.1	1.4	0.8
Other myeloid/ monocytic leukemia	0.1	0.2	-	0.1	0.1	0.1	-	-	0.0	-	-	-	0.1	0.1	0.1	0.1	0.1	0.1
Other leukemia	0.1	0.3	0.0	0.6	0.8	0.5	0.7	0.7	0.7	1.1	1.3	0.9	0.7	0.9	0.5	0.4	0.5	0.4
Other acute leukemia	0.1	0.2	0.0	0.4	0.5	0.3	0.4	0.3	0.4	0.1	0.2	0.1	0.5	0.6	0.3	0.2	0.2	0.2
Aleukemic, subleukemic, and NOS§	-	-	0.0	0.2	0.3	0.2	0.3	0.3	0.3	1.0	1.1	0.8	0.2	0.3	0.2	0.2	0.3	0.2
Miscellaneous	3.1	3.5	2.7	11.7	13.1	10.5	8.9	10.6	7.3	8.0	9.5	6.6	3.8	3.9	3.7	6.1	7.0	5.4

*Rates are per 100,000 and are age-standardized to the World Standard Million.
†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.
§NOS indicates "not otherwise specified."

Table 1.8. Overview and Summary Data: Standard Errors of the Age-Standardized Incidence Rates* Shown in Table 1.7, by Site 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		
Site	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female
All Sites	2.2	3.2	3.0	0.9	1.3	1.2	2.0	3.3	2.6	1.5	2.2	1.9	0.9	1.3	1.2	0.5	0.8	0.6
Oral cavity and pharynx	0.3	0.4	0.3	0.1	0.2	0.2	0.3	0.5	0.3	0.3	0.4	0.4	0.1	0.2	0.2	0.1	0.1	0.1
Lip	*0.1*	*0.1*	-	0.1	0.1	0.1	0.2	0.3	*0.2*	*0.0*	*0.1*	-	0.1	0.1	*0.1*	0.0	0.0	0.0
Tongue	0.1	*0.2*	*0.1*	0.0	0.1	0.1	*0.1*	*0.2*	*0.1*	0.1	0.2	0.1	0.1	0.1	0.1	0.0	0.1	0.0
Salivary gland	0.1	*0.1*	*0.2*	0.0	0.1	0.1	0.1	*0.2*	*0.2*	0.1	0.2	0.2	0.1	0.1	0.1	0.0	0.0	0.0
Floor of mouth	*0.1*	*0.1*	*0.0*	0.0	0.0	*0.0*	-	-	*0.0*	*0.0*	-	-	*0.0*	*0.0*	*0.0*	0.0	0.0	0.0
Gum and other mouth	0.1	*0.2*	*0.1*	0.0	0.1	0.1	0.1	*0.2*	*0.1*	0.1	0.2	0.2	0.0	0.1	*0.0*	0.0	0.0	0.0
Nasopharynx	*0.1*	*0.2*	*0.1*	0.0	0.1	0.0	0.1	0.2	*0.2*	0.1	0.2	0.1	0.1	0.1	0.1	0.0	0.0	0.0
Tonsil	*0.1*	*0.1*	-	0.0	0.0	*0.0*	*0.1*	*0.1*	*0.0*	*0.0*	*0.1*	*0.1*	*0.0*	*0.0*	*0.0*	0.0	0.1	0.0
Oropharynx	-	-	*0.0*	0.0	0.0	0.0	*0.0*	-	-	*0.0*	-	*0.0*	*0.0*	*0.0*	-	0.0	0.0	0.0
Hypopharynx	*0.1*	-	-	0.0	0.0	*0.0*	*0.1*	*0.1*	-	0.1	0.2	0.2	*0.0*	*0.0*	*0.0*	0.0	0.0	0.0
Other oral cavity and pharynx	*0.0*	-	-	0.0	0.0	*0.0*	*0.0*	-	-	*0.0*	*0.1*	*0.1*	-	-	-	0.0	0.0	0.0
Digestive system	0.9	1.4	1.2	0.4	0.6	0.5	0.9	1.5	1.1	0.7	1.1	0.7	0.4	0.6	0.6	0.2	0.3	0.2
Esophagus	0.1	0.2	*0.1*	0.1	0.1	0.1	0.1	*0.2*	*0.1*	0.1	0.2	0.2	0.1	0.1	0.1	0.0	0.1	0.0
Stomach	0.4	0.6	0.5	0.2	0.3	0.2	0.4	0.6	0.4	0.2	0.3	0.2	0.2	0.3	0.2	0.1	0.1	0.1
Small intestine	*0.1*	*0.2*	-	0.0	0.1	0.1	0.1	*0.2*	*0.2*	0.1	0.1	*0.1*	0.1	0.1	0.1	0.0	0.0	0.0
Colon and rectum	0.7	1.0	0.9	0.3	0.5	0.4	0.7	1.1	0.9	0.3	0.4	0.4	0.3	0.4	0.4	0.1	0.2	0.2
Colon excluding rectum	0.6	0.9	0.8	0.3	0.4	0.4	0.5	0.8	0.7	0.2	0.4	0.3	0.2	0.3	0.3	0.1	0.2	0.2
Cecum	0.2	0.3	0.3	0.1	0.1	0.1	0.1	*0.2*	*0.2*	0.1	*0.1*	*0.1*	0.0	0.1	0.1	0.1	0.1	0.1
Appendix	*0.1*	*0.1*	-	0.0	0.0	0.0	*0.1*	-	-	-	*0.0*	-	*0.0*	*0.0*	*0.0*	0.0	0.0	0.0
Ascending colon	0.1	*0.2*	0.2	0.1	0.2	0.1	0.2	0.3	0.3	0.1	*0.1*	*0.1*	0.0	0.1	0.1	0.0	0.1	0.1
Hepatic flexure	*0.1*	*0.1*	*0.1*	0.0	0.1	0.1	*0.1*	*0.1*	*0.1*	0.1	*0.1*	*0.0*	0.0	*0.0*	*0.0*	0.0	0.0	0.0
Transverse colon	0.1	*0.2*	*0.2*	0.1	0.1	0.1	*0.1*	*0.1*	*0.2*	0.1	*0.1*	*0.1*	0.0	0.1	0.1	0.0	0.1	0.0
Splenic flexure	*0.1*	*0.1*	*0.1*	0.0	0.1	0.1	*0.1*	*0.1*	*0.1*	*0.0*	*0.1*	*0.1*	0.0	*0.0*	*0.0*	0.0	0.0	0.0
Descending colon	0.1	*0.2*	*0.1*	0.1	0.1	0.1	0.1	0.3	*0.2*	0.1	*0.1*	*0.1*	0.0	0.1	*0.1*	0.0	0.1	0.0
Sigmoid colon	0.3	0.5	0.4	0.2	0.2	0.2	0.3	0.5	0.4	0.1	0.1	0.1	0.1	0.2	0.2	0.1	0.1	0.1
Colon, NOS§	0.3	0.5	0.4	0.1	0.2	0.2	0.3	0.4	0.4	0.2	0.3	0.2	0.2	0.3	0.2	0.0	0.0	0.0
Rectum and rectosigmoid junction	0.4	0.6	0.5	0.2	0.3	0.2	0.4	0.7	0.5	0.2	0.3	0.2	0.2	0.2	0.2	0.1	0.1	0.1
Rectosigmoid junction	0.2	0.3	0.2	0.1	0.1	0.1	0.2	0.3	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.0	0.1	0.1
Rectum	0.3	0.5	0.5	0.1	0.2	0.2	0.4	0.6	0.4	0.1	0.2	0.2	0.1	0.2	0.2	0.1	0.1	0.1
Anus, anal canal, and anorectum	*0.1*	*0.1*	*0.1*	0.0	0.1	0.1	*0.1*	*0.1*	*0.1*	0.1	*0.1*	0.1	0.1	0.1	0.1	0.0	0.0	0.0
Liver and intrahepatic bile duct	0.2	0.4	0.2	0.1	0.1	0.1	0.2	0.4	0.2	0.4	0.8	0.4	0.1	0.2	0.1	0.1	0.1	0.1
Liver	0.2	0.4	0.2	0.1	0.1	0.1	0.2	0.4	*0.2*	0.4	0.8	0.4	0.1	0.2	0.1	0.1	0.1	0.1
Intrahepatic bile duct	*0.1*	*0.1*	-	0.0	0.0	0.0	-	-	-	0.1	0.1	-	0.0	*0.0*	0.1	0.0	0.0	0.0
Gallbladder	0.2	0.3	0.3	0.0	0.0	0.1	0.2	*0.2*	0.3	0.1	*0.1*	*0.1*	0.1	0.1	0.2	0.0	0.0	0.0
Other biliary	*0.1*	*0.1*	*0.1*	0.0	0.1	0.1	0.2	0.3	*0.2*	0.1	0.2	0.1	0.1	0.1	0.1	0.0	0.0	0.0
Pancreas	0.3	0.5	0.3	0.1	0.2	0.2	0.3	0.6	0.3	0.2	0.4	0.3	0.1	0.2	0.1	0.1	0.1	0.1
Retroperitoneum	*0.0*	-	-	0.0	0.1	0.0	*0.0*	*0.1*	*0.1*	0.1	*0.1*	0.1	0.0	0.1	*0.0*	0.0	0.0	0.0

Table 1.8. continued

Site	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
Peritoneum, omentum, and mesentery	0.1	0.0	0.1	0.0	0.0	0.1	0.1	-	0.1	0.0	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.0
Other digestive organs	-	-	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.1	0.2	0.1	0.0	0.0	0.0	0.0	0.0	0.0
Respiratory system	0.7	1.3	0.5	0.3	0.5	0.3	0.9	1.7	0.6	0.4	0.8	0.4	0.3	0.6	0.2	0.2	0.3	0.2
Nose, nasal cavity, and middle ear	0.1	0.1	0.1	0.0	0.1	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.0	0.1	0.1	0.0	0.0	0.0
Larynx	0.2	0.4	0.1	0.1	0.2	0.1	0.3	0.6	0.2	0.2	0.4	0.1	0.1	0.3	0.1	0.0	0.1	0.0
Lung and bronchus	0.6	1.2	0.5	0.2	0.4	0.2	0.8	1.6	0.5	0.4	0.6	0.3	0.3	0.5	0.2	0.2	0.3	0.2
Pleura	0.1	0.1	-	0.0	0.1	0.0	0.1	0.2	0.1	0.1	0.1	0.1	0.0	0.1	0.1	0.0	0.0	0.0
Trachea, mediastinum, and other respiratory organs	0.1	0.2	0.1	0.0	0.1	0.0	0.1	0.2	0.1	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.0	0.0
Bones and joints	0.2	0.4	0.2	0.1	0.1	0.1	0.1	0.2	0.2	0.1	0.2	0.2	0.1	0.1	0.1	0.0	0.0	0.0
Soft tissue including heart	0.2	0.3	0.3	0.1	0.1	0.1	0.2	0.3	0.3	0.2	0.3	0.3	0.1	0.1	0.1	0.0	0.1	0.1
Skin excluding basal and squamous	0.3	0.4	0.4	0.2	0.3	0.3	0.2	0.4	0.3	0.1	0.2	0.1	0.1	0.1	0.1	0.1	0.2	0.1
Melanoma of the skin	0.3	0.4	0.4	0.2	0.3	0.2	0.2	0.3	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.2	0.1
Other non-epithelial skin	0.1	0.2	0.1	0.1	0.2	0.1	0.2	0.3	0.2	0.1	0.2	0.1	0.1	0.1	0.1	0.0	0.1	0.0
Breast	0.9	0.2	1.8	0.4	0.1	0.7	0.7	0.2	1.4	0.6	0.2	1.2	0.4	0.1	0.7	0.2	0.0	0.4
Female genital system	0.6	0.0	1.2	0.2	0.0	0.4	0.5	0.0	0.9	0.3	0.0	0.6	0.2	0.0	0.4	0.1	0.0	0.2
Cervix uteri	0.2	0.0	0.5	0.1	0.0	0.2	0.2	0.0	0.4	0.1	0.0	0.3	0.1	0.0	0.2	0.1	0.0	0.1
Corpus and uterus, NOS§	0.4	0.0	0.8	0.2	0.0	0.3	0.4	0.0	0.7	0.2	0.0	0.3	0.1	0.0	0.3	0.1	0.0	0.2
Corpus uteri	0.4	0.0	0.8	0.1	0.0	0.3	0.3	0.0	0.7	0.1	0.0	0.2	0.1	0.0	0.2	0.1	0.0	0.2
Uterus, NOS§	0.1	0.0	0.1	0.1	0.0	0.1	0.1	0.0	0.2	0.1	0.0	0.2	0.1	0.0	0.2	0.0	0.0	0.0
Ovary	0.3	0.0	0.7	0.1	0.0	0.2	0.2	0.0	0.4	0.2	0.0	0.4	0.1	0.0	0.3	0.1	0.0	0.1
Vagina	0.1	0.0	0.1	0.0	0.0	0.0	0.1	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0
Vulva	0.1	0.0	0.2	0.0	0.0	0.1	0.1	0.0	0.1	0.1	0.0	0.2	0.0	0.0	0.1	0.0	0.0	0.0
Other female genital organs	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.0
Male genital system	0.7	1.5	0.0	0.3	0.6	0.0	0.5	1.2	0.0	0.3	0.6	0.0	0.2	0.4	0.0	0.2	0.4	0.0
Prostate	0.6	1.4	0.0	0.2	0.5	0.0	0.5	1.1	0.0	0.3	0.5	0.0	0.2	0.4	0.0	0.2	0.4	0.0
Testis	0.3	0.5	0.0	0.1	0.2	0.0	0.1	0.2	0.0	0.1	0.1	0.0	0.1	0.1	0.0	0.0	0.1	0.0
Penis	0.1	0.2	0.0	0.0	0.0	0.0	0.1	0.1	0.0	-	-	0.0	-	-	0.0	0.0	0.0	0.0
Other male genital organs	-	-	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
Urinary system	0.6	1.2	0.6	0.3	0.5	0.2	0.6	1.1	0.5	0.6	1.0	0.5	0.3	0.5	0.2	0.1	0.2	0.1
Urinary bladder	0.5	1.1	0.4	0.2	0.4	0.2	0.5	1.0	0.3	0.5	1.0	0.4	0.2	0.4	0.2	0.1	0.2	0.1
Kidney and renal pelvis	0.3	0.5	0.4	0.2	0.3	0.2	0.3	0.5	0.3	0.2	0.3	0.2	0.1	0.2	0.2	0.1	0.1	0.1
Ureter	-	-	-	0.0	0.1	0.0	0.1	0.1	0.0	0.0	0.1	-	0.0	0.0	-	0.0	0.0	0.0
Other urinary organs	-	-	-	0.0	0.1	0.0	0.1	-	-	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Eye and orbit	0.1	0.1	0.1	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.0	0.1	0.1	0.0	0.0	0.0

Table 1.8. continued

Site	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
Brain and other nervous system	0.4	0.6	0.6	0.1	0.2	0.2	0.3	0.5	0.4	0.2	0.3	0.3	0.2	0.2	0.2	0.1	0.1	0.1
Brain	0.4	0.5	0.5	0.1	0.2	0.2	0.3	0.5	0.4	0.2	0.3	0.3	0.1	0.2	0.2	0.1	0.1	0.1
Cranial nerves and other nervous system	0.2	*0.3*	*0.2*	0.0	0.0	0.0	*0.1*	*0.1*	*0.1*	0.1	0.1	0.1	0.0	0.1	0.1	0.0	0.0	0.0
Endocrine system	0.5	0.5	0.8	0.2	0.2	0.3	0.3	0.3	0.5	0.2	0.2	0.3	0.1	0.2	0.2	0.1	0.1	0.1
Thyroid	0.4	0.4	0.7	0.2	0.2	0.3	0.3	0.3	0.5	0.2	0.2	0.3	0.1	0.1	0.2	0.1	0.1	0.1
Other endocrine including thymus	*0.1*	*0.2*	*0.2*	0.0	0.1	0.1	0.1	0.1	*0.1*	0.1	0.2	*0.1*	0.0	0.1	0.1	0.0	0.0	0.0
Lymphoma	0.6	0.9	0.8	0.2	0.4	0.3	0.6	0.9	0.7	0.5	0.7	0.6	0.2	0.4	0.3	0.1	0.2	0.1
Hodgkin lymphoma	0.3	0.5	0.5	0.1	0.2	0.2	0.2	0.3	0.3	0.2	0.3	0.2	0.1	0.2	0.1	0.0	0.1	0.1
Hodgkin - Nodal	0.3	0.4	0.5	0.1	0.2	0.1	0.2	0.3	0.3	0.1	0.2	0.2	0.1	0.2	0.1	0.0	0.1	0.1
Hodgkin - Extranodal	*0.1*	-	*0.1*	0.0	*0.0*	*0.0*	*0.0*	-	*0.1*	*0.0*	*0.0*	*0.0*	0.0	0.0	*0.0*	0.0	0.0	0.0
Non-Hodgkin lymphoma	0.5	0.8	0.6	0.2	0.3	0.3	0.5	0.8	0.7	0.4	0.7	0.6	0.2	0.3	0.3	0.1	0.2	0.1
NHL - Nodal	0.4	0.7	0.5	0.2	0.3	0.2	0.5	0.7	0.6	0.4	0.6	0.5	0.2	0.3	0.2	0.1	0.1	0.1
NHL - Extranodal	0.3	0.4	0.3	0.1	0.2	0.1	0.2	0.4	0.3	0.2	0.3	0.3	0.1	0.2	0.1	0.1	0.1	0.1
Myeloma	0.2	0.4	0.3	0.1	0.2	0.1	0.3	0.4	0.4	0.1	0.2	0.1	0.1	0.2	0.2	0.0	0.1	0.1
Leukemia	0.5	0.8	0.6	0.2	0.3	0.2	0.4	0.6	0.5	0.3	0.4	0.4	0.2	0.3	0.3	0.1	0.1	0.1
Lymphocytic leukemia	0.4	0.6	0.5	0.1	0.2	0.1	0.2	0.4	0.3	0.2	0.3	0.2	0.1	0.2	0.2	0.1	0.1	0.1
Acute lymphocytic leukemia	0.3	0.4	0.4	0.1	0.1	0.1	0.1	0.2	0.1	0.1	0.2	0.1	0.1	0.1	0.1	0.0	0.1	0.1
Chronic lymphocytic leukemia	0.2	0.4	0.2	0.1	0.2	0.1	0.2	0.3	0.3	0.1	0.2	0.2	0.1	0.1	0.1	0.0	0.1	0.0
Other lymphocytic leukemia	*0.1*	*0.2*	-	0.0	0.1	0.0	*0.1*	*0.2*	-	*0.0*	*0.1*	*0.1*	0.0	0.1	*0.0*	0.0	0.0	0.0
Myeloid and monocytic leukemia	0.3	0.5	0.4	0.1	0.2	0.1	0.3	0.4	0.3	0.2	0.2	0.2	0.1	0.2	0.2	0.1	0.1	0.1
Acute myeloid leukemia	0.2	0.4	0.3	0.1	0.1	0.1	0.2	0.4	0.3	0.1	0.2	0.2	0.1	0.1	0.1	0.0	0.1	0.1
Acute monocytic leukemia	-	-	*0.0*	0.0	0.0	*0.0*	*0.1*	*0.1*	-	-	*0.0*	-	0.0	*0.0*	*0.0*	0.0	0.0	0.0
Chronic myeloid leukemia	0.1	*0.2*	*0.2*	0.1	0.1	0.1	0.1	0.2	0.2	0.1	0.2	0.2	0.1	0.1	0.1	0.0	0.0	0.0
Other myeloid/ monocytic leukemia	*0.1*	*0.1*	-	0.0	0.0	0.0	-	-	*0.0*	-	-	-	0.0	*0.0*	*0.0*	0.0	0.0	0.0
Other leukemia	*0.1*	*0.1*	*0.0*	0.0	0.1	0.1	0.1	0.2	0.2	0.1	0.2	0.2	0.1	0.1	0.1	0.0	0.0	0.0
Other acute leukemia	*0.1*	*0.1*	*0.0*	0.0	0.1	0.0	0.1	*0.1*	*0.1*	0.0	*0.1*	*0.0*	0.1	0.1	0.1	0.0	0.0	0.0
Aleukemic, subleukemic, and NOS§	-	-	*0.0*	0.0	0.0	0.0	0.1	*0.1*	*0.1*	0.1	0.2	0.2	0.0	0.1	0.1	0.0	0.0	0.0
Miscellaneous	0.3	0.5	0.4	0.2	0.3	0.2	0.5	0.8	0.6	0.4	0.6	0.5	0.2	0.2	0.2	0.1	0.1	0.1

*Rates are per 100,000 and are age-standardized to the World Standard Million.
†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.
§NOS indicates "not otherwise specified."

REFERENCES

[1] Middle East Cancer Consortium. Manual of standards for cancer registration. 2005. Available at: http://mecc.cancer.gov/MECC_Manual_of_Standards.PDF. [Last Accessed: 1/06].

[2] Surveillance, Epidemiology and End Results, NCI. SEER*Stat 6.1. 2005 Available at: http://seer.cancer.gov/seerstat/. [Last Accessed: 1/06].

[3] 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.

[4] Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2002: cancer incidence. Mortality and prevalence worldwide. IARC cancer base no. 5, version 2.0. Lyon (France): IARC Press; 2004.

Gül Ergör

BACKGROUND

Cancer of the esophagus is the eighth most common cancer worldwide *[1]*, with more than 400,000 cases per year. Incidence is highest in western and south central Asia. The geographical differences in incidence that are observed are more extreme than for any other cancer. A high-risk area known as the "esophageal cancer belt" ranges from northern Iran all the way to north central China *[2]*.

The 2 main types of esophageal cancer are squamous cell carcinoma and adenocarcinoma. Squamous cell carcinoma is seen predominantly in developing countries and is associated with tobacco and alcohol consumption as well as with hot beverage consumption and malnutrition. Low intakes of fruits and vegetables are also risk factors for squamous cell cancers. Adenocarcinoma is mostly found in developed countries, and is mostly related to obesity and chronic gastroesophageal reflux. This reflux causes a clinical condition called Barrett's esophagus, which is considered a premalignant lesion *[3]*.

Many risk factors play a role in the etiology of esophageal cancer, although these vary with geographic region. For example, betel chewing and oral consumption of opium are factors primarily found in Southeast Asia and the Caspian Sea area *[2]*. The factor for which there is the most convincing evidence is alcohol consumption, and this risk is even greater among drinkers who also smoke. The alcohol relationship is not specific to a type of drink, but to the level of consumption.

McCredie et al. reported that migrants from the Middle East to Australia had a lower cancer incidence than other Australians for many sites, including the esophagus *[4]*. A characteristic of this disease is that it shows marked differences between ethnic groups in the same country or same geographical areas. For example, Scotland has very high rates compared with England and Ireland *[5]*. In a recent study by de Martel et al., high prevalence of *Helicobacter pylori* was reported as a protective factor for esophageal adenocarcinoma (OR = 0.37; 95% CI, 0.16-0.88) *[6]*.

RESULTS

Overall Incidence

Table 2.1 displays the age-standardized incidence rates in the MECC countries and US SEER. The incidence of esophageal cancer in the MECC countries during this period (1996-2001) was among the lowest in the world. The rates worldwide were 11.5 in males and 4.7 in females *[7]*. In MECC countries, the highest rate was in Israeli Jews (1.5), and the lowest was in Israeli Arabs and Cypriots (0.6). Egyptians (1.4) showed a rate similar to that of Israeli Jews, while Jordanians had a slightly lower rate (1.1). In comparison, US SEER rates for the same years were more than twice as high (3.0). Because the MECC countries are outside the esophageal cancer belt, lower rates than in this high-risk region are expected.

The low rates of esophageal cancer in the MECC countries might also be explained by the relatively low levels of alcohol consumption in Arab countries with a Muslim majority. Alcohol consumption by Israeli Jews is lower than in most Western countries, but higher than consumption by Israeli Arabs. According to Neumark et al., the prevalence of any non-ritual alcohol consumption by males over a 1-month period was 67% in Israeli Jews and 46% in Israeli Arabs. The differences were even more marked in females: 33% in Israeli Jews and 7% in Israeli Arabs *[8]*. Data from the

same study showed that Ashkenazi Israeli Jews had higher drinking patterns than Sephardi Israeli Jews (68% and 59%, respectively) *[9]*.

In contrast to alcohol, in almost all of the MECC countries there is a high prevalence of smoking, which would tend to increase esophageal cancer rates. Smoking prevalence in Israel was 39% in males during 1999-2001, according to the First Israeli National Health and Nutrition Survey *[10]*. Similarly, smoking is very common in the other MECC countries. The low esophageal cancer rates suggest under-diagnosis of esophageal cancers in all the countries in the region.

As indicated above, world esophageal cancer rates were 2 to 3 times higher in males (11.5) than in females (4.7). Sex ratios for Middle Eastern populations can be judged from data taken from GLOBOCAN, which are presented in Table 2.2. The ratios are similar to those seen in the MECC data. Most ratios in the MECC data were around 2, except in Israeli Arabs, where the male rate was 3 times the female rate, and in Cyprus, where the male rate was 5 times the female rate (Table 2.1). However, due to the very small numbers, these differences in ratios should be interpreted with caution. The sex ratio in the United States was more than 4 (Table 2.1), which may be explained by the fact that the majority of these cancers were adenomatous, originating from Barrett's esophagus, which is 7 times more commonly seen in males *[2]*.

Age

Esophageal cancer incidence increases with age in all countries. In the MECC populations and in SEER, the age-specific rates were very low below 50 years of age (Table 2.1). Between ages 50-69 years, the rates were 5.0 in Egyptians, 4.5 in Israeli Jews, 3.4 in

Table 2.1. Esophageal 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	23	19	4	665	390	275	20	14	6	94	58	36	144	99	45	4,826	3,616	1,210
Age Groups (Distribution)																		
<50 y	-	-	*0.0%*	5.6%	6.9%	*3.6%*	*15.0%*	-	-	26.6%	27.6%	*25.0%*	18.1%	18.2%	*17.8%*	7.6%	8.2%	5.6%
50-69 y	*43.5%*	*42.1%*	-	32.2%	36.9%	25.5%	*35.0%*	*50.0%*	*0.0%*	55.3%	56.9%	52.8%	48.6%	48.5%	48.9%	44.6%	48.1%	33.9%
70+ y	*47.8%*	*47.4%*	-	62.3%	56.2%	70.9%	*50.0%*	*35.7%*	*83.3%*	18.1%	*15.5%*	*22.2%*	33.3%	33.3%	*33.3%*	47.9%	43.7%	60.5%
Age Groups (Rates)‡																		
Total rate	0.6	1.0	*0.2*	1.5	2.1	1.0	0.6	*0.9*	*0.3*	1.4	1.7	1.0	1.1	1.5	0.7	3.0	5.1	1.2
<50 y	-	-	*0.0*	0.1	0.2	*0.1*	*0.1*	-	-	0.3	0.4	*0.2*	0.2	0.2	*0.1*	0.3	0.5	0.1
50-69 y	*2.0*	*3.3*	-	4.5	6.6	2.7	*1.3*	*2.8*	*0.0*	5.0	6.6	3.6	3.4	4.4	2.2	11.2	19.1	4.1
70+ y	*4.6*	*8.8*	-	16.6	21.2	13.3	*7.7*	*8.9*	*6.8*	8.2	*8.9*	*7.6*	9.8	14.4	*5.7*	24.5	42.0	12.2

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.

Table 2.2. Esophageal Cancer: Age-Standardized Incidence Rates,* by Sex, in Middle Eastern Countries − 1998-2002

Country	Male	Female
Cyprus	1.7	0.3
Iraq	1.2	0.9
Israel	2.3	1.1
Jordan	1.4	0.7
Kuwait	1.7	1.8
Lebanon	1.4	0.7
Syrian Arab Republic	1.4	0.9
Turkey	2.1	1.5

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

Source: Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2002: cancer incidence. Mortality and prevalence worldwide. IARC cancer base no. 5, version 2.0. Lyon (France): IARC Press; 2004.

Jordanians, 2.0 in Cypriots, and 1.3 in Israeli Arabs. The highest rates in the MECC populations were in the 70-and-older group, ranging from 4.6 in Cypriots to 16.6 in Israeli Jews. The age-specific rates also varied by sex.

Histology

Squamous cell carcinoma was the most common type of esophageal cancer in each of the MECC populations (Table 2.3). However, it is important to note that the ratio of squamous cell carcinoma to adenocarcinoma (the other main type of esophageal cancer) was far higher in females than in males. Overall, approximately half of the esophageal cancers were of the squamous cell type in Cyprus and Israel. In Egypt and Jordan, the proportions reached above 60%, which is typical for developing countries. In the United States, the proportion of adenocarcinomas was higher than for squamous cell carcinomas, as in other Western countries (Table 2.3).

Subsites

The MECC registries record the localization of tumors within the esophagus; however, the majority of the esophageal cancers were recorded as occurring at an unspecified site in 4 of the populations: Cypriots (56.5%), Israeli Jews (60.8%), Israeli Arabs (60.0%), and Jordanians (72.2%) (Table 2.4). Only in Egypt were a majority recorded for a specified site. The most common specific site of localization in the MECC countries was in the "abdominal and one-third distal" part of the esophagus, which was recorded far more frequently than were cancers localized in the upper one-third and middle one-third of the esophagus.

Basis of Diagnosis

The proportion of microscopically confirmed esophageal cancer cases varied from 85.4% to 100% in the MECC countries (Table 2.3). US SEER results had a very high (96.1%) microscopic confirmation, which could be explained by the country's highly technology-dependent health care system. This high rate is less expected in MECC countries, where patients may generally receive less aggressive management of their disease.

In Cyprus, all cases were microscopically confirmed. This may indicate that some cases were missing, because one would expect that there would be patients treated palliatively whose cancers were not microscopically confirmed. Evidently, if there were such patients, they were not notified to the registry. Likewise, the very high proportion of microscopically confirmed cases among Israeli Arabs and Jordanians suggests that some clinically diagnosed cases were missed.

SUMMARY AND CONCLUSIONS

The low incidence rates reported for esophageal cancer are most probably due to low consumption of alcohol in the Middle East compared with other parts of the world. However, the possibility of under-diagnosis is also a partial explanation. In some countries, male/female ratios were very high; this might be a result of gender-related problems of access to health care due to traditional or organizational factors, though it could also be due to fluctuations in small numbers. Discrepancies between Israeli Jews and Arabs might be partly due to ethnic distinctions, but differences in alcohol consumption and smoking are the most likely contributing causes.

Table 2.3. Esophageal Cancer: Number of Cases and Proportions of Histologic Type and Microscopic Confirmation, 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
Total cases microscopically confirmed	23	19	4	568	338	230	19	*14*	*5*	83	54	29	141	96	45	4640	3499	1141
Microscopically confirmed	100.0%	100.0%	100.0%	85.4%	86.7%	83.6%	95.0%	*100.0%*	*83.3%*	88.3%	93.1%	80.5%	97.9%	97.0%	100.0%	96.1%	97.0%	94.3%
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	100.0%	100.0%	*100.0%*	98.1%	97.0%	99.6%	94.7%	*92.9%*	*100.0%*	100.0%	100.0%	100.0%	97.2%	97.9%	95.6%	98.9%	98.9%	98.8%
Squamous cell carcinoma	*56.5%*	*52.6%*	*75.0%*	50.5%	39.6%	66.5%	*52.6%*	*50.0%*	*60.0%*	67.5%	61.1%	79.3%	62.4%	56.3%	75.6%	41.5%	35.7%	59.4%
Adenocarcinoma	*43.5%*	*47.4%*	-	39.1%	48.5%	25.2%	*42.1%*	*42.9%*	-	20.5%	*25.9%*	*10.3%*	29.8%	37.5%	*13.3%*	50.5%	57.1%	30.4%
Other specified carcinoma	*0.0%*	*0.0%*	*0.0%*	3.0%	*3.8%*	*1.7%*	*0.0%*	*0.0%*	*0.0%*	-	-	*0.0%*	*0.0%*	*0.0%*	*0.0%*	1.9%	1.8%	2.5%
Unspecified carcinoma	*0.0%*	*0.0%*	*0.0%*	5.5%	5.0%	*6.1%*	*0.0%*	*0.0%*	*0.0%*	*9.6%*	*9.3%*	*10.3%*	*5.0%*	*4.2%*	*6.7%*	4.9%	4.3%	6.5%
Sarcoma	*0.0%*	*0.0%*	*0.0%*	*0.5%*	*0.9%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.2%*	*0.2%*	-
Other histologies	*0.0%*	*0.0%*	*0.0%*	*0.5%*	-	-	-	-	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	0.4%	*0.4%*	*0.4%*
Unspecified cancer	*0.0%*	*0.0%*	*0.0%*	*0.9%*	*1.5%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*2.8%*	-	-	0.6%	0.5%	*0.8%*

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%.

Table 2.4. Esophageal Cancer: Number of Cases and Proportions of Subsites, 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
Total cases	23	19	4	665	390	275	20	14	6	94	58	36	144	99	45	4,826	3,616	1,210
Total percentage†	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%
Abdominal and distal 1/3	*26.1%*	*31.6%*	*0.0%*	25.9%	29.2%	21.1%	*25.0%*	*28.6%*	-	48.9%	60.3%	*30.6%*	18.1%	16.2%	*22.2%*	53.6%	58.2%	40.0%
Other subsites	*17.4%*	-	-	13.4%	9.7%	18.5%	*15.0%*	*21.4%*	*0.0%*	20.2%	*15.5%*	*27.8%*	*9.7%*	*8.1%*	*13.3%*	36.3%	32.6%	47.5%
NOS‡	*56.5%*	*57.9%*	-	60.8%	61.0%	60.4%	*60.0%*	*50.0%*	*83.3%*	30.9%	*24.1%*	*41.7%*	72.2%	75.8%	64.4%	10.1%	9.3%	12.5%

*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%.

‡NOS indicates "not otherwise specified."

REFERENCES

[1] Parkin DM, Pisani P, Ferlay J. Estimates of the worldwide incidence of 25 major cancers in 1990. Int J Cancer 1999;80:827-41.

[2] Stewart BW, Kleihues P, editors. World cancer report. Lyon (France): International Agency for Research on Cancer; 2003.

[3] Forman D. Review article: oesophago-gastric adenocarcinoma – an epidemiological perspective. Aliment Pharmacol Ther 2004;20:55-60.

[4] McCredie M, Coates M, Grulich A. Cancer incidence in migrants to New South Wales (Australia) from the Middle East, 1972-91. Cancer Causes Control 1994;5:414-21.

[5] Corley DA, Buffler PA. Oesophageal and gastric cardia adenocarcinomas: analysis of regional variation using the Cancer Incidence in Five Continents database. Int J Epidemiol 2001;30:1415-25.

[6] de Martel C, Llosa AE, Farr SM, Friedman GD, Vogelman JH, Orentreich N, et al. Helicobacter pylori infection and the risk of development of esophageal adenocarcinoma. J Infect Dis 2005;191:761-7.

[7] Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2002: cancer incidence. Mortality and prevalence worldwide. IARC cancer base no. 5, version 2.0. Lyon (France): IARC Press; 2004.

[8] Neumark YD, Rahav G, Teichman M, Hasin D. Alcohol drinking patterns among Jewish and Arab men and women in Israel. J Stud Alcohol 2001;62:443-7.

[9] Aharonovich E, Hasin D, Rahav G, Meydan J, Neumark Y. Differences in drinking patterns among Ashkenazic and Sephardic Israeli adults. J Stud Alcohol 2001;62:301-5.

[10] Baron-Epel O, Haviv-Messika A, Tamir D, Nitzan-Kaluski D, Green M. Multiethnic differences in smoking in Israel: pooled analysis from three national surveys. Eur J Public Health 2004;14:384-9.

Gül Ergör

BACKGROUND

Stomach, or gastric, cancer incidence is second only to lung cancer worldwide, with an estimated 870,000 new cases and 650,000 deaths every year. The high-risk areas are East Asia, South America, and Eastern Europe. Data show that second-generation migrants from the high- to low-risk areas have lower incidence rates than their parents. Incidence rates are twice as high in males as in females. Thirty-eight percent of the world's stomach cancer cases occur in China, and it is the most frequent cancer in males in other parts of East Asia. Age-standardized incidence rates (ASRs) are the highest in the world in Japan (77.9 per 100,000 in men; 33.3 in women) *[1,2]*.

The major risk factors for stomach cancer are hypothesized to be nutritional, including inadequate intake of fresh fruits and vegetables, and high intake of salt, smoked fish, and meat. Refrigeration of food is considered protective. Vitamin C, contained in vegetables and fruits, may be protective for stomach cancer. Other possibly protective nutritional factors are whole-grain cereal, carotenoids, allium compounds (e.g., garlic), and green tea *[3]*. Smoking carries a slightly increased risk for stomach cancer *[4]*, and alcohol does not affect risk other than in the gastric cardia *[5]*. Smoking is quite common in countries of the Middle East Cancer Consortium (MECC) *[6-9]*.

Another important risk factor is *Helicobacter pylori* infection. Other gastric diseases, such as ulcer and atrophic gastritis, elevate gastric pH, thus causing anaerobic bacterial colonization in the stomach. *H. pylori* prevalence ranges from 25% in developed countries to 80%-90% in the developing countries *[10]*. It is now considered as the principal cause of chronic gastritis and peptic ulcer disease, and is a key risk factor for the development of gastric cancer *[11,12]*. The prevalence of *H. pylori* is thought to be high in MECC countries. In Israel, the prevalence has been reported to be 72% in a rural population and 65% in an urban population, which is higher than in the United States and Western Europe, but lower than in developing countries *[13]*. Another study has reported 33% positive for *H. pylori* in an elderly population in Israel *[14]*, and a case-control study in Israel found 63% positivity among the healthy controls *[15]*. In a population of Jordanian endoscopy patients, 82% prevalence was reported *[16]*, but there is no information for the general population.

RESULTS

Overall Incidence

Stomach cancer incidence in the MECC countries during the period 1996-2001 was low (Table 3.1), compared with the world ASR of 10.3 in females and 22.0 in males *[1]*. The incidence was highest in Israeli Jews (8.5), followed by Cypriots (4.9), Jordanians (4.8), and Israeli Arabs (4.6) (Table 3.1). Although a study from Jordan reports that the characteristics of gastric cancers diagnosed there resemble those in high-risk countries *[17]*, it nevertheless appears to be a low-incidence country. Egypt had the lowest incidence in the region, with 2.9. US SEER incidence was 5.3 for the same years (Table 3.1). These rates are 5 to 15 times lower than in Japan, where the overall rate is more than 50 *[1]*.

The Middle East has better access to fruits and vegetables throughout the year than in many places, and the nutritional practices have Mediterranean influences. This may result in the low incidence rates that were observed. On the other hand, *H. pylori* seroprevalence may be high in these countries, but this was not reflected in the observed cancer incidence.

Worldwide, the stomach cancer ASR in males is twice that in females *[1]*. Cyprus did not show this pattern; the male-to-female ratio was closer to 1 (1.44). Egypt's ratio was closer to the world pattern (1.64), while a ratio close to 2 was observed in Israeli Jews and Arabs, Jordanians, and in US SEER. A low male incidence rate was especially noticeable in Egypt and may be partially due to undiagnosed cases of stomach cancer, especially among the elderly.

The incidence rates of stomach cancer reported by GLOBOCAN *[2]* for countries in the Middle East (including some MECC populations) in 2002 are shown in Table 3.2. The Arab countries in the region had low rates, while Israel and Turkey had higher rates. In addition, all of the male-to-female rate ratios were lower than 2 for Cyprus and the Arab countries, while they were approximately 2 for Israel and Turkey. This may be partly due to ethnic differences and the more Western lifestyle in Israel and Turkey.

Age

The incidence of stomach cancer rises from age 50 years and is highest in the 70-and-older group. The highest incidence in that group was in Israeli Jews (121.2 in males; 60.5 in females), and the lowest was in Egyptians (17.5 in males; 5.4 in females) (Table 3.1). The high incidence in older Israeli Jews, many of whom originated from Europe, could be related to the deprived environmental and nutritional conditions they suffered during the Second World War. This is supported by data showing that Israeli Jews born in Europe have a higher stomach cancer incidence than Israeli Jews born elsewhere *[18]*. The low rates in Egypt in this oldest age group, among both males and females, strongly suggests that older cases have not been diagnosed, perhaps due to elderly patients' underuse of health care services.

Table 3.1. Stomach 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	198	112	86	3,605	2,169	1,436	177	108	69	206	126	80	687	434	253	9,235	5,541	3,694
Age Groups (Distribution)																		
<50 y	16.2%	16.1%	16.3%	7.9%	7.1%	9.1%	30.5%	28.7%	33.3%	34.0%	31.0%	38.8%	29.5%	26.5%	34.8%	10.8%	10.8%	10.7%
50-69 y	37.9%	36.6%	39.5%	33.7%	35.9%	30.3%	39.0%	42.6%	33.3%	54.9%	55.6%	53.8%	47.5%	48.6%	45.5%	33.3%	36.7%	28.0%
70+ y	46.0%	47.3%	44.2%	58.4%	56.9%	60.7%	30.5%	28.7%	33.3%	11.2%	13.5%	*7.5%*	23.0%	24.9%	19.8%	56.0%	52.5%	61.2%
Age Groups (Rates)‡																		
Total rate	4.9	5.9	4.1	8.5	11.7	6.0	4.6	6.0	3.4	2.9	3.6	2.2	4.8	6.0	3.5	5.3	7.4	3.6
<50 y	1.2	1.4	1.1	1.2	1.3	1.0	1.1	1.2	1.0	0.9	1.0	0.8	1.3	1.4	1.1	0.9	1.0	0.7
50-69 y	14.4	16.4	12.7	26.0	36.3	17.1	13.2	18.5	8.4	10.8	13.3	8.3	15.0	18.5	11.2	16.1	22.5	10.4
70+ y	40.2	54.6	29.0	85.9	121.2	60.5	40.1	52.3	30.7	11.1	17.5	*5.4*	33.5	48.3	20.1	51.8	75.0	36.1

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.

Histology

According to Table 3.3, the majority of stomach cancers in the MECC and US SEER registries were adenocarcinomas. The proportion of adenocarcinomas was highest in Cyprus (78.1%) and lowest in Egypt (43.9%). According to US SEER data, adenocarcinomas comprised 50.1% of the total cases. The second most common histologic type in all MECC populations was signet ring cell carcinoma. This pattern was the same in the SEER results.

Basis of Diagnosis

The percentage of stomach cancer cases that were microscopically confirmed ranged from 80% to 99% (Table 3.3). Stomach cancer is among those cancers that are more difficult to detect, and is mostly diagnosed at a later stage, often with metastasis to other sites. Therefore, the high levels of microscopic confirmation reported in Cyprus (99.0%) and Jordan (98.8%) suggest either undercoverage of cases by the registries or underdiagnosis by the health care systems. Note that the high proportion (96.8%) of microscopically confirmed cases in the United States might be expected for a country with a highly equipped health care service, but lower proportions would be expected for Cyprus and Jordan. Conversely, in Egypt, only 79.6% of cases were reported as microscopically confirmed, and this may raise questions about the validity of the remaining diagnoses. These observations argue for caution in the interpretation of the trends discussed in this chapter.

Table 3.2. Stomach Cancer: Age-Standardized Incidence Rates,* by Sex, in Middle Eastern Countries − 1998-2002

Country	Male	Female
Cyprus	6.8	4.3
Iraq	4.5	3.8
Israel	12.5	6.9
Jordan	6.6	4.0
Kuwait	4.8	3.0
Lebanon	7.0	4.6
Syrian Arab Republic	7.2	5.5
Turkey	12.2	6.4

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

Source: Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2002: cancer incidence. Mortality and prevalence worldwide. IARC cancer base no. 5, version 2.0. Lyon (France): IARC Press; 2004.

SUMMARY AND CONCLUSIONS

Among the MECC countries, stomach cancer presents as a larger problem in Israel, especially for Israeli Jews. Rates are especially low in Egypt, and quite low in Jordan and Cyprus, but the low rates may be partly due to underdiagnosis. The lower socioeconomic groups who are more prone to stomach cancer due to lifestyle and environment may have less access to health care services, and thus might be missed in the registration systems because they remain undiagnosed or are not hospitalized. Equal access to health care will eventually lead to improved reliability in registration records.

Although H. pylori infection is common in developing countries in the Middle East, this is not reflected in the relatively low stomach cancer ASRs in these countries. Studies on the effect of H. pylori infection in this region and possible interactions with nutritional behaviors may give further insight into the etiology of stomach cancer in Middle Eastern populations.

Table 3.3. Stomach Cancer: Number of Cases and Proportions of Microscopic Confirmation and Histologic Type, 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
Total cases microscopically confirmed	196	110	86	3,241	1,964	1,277	165	103	62	164	102	62	679	429	250	8,936	5,419	3,517
Microscopically confirmed	99.0%	98.2%	100.0%	89.9%	90.5%	88.9%	93.2%	95.4%	89.9%	79.6%	81.0%	77.5%	98.8%	98.8%	98.8%	96.8%	97.8%	95.2%
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%
Neoplasm, NOS§	*0.0%*	*0.0%*	*0.0%*	0.7%	*0.4%*	*1.1%*	*0.0%*	*0.0%*	*0.0%*	*4.3%*	*3.9%*	*4.8%*	*1.3%*	*1.2%*	*1.6%*	0.6%	0.5%	0.8%
Carcinoma, NOS§	*0.0%*	*0.0%*	*0.0%*	4.1%	4.3%	3.9%	-	*0.0%*	-	-	-	*0.0%*	7.4%	7.2%	7.6%	2.3%	1.9%	2.8%
Carcinoma undifferentiated, NOS§	*0.0%*	*0.0%*	*0.0%*	*0.5%*	*0.4%*	*0.6%*	-	-	*0.0%*	*4.9%*	*3.9%*	*6.5%*	*0.6%*	*0.9%*	*0.0%*	0.2%	*0.3%*	*0.1%*
Carcinoma anaplastic, NOS§	*0.0%*	*0.0%*	*0.0%*	0.9%	0.9%	*0.9%*	-	*0.0%*	-	*9.1%*	*8.8%*	*9.7%*	*0.0%*	*0.0%*	*0.0%*	*0.1%*	-	*0.1%*
Adenocarcinoma	78.1%	77.3%	79.1%	54.9%	57.6%	50.7%	44.2%	44.7%	43.5%	43.9%	50.0%	33.9%	67.3%	71.6%	60.0%	50.1%	55.1%	42.5%
Intestinal adenocarcinoma	*5.6%*	*7.3%*	*3.5%*	7.4%	7.7%	7.0%	*6.1%*	*6.8%*	*4.8%*	*0.0%*	*0.0%*	*0.0%*	*0.9%*	*0.7%*	*1.2%*	9.1%	9.7%	8.2%
Diffuse carcinoma	*5.1%*	*5.5%*	*4.7%*	0.9%	0.9%	*0.9%*	*1.8%*	-	-	*0.0%*	*0.0%*	*0.0%*	*1.5%*	*1.2%*	*2.0%*	3.6%	3.2%	4.4%
Carcinoid tumor	-	*0.0%*	-	1.5%	0.8%	2.4%	*6.1%*	*4.9%*	*8.1%*	-	-	*0.0%*	*2.2%*	*1.4%*	*3.6%*	2.6%	1.6%	4.2%
Mucinous adenocarcinoma	-	*0.0%*	-	2.3%	2.3%	2.2%	*3.6%*	*3.9%*	-	*6.1%*	*6.9%*	*4.8%*	*1.5%*	*1.6%*	*1.2%*	1.5%	1.5%	1.5%
Mucin-producing adenocarcinoma	-	-	*0.0%*	2.1%	1.8%	2.6%	*1.8%*	*2.9%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	-	-	*0.0%*	1.4%	1.4%	1.3%
Signet ring cell carcinoma	*6.6%*	*5.5%*	*8.1%*	21.0%	18.6%	24.5%	27.9%	28.2%	27.4%	21.3%	17.6%	27.4%	13.5%	10.5%	18.8%	18.0%	15.1%	22.5%
Leiomyosarcoma	-	-	*0.0%*	*0.3%*	*0.3%*	*0.4%*	*0.0%*	*0.0%*	*0.0%*	*3.0%*	-	*6.5%*	*0.9%*	*0.9%*	-	0.5%	0.4%	0.5%
Gastrointestinal stromal sarcoma	-	*0.0%*	-	*0.2%*	*0.3%*	-	-	-	*0.0%*	*1.8%*	-	-	*0.4%*	-	-	2.6%	2.1%	3.4%

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.

‡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%.

§NOS indicates "not otherwise specified."

REFERENCES

[1] Parkin DM, Pisani P, Ferlay J. Estimates of the worldwide incidence of 25 major cancers in 1990. Int J Cancer 1999;80:827-41.

[2] Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2002: cancer incidence. Mortality and prevalence worldwide. IARC cancer base no. 5, version 2.0. Lyon (France): IARC Press; 2004.

[3] World Cancer Research Fund and American Institute for Cancer Research. Food nutrition and the prevention of cancer: a global perspective. Washington (DC): World Cancer Research Fund; 1997.

[4] Koizumi Y, Tsubono Y, Nakaya N, Kuriyama S, Shibuya D, Matsuoka H, et al. Cigarette smoking and the risk of gastric cancer: a pooled analysis of two prospective studies in Japan. Int J Cancer 2004;112:1049-55.

[5] Stewart BW, Kleihues P, editors. World cancer report. Lyon (France): International Agency for Research on Cancer; 2003.

[6] Ministry of Health. National survey of tobacco, MOH. (Jordan): Ministry of Health; 1999.

[7] Ministry of Health. First Israeli National Health and Nutrition Survey-MABAT, 1999-2001. (Israel): Ministry of Health; 2000.

[8] Countrywide Integrated Non Communicable Disease Intervention (CINDI) and Conjunto de Acciones para la Reduccion Multifactorial de las Enfermedades No Transmisibles (CARMEN). Survey on tobacco prevention. Cyprus (Italy): World Health Organization; 1998.

[9] Ministry of Health. National survey of tobacco, MOH. (Egypt): Ministry of Health; 1998.

[10] Paunder RE. The prevention of H. pylori in different countries. Aliment Pharmacol Ther 1995;9:33-40.

[11] Logan RP, Walker MM. Epidemiology and diagnosis of H. pylori infection. Br Med J 2001;323:920-2.

[12] Parsonnet J, Friedman GD, Vandersteen DP, Chang Y, Vogelman JH, Orentreich N, et al. Helicobacter pylori infection and the risk of gastric carcinoma. N Engl J Med 1991;325:1127-31.

[13] Gilboa S, Gabay G, Zamir D, Zeev A, Novis B. Helicobacter pylori infection in rural settlements (Kibbutzim) in Israel. Int J Epidemiol 1995;24:232-7.

[14] Niv Y, Niv G, Koren R. 13C-urea breath test for diagnosis of Helicobacter pylori infection in the elderly. Dig Dis Sci 2004;49:1840-4.

[15] Fireman Z, Trost L, Kopelman Y, Segal A, Sternberg A. Helicobacter pylori: seroprevalence and colorectal cancer. Isr Med Assoc J 2000;2:6-9.

[16] Bani-Hani KE, Hammouri SM. Prevalence of Helicobacter pylori in Northern Jordan. Endoscopy based study. Saudi Med J 2001;22:843-7.

[17] Bani-Hani KE, Yaghan RJ, Heis HA, Shatnawi NJ, Matalka II, Bani-Hani AM, et al. Gastric malignancies in Northern Jordan with special emphasis on descriptive epidemiology. World J Gastroenterol 2004;10:2174-8.

[18] Health.Gov (Israel). Stomach 2001. 2001. Available at: http://www.health.gov.il/download/sartan/2001/Stomach2.xls. [Last Accessed: 1/06].

Micha Barchana

BACKGROUND

Environmental and Lifestyle Risk Factors

Colorectal cancer (CRC) is common in the Western world and usually ranks high in incidence and mortality among malignancies in those countries. Two observations have led researchers to look for diet and lifestyle as explanatory factors of risk for CRC. First, ecological studies comparing large populations have shown that rates of CRC differ dramatically among countries, varying by as much as 10-fold, from low-incidence areas in Asia and Africa, to much higher rates in northern Europe and the United States. Second, studies have shown that migrants from low-risk areas to high-risk Western countries experience rapid increases in CRC risk within the same generation *[1-5]*. Diet appeared to be the major explanatory factor for these phenomena: Namely, low consumption of red meat and dietary fat and high consumption of fiber in Asian and African countries, with an opposite dietary pattern in northern Europe and the United States. Recent data, however, do not support an association between dietary fiber and risk of CRC *[6-8]*. Emerging data suggest that low levels of physical activity and greater adiposity increase risks *[9-11]*. Since high levels of physical activity and low rates of adiposity characterize low-risk countries in general, these factors may account for much of the international differences in CRC rates. In other studies, cigarette smoking has been associated with increased risks of CRC, as has high alcohol consumption. These findings were reported in many, although not all, studies, and the role of tobacco and alcohol use in the etiology of CRC has yet to be determined *[12-18]*. On the other hand, there are several known protecting factors. Nonsteroidal anti-inflammatory drugs, in particular aspirin, are thought to be protective *[19,20]*. Calcium supplementation has been shown in randomized studies to reduce the recurrence of adenomatous colorectal polyps that are thought to be precursors to CRC *[21,22]*. On the behavioral side, it has been shown that physical activity and maintaining a desired body mass index may reduce the occurrence of CRC *[10,23]*.

Genetic Risk Factors

The essential element in the etiology of CRC is a process of genetic change in the epithelial cells of the colonic mucosa *[24,25]*. Chief among the factors that can initiate CRC development is a predisposition to mutagenic effects, where metabolic pathways may be altered by polymorphisms in genes responsible for detoxifying mutagens. Thus, differences in polymorphisms among individuals can account for their differing susceptibility to mutagens from the diet. Fecal mutagens in the stool may be produced by the interaction of digestion and food products. Changes in the fecal microflora indicate that changes in diet may alter mutagenic activity by altering extracellular superoxide formation *[26]*.

Family history – the occurrence of CRC in a first- or second-degree relative – is an identified risk factor for CRC. An increased risk among siblings of an affected person has been observed, and in one study was particularly high for cancer in the proximal colon (from the cecum up to the distal third of the transverse colon) *[27]*. An increased risk has also been observed among children of affected persons, both for CRC overall and for cancers of the proximal colon, distal colon, and rectum, with relative risks of approximately 1.8 *[28]*.

People affected with inflammatory bowel disease, either Crohn's disease or ulcerative colitis, are at increased risk for developing cancers of the gastrointestinal tract, particularly CRC *[29]*. The current literature suggests that these persons have a genetic predisposition to CRC and that long-standing inflammation is not of primary importance in the promotion of cancer *[30-34]*.

Familial polyposis syndromes are characterized by the early onset of multiple polyps and a very high risk of CRC development *[35]*. These syndromes have autosomal dominant inheritance with high but variable penetrance. Hereditary nonpolyposis colon cancer (HNPCC) syndrome is inherited as an autosomal dominant trait with high penetrance. Its phenotypic features are early-onset CRC (mean age: 46 years), multiple synchronous or metachronous CRCs (35%), and CRCs usually, but not always, located in the proximal colon *[36]*. HNPCC cancers are more likely to be signet-ring cancers and poorly differentiated, with extensive inflammatory infiltrates *[37,38]*. Particularly relevant to this MECC report is the feature of inherited CRC in Ashkenazi Jews (Jews of European origin). Israeli Ashkenazi Jews have the highest CRC incidence of any Israeli ethnic group. There are reports of a missense mutation (I1307K) in the *APC* gene, unique to Ashkenazi Jews and found in 6% of the Ashkenazi Jewish population and in 28% of those in this population with a family history of CRC. Among the carriers of the mutation, CRC is found in 13% of those who have polyps *[39,40]*. There do not appear to be any differences in clinical presentation between carriers of the mutation and noncarriers, so genetic testing in this population may be required to identify high-risk individuals for screening.

Early Detection

CRCs are among the very few cancer sites where screening and early detection are both feasible and proven to reduce mortality. The recommended test for mass screening is the fecal occult blood test (FOBT), which has been extensively studied and used since the early 1980s. This test, which acts as a first screen for possible malignancy, is designed to detect blood traces in the stool on a guaiac-based testing sample. Persons testing positive usually undergo colonoscopy as a more invasive but definitive examination. Newer technologies combine the guaiac-based test with tests based on molecular biology to look for cancer biomarkers in the stool. Serial guaiac-based FOBT is simple, inexpensive, and proven effective at reducing mortality from CRC. Immunochemical FOBT facilitates compliance and offers improved specificity, but at increased cost relative to guaiac-based FOBT. Fecal DNA testing may provide enhanced sensitivity for detection of CRC compared with FOBT, but its high cost limits its use for generalized screening. Other noninvasive tests, such as rectal mucin testing, have been developed more recently and require evaluation and comparison with guaiac-based FOBT. Serum tests, such as proteomics, nuclear matrix proteins, and serum DNA, are still in their infancy but remain a hope for the future *[41-46]*.

More direct methods for detecting colonic premalignant and malignant tumors include the use of colonoscopy or flexible sigmoidoscopy *[47,48]*. An exciting new CRC screening option is virtual colonoscopy (VC), which, by screening out persons without neoplasia, allows colonoscopy to be reserved for those requiring therapeutic intervention. The sensitivity of VC for large adenomas and CRC appears to be high, although results vary by center, and sensitivity for small adenomas is low. Some investigators have suggested that VC might be a useful option for investigating patients who test positive with stool-based screening tests *[49-51]*. Because no CRC screening technology program has been implemented in a substantial proportion of any MECC population, screening has yet to reduce the incidence or mortality of CRC in the Middle East.

Worldwide Incidence

Globally, the age-standardized incidence rate (ASR) of CRC is 20.1 per 100,000 males and 14.6 per 100,000 females. As mentioned earlier, there are notable differences between CRC incidence rates in more developed versus less developed countries. In the developed parts of the world, the ASR is 40.0 in males and 26.6 in females; in less developed areas, the rates are 10.2 and 7.7, respectively. The highest ASRs in males are observed in Australia/New Zealand (48.2), followed by North America (44.4) and Western Europe (42.9). At the other end of the scale, the rates in South-Central Asia (4.7) and Central Africa (2.3) are lowest *[52]*.

Incidence-to-mortality ratios also differ substantially between developed and less developed countries. The rate ratio varies from 2.9 in North America (indicating 2.9 incident cases for every death

from CRC) to 1.0 in Central and North Africa (indicating that for every new case of CRC, there is a death from this cancer) *[52]*.

The pattern of CRC incidence rates in females is similar to that in males, with the Australian continent presenting the highest rate (36.9), followed by North America (32.9). The lowest CRC rates in females are found throughout Africa (3.3-4.0), except South Africa, and also in South-Central Asia (3.5). Incidence-to-mortality rate ratios are high in North America and Australia (2.8 and 2.6, respectively) and low in all African countries (1.07-1.10), except South Africa *[52]*.

RESULTS

The total number of CRC cases reported to the registries during the study period was 74,369: 455 cases in Egyptians, 550 in Israeli Arabs, 697 in Cypriots, 1,654 in Jordanians, 15,533 in Israeli Jews, and 55,480 in US SEER (see Table 1.5).

Data Quality Indices

The gold standard for defining a cancer is the microscopic proof of malignant cells. Cancer registries rely, for the most part, on histological or cytological reports when defining incident cases. However, cancer registries collect information from other sources, such as death notifications and imaging procedures, that can supply information of lesser accuracy on the disease. The percentage of microscopically confirmed cases is often used as a quality indicator. Another way to assess quality of data is through the coding of subsites. The coding system adopted by MECC countries, the International Classification of Diseases in Oncology (ICD-O) (3rd edition), is based, for CRCs, on the anatomic location of the lesion, and reserves a code for a more general definition: "Colon, not otherwise specified (NOS)." This term is usually reserved for those cases where the exact location of the tumor cannot be accurately defined. The percentage of use of this more general code can also be used as a measure of accuracy.

Table 4.1 shows the percentage of microscopically confirmed total cases and the percentage of cases coded "Colon, NOS" for each of the populations.

The percentage of microscopic confirmation of CRC varied between 84.6% (Egypt) and 99.0% (Cyprus and Jordan). The higher values correspond to registries that do active registration where patient data and records are easily accessed for further exploration, but a very high value may also indicate that death certificates are not used, which would result in underestimated incidence rates. The US SEER microscopic confirmation rate was high (97.5%), but SEER has an

Table 4.1. Colorectal Cancer: Proportions of Total Cases Microscopically Confirmed and of Cases Coded "Colon, NOS"* in Cyprus, Israel (Jews and Arabs), Egypt, Jordan, and US SEER − 1996-2001

Registry	Proportion Microscopically Confirmed	Proportion Colon, NOS*
Cyprus 1998-2001	99.0%	20.1%
Israel (Jews) 1996-2001	91.4%	17.7%
Israel (Arabs) 1996-2001	91.5%	17.8%
Egypt 1999-2001	84.6%	23.1%
Jordan 1996-2001	99.0%	35.9%
US SEER† 1999-2001	97.5%	2.9%

*NOS indicates "not otherwise specified."

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

active follow-up program to check cases that are initially found by death certificate.

The percentage of cases coded "Colon, NOS" was 20.1% for Cypriots, 17.7% for Israeli Jews, 17.8% for Israeli Arabs, 23.1% for Egyptians, 35.9% for Jordanians, and 2.9% for US SEER (Table 4.1). A large proportion of cases coded in this less accurate way can result in less accurate data, although it should not greatly impact the estimates of overall incidence of CRC.

Overall Rates

As mentioned earlier, CRC is one of the most common cancers in the Western world, and constitutes about 13% of all cancers occurring in these countries. In MECC countries, CRC in Israeli Jews constituted 14.8% of all new cases in this population, followed by Cypriots and US SEER, where it was approximately 11% of all new cancer cases. Among Israeli Arabs and Jordanians, only approximately 9% of cancers were CRC, and in Egypt, 4.4%. (See Table 1.6.)

Observing the incidence rate of CRC (Table 4.2), we can subdivide the MECC countries into high-, middle-, and low-incidence countries. Israeli Jews had the highest incidence rate among all the populations considered (36.9). The ASR for Israeli Jewish males was 41.7, followed by US males (37.7), Israeli Jewish females (33.3), and US females (27.4). Cypriots had a lower incidence rate (17.3), similar to that of Israeli Arabs (15.2). Jordanians and Egyptians presented the lowest rates: 11.3 and 6.0, respectively.

The male-to-female incidence rate ratio (IRR) is another characteristic of CRC patterns. In developed countries, the male-to-female IRR tends to about 1.5, and in less developed countries it is about 1.3 *[52]*. In the MECC data, the IRR was 1.38 for US SEER, 1.35 for Egyptians, 1.27 for Israeli Arabs, 1.25 for Israeli Jews, 1.19 for Cypriots, and 1.03 for Jordanians. These findings do not completely follow the general trend of higher IRRs in more developed countries (Table 4.2)

Table 4.2. Colorectal Cancer: Number of Cases and Age-Standardized Incidence Rates,* by Age and Sex, in Cyprus, Israel, 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	697	355	342	15,533	7,805	7,728	550	287	263	455	261	194	1,654	845	809	55,480	27,892	27,588
Total rate*	17.3	19.0	16.0	36.9	41.7	33.3	15.2	17.3	13.6	6.0	6.9	5.1	11.3	11.5	11.2	32.0	37.7	27.4
<40 y	1.2	*1.2*	*1.1*	1.0	1.0	1.1	1.0	0.7	1.4	1.4	1.7	1.1	1.2	1.1	1.2	1.2	1.3	1.2
40-59 y	20.1	17.6	22.7	40.5	38.9	42.0	21.6	22.6	20.6	13.3	13.4	13.1	20.9	18.4	23.7	37.9	43.3	32.8
60-69 y	84.5	96.6	73.8	181.1	210.6	156.9	76.4	80.2	73.1	19.6	27.2	12.4	52.6	54.0	51.0	154.0	185.4	126.4
70+ y	159.2	193.4	132.3	374.0	451.5	318.4	116.5	161.2	80.0	20.8	25.1	17.1	60.7	78.6	44.4	311.3	369.8	270.8

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

†"*[Numeral]*" (italic) = 0 or 3-15 cases.

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

Colon versus Rectal Cancers

The MECC project focuses on cross-sectional data collection and does not include data on trends of the disease. Data on secular trends in CRC incidence emphasize the different behavior of cancers of the colon and rectum. Colon cancer incidence has been rising in the last decade in many developed and developing countries, and rectal cancer incidence has been falling. The pattern of CRC site incidence in industrialized and "Westernized" countries is that of a decrease in rectal cancer and an increase in proximal colon cancer. This has been noted worldwide in diverse populations *[53-68]*. The United States has the unique pattern of a decreasing incidence of total CRC and distal (left-sided) CRC, but a stable incidence of proximal right-sided CRC *[69]*. In many countries, the increase in proximal CRC has been noted to be more prominent in females *[70]*. Norway and Denmark are exceptional because distal is more prominent than proximal CRC in these countries *[67,71]*. Reasons for the changing CRC trends and the epidemiology of the CRC site distribution are assumed to be related to changes in diet and lifestyle associated with industrialization *[56]*. Worldwide, industrialization is associated with an increasing life expectancy, especially among females, and there is now a substantially increased proportion of females who are older than 65 years *[38,72]*. However, the reason for their greater tendency to develop proximal cancer is unclear.

Table 4.3 shows the colon-to-rectal cancer IRR in some selected countries *[73]* and for MECC populations for the years 1993-1997. According to the above theory, industrialized countries would tend to have more colon cancer and less rectal cancer, and therefore higher colon-to-rectal cancer IRRs. The table shows that the MECC populations did not follow this pattern, with Egyptians and Jordanians (less industrialized populations) having IRRs only a little lower than those of US SEER Whites, and higher than those in China and Poland. However, Israeli Jews (a more industrialized population) did have a high IRR.

Subsites of Colorectal Cancer

Proportions of cases diagnosed by anatomic location within the colon (excluding the rectum) are presented in Figure 4.1. It is difficult to interpret the data from Egypt and Jordan because a substantial proportion of the cases are coded "Colon, NOS." The proportion of ascending colon cancer appears similar in the United States and Israel and accounts for about 15% of all colon cancers, whereas in Cyprus, ascending colon cancer accounts for about 5% of cases. Cancers of the cecum occur in greater proportions in Cyprus and the United States (15% and 21%, respectively) than in Israel (less than 10%). The sigmoid colon is involved in about 30% of

Table 4.3: Colorectal Cancer: Age-Standardized Incidence Rates* and Incidence Rate Ratios (IRR) of Colon and Rectal Cancers in Selected Countries and in Cyprus, Israel (Jews and Arabs), Egypt, Jordan, and US SEER − 1993-1997

Country/Registry	Male			Female		
	Colon	Rectum	IRR	Colon	Rectum	IRR
Canada	25.7	15.8	1.6	19.8	8.8	2.2
China - Shanghai	11.5	9.0	1.3	12.0	7.5	1.6
Japan - Osaka	24.7	15.1	1.6	15.5	7.3	2.1
Denmark	20.5	17.6	1.2	18.4	11.2	1.6
Poland - Krakow	14.5	11.7	1.2	10.4	6.9	1.5
Cyprus	12.7	6.3	2.0	11.2	4.8	2.3
Israel (Jews)	29.6	12.1	2.4	24.7	8.6	2.9
Israel (Arabs)	10.5	6.8	1.5	9.4	4.2	2.2
Egypt	4.6	2.3	2.0	3.3	1.8	1.8
Jordan	7.6	3.9	1.9	7.2	4.0	1.8
US SEER (Whites)	25.9	13.0	2.0	19.6	8.2	2.4
US SEER (Blacks)	32.3	12.7	2.5	26.0	8.2	3.2

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

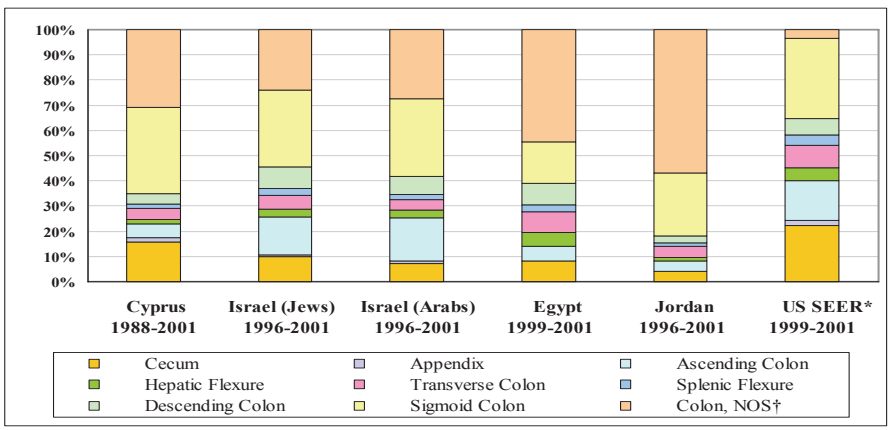
Source: Parkin, D. M., Whelan, S. L., Ferlay, J., Teppo, L., and eds. Cancer incidence in five continents, volume VIII. Lyon (France): International Agency for Research on Cancer; 2002. IARC Scientific Publication No. 155.

colon cancers in Cypriots, Israeli Jews and Arabs, and US SEER. Cancers involving the transverse colon occur in about the same proportion in the Israeli populations and in Cypriots (4% to 5%), but the proportion is higher in US SEER (about 9%). In Israel, the percentage of descending colon cancers is somewhat higher (8%) than in US SEER and Cyprus (6% and 4%, respectively).

Age-Specific Incidence Rates

CRC is rare under 40 years of age, and rates begin to rise sharply after this age. By the age of 40 to 59 years, Israeli Jews and the US SEER population had a substantially higher rate (about 40) than the other populations (13 to 22). The same pattern, with Israeli Jews and US SEER having the highest age-specific rates, occurred in all age groups over 40 years (Table 4.2). Figure 4.2 presents the pattern graphically, showing ASRs by 5-year age groups for ages 50 years and above. Rates in Israeli Jews and the US SEER population display a sharp rise with age, while rates in the other populations increase with age more slowly. In fact, rates remain almost invariable from the age of 50 years in Egyptians, who have very low rates. In Jordanians and Israeli Arabs, the rates rise by about 20% and 40%, respectively, for each 5-year period between the ages of 50 and 75 years. In Cypriots, the percentage rise per 5-year period over this age range is about 50%, which is the same as the rise in Israeli Jews and US SEER. However, because the Cypriot rate at age 50-54 years is about half that of Israeli Jews and the US SEER population, the 50% rise in the Cypriot rate constitutes a much smaller increase.

Figure 4.1. Colorectal Cancer: Proportions of Colon Cancers Diagnosed in Different Anatomical Subsites in Cyprus, Israel (Jews and Arabs), Egypt, Jordan, and US SEER – 1996-2001

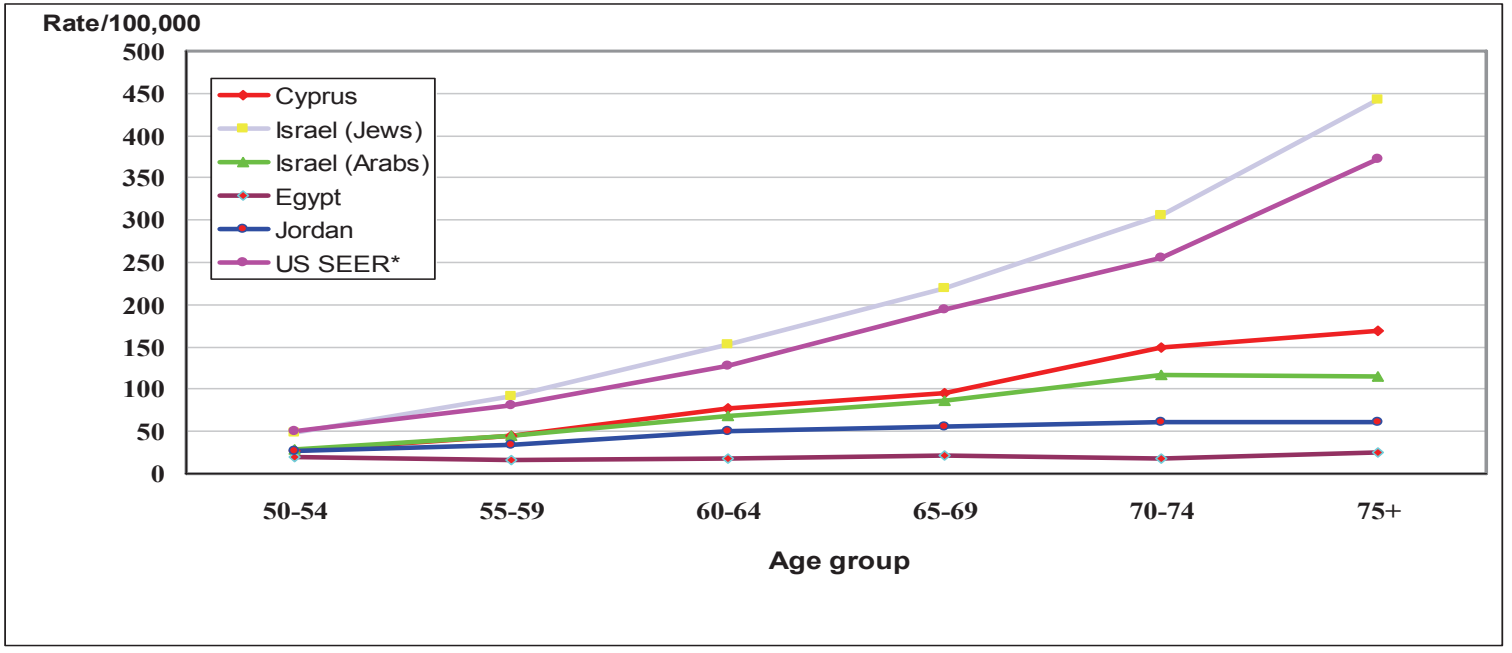


*SEER 13 Registries, Public Use Data, from data submitted November 2004.
†NOS indicates not otherwise specified.

SUMMARY AND CONCLUSIONS

The comparison of incidence rates among several Middle Eastern populations provides the opportunity to explore one of the most significant types of cancer in a new perspective. The comparison comprises 4 countries and 5 subpopulations situated in close proximity that have some similarities and also some marked differences in lifestyle. Egypt and Jordan are classified by the World Bank *[74]* as developing countries, while Cyprus and Israel are considered developed countries. The data presented support the existence of a link between economic status and CRCs, where higher rates were observed in Israeli Jews (similar to US rates) and, to a lesser extent, in Cypriots. The burden of CRC was high among Israeli Jews (higher even than in the United States), and other published data show very high rates among Israeli Jews originating from European countries *[70]*. The high socioeconomic status and the elevated rate of genetic mutations and polymorphisms in this subpopulation are probably both factors related to the increased incidence of CRC. The very low incidence of CRC in Egypt might be explained by other competing diseases (e.g., carcinoma of the urinary bladder), low detection rates, or local nutritional factors that are protective.

Figure 4.2. Colorectal Cancer: Age-Specific Incidence Rates in 5-Year Age Groups for Ages 50 Years and Older 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.

Colon cancer was more common than rectal cancer in all the MECC populations studied, and it constituted over 65% of all CRCs. Examination of the rates of proximal and distal cancers confirms the pattern of a greater proportion of proximal cancers in the more industrialized populations.

This comparison can add to the already established observation that CRC is mainly a result of lifestyle and behavior, including diet and body mass. The correlation found in this comparison between CRC incidence and level of economic development of the various populations is consistent with published literature that more developed countries present with higher rates. It would be interesting to conduct further research in this direction, especially to study in greater depth the apparently low incidence rates presented for Egypt.

REFERENCES

[1] Nilsson B, Gustavson-Kadaka E, Rotstein S, Hakulinen T, Rahu M, Aareleid T. Cancer incidence in Estonian migrants to Sweden. Int J Cancer 1993;55:190-5.

[2] Monroe KR, Hankin JH, Pike MC, Henderson BE, Stram DO, Park S, et al. Correlation of dietary intake and colorectal cancer incidence among Mexican-American migrants: the multiethnic cohort study. Nutr Cancer 2003;45:133-47.

[3] Wogan GN. Diet and nutrition as risk factors for cancer. Princess Takamatsu Symp 1985;16:3-10.

[4] Levin KE, Dozois RR. Epidemiology of large bowel cancer. World J Surg 1991;15:562-7.

[5] Kune S, Kune GA, Watson L. The Melbourne colorectal cancer study: incidence findings by age, sex, site, migrants and religion. Int J Epidemiol 1986;15:483-93.

[6] Tsubono Y, Otani T, Kobayashi M, Yamamoto S, Sobue T, Tsugane S. No association between fruit or vegetable consumption and the risk of colorectal cancer in Japan. Br J Cancer 2005;92:1782-4.

[7] Michels KB, Fuchs CS, Giovannucci E, Colditz GA, Hunter DJ, Stampfer MJ, et al. Fiber intake and incidence of colorectal cancer among 76,947 women and 47,279 men. Cancer Epidemiol Biomarkers Prev 2005;14:842-9.

[8] Campos FG, Logullo Waitzberg AG, Kiss DR, Waitzberg DL, Habr-Gama A, Gama-Rodrigues J. Diet and colorectal cancer: current evidence for etiology and prevention. Nutr Hosp 2005;20:18-25.

[9] Steindorf K, Jedrychowski W, Schmidt M, Popiela T, Penar A, Galas A, et al. Case-control study of lifetime occupational and recreational physical activity and risks of colon and rectal cancer. Eur J Cancer Prev 2005;14:363-71.

[10] Samad AK, Taylor RS, Marshall T, Chapman MA. A meta-analysis of the association of physical activity with reduced risk of colorectal cancer. Colorectal Dis 2005;7:204-13.

[11] Cerin E, Leslie E, Bauman A, Owen N. Levels of physical activity for colon cancer prevention compared with generic public health recommendations: population prevalence and sociodemographic correlates. Cancer Epidemiol Biomarkers Prev 2005;14:1000-2.

[12] Correa Lima MP, Gomes-da-Silva MH. Colorectal cancer: lifestyle and dietary factors. Nutr Hosp 2005;20:235-41.

[13] Zimmerman DD, Gosselink MP, Mitalas LE, Delemarre JB, Hop WJ, Briel JW, et al. Smoking impairs rectal mucosal bloodflow – a pilot study: possible implications for transanal advancement flap repair. Dis Colon Rectum 2005;48:1228-32.

[14] Luchtenborg M, Weijenberg MP, Kampman E, van Muijen GN, Roemen GM, Zeegers MP, et al. Cigarette smoking and colorectal cancer: APC mutations, hMLH1 expression, and GSTM1 and GSTT1 polymorphisms. Am J Epidemiol 2005;161:806-15.

[15] Perez-Holanda S, Rodrigo L, Vinas-Salas J, Pinol-Felis C. Effect of ethanol consumption on colon cancer in an experimental model. Rev Esp Enferm Dig 2005;97:87-96.

[16] Chen K, Jiang Q, Ma X, Li Q, Yao K, Yu W, et al. Alcohol drinking and colorectal cancer: a population-based prospective cohort study in China. Eur J Epidemiol 2005;20:149-54.

[17] Yeh CC, Hsieh LL, Tang R, Chang-Chieh CR, Sung FC. Vegetable/fruit, smoking, glutathione S-transferase polymorphisms and risk for colorectal cancer in Taiwan. World J Gastroenterol 2005;11:1473-80.

[18] Larsson SC, Giovannucci E, Wolk A. A prospective study of dietary folate intake and risk of colorectal cancer: modification by caffeine intake and

cigarette smoking. Cancer Epidemiol Biomarkers Prev 2005;14:740-3.
[19] Chan AT, Giovannucci EL, Meyerhardt JA, Schernhammer ES, Curhan GC, Fuchs CS. Long-term use of aspirin and nonsteroidal anti-inflammatory drugs and risk of colorectal cancer. JAMA 2005;294:914-23.
[20] Courtney ED, Melville DM, Leicester RJ. Review article: chemoprevention of colorectal cancer. Aliment Pharmacol Ther 2004;19:1-24.
[21] Weingarten MA, Zalmanovici A, Yaphe J. Dietary calcium supplementation for preventing colorectal cancer and adenomatous polyps. Cochrane Database Syst Rev 2005;CD003548.
[22] Pence BC. Role of calcium in colon cancer prevention: experimental and clinical studies. Mutat Res 1993;290:87-95.
[23] Chao A, Connell CJ, Jacobs EJ, McCullough ML, Patel AV, Calle EE, et al. Amount, type, and timing of recreational physical activity in relation to colon and rectal cancer in older adults: the Cancer Prevention Study II Nutrition Cohort. Cancer Epidemiol Biomarkers Prev 2004;13:2187-95.
[24] Vogelstein B, Fearon ER, Hamilton SR, Kern SE, Preisinger AC, Leppert M, et al. Genetic alterations during colorectal-tumor development. N Engl J Med 1988;319:525-32.
[25] Winawer SJ, Shike M. Dietary factors in colorectal cancer and their possible effects on earlier stages of hyperproliferation and adenoma formation. J Natl Cancer Inst 1992;84:74-5.
[26] Winters MD, Schlinke TL, Joyce WA, Glore SR, Huycke MM. Prospective case-cohort study of intestinal colonization with enterococci that produce extracellular superoxide and the risk for colorectal adenomas or cancer. Am J Gastroenterol 1998;93:2491-500.
[27] Hemminki K, Chen B. Familial risk for colorectal cancers are mainly due to heritable causes. Cancer Epidemiol Biomarkers Prev 2004;13:1253-6.
[28] Marchand LL. Combined influence of genetic and dietary factors on colorectal cancer incidence in Japanese Americans. J Natl Cancer Inst Monogr 1999;101-5.
[29] Lichtenstein GR. Reduction of colorectal cancer risk in patients with Crohn's disease. Rev Gastroenterol Disord 2002;2:S16-S24.
[30] Riegler G, Carratu R, Tartaglione M, Morace F, Manzione R, Arimoli A. Prevalence and relative risk of malignancy in relatives of inflammatory bowel disease patients and control subjects. J Clin Gastroenterol 1998;27:211-4.
[31] Jain SK, Peppercorn MA. Inflammatory bowel disease and colon cancer: a review. Dig Dis 1997;15:243-52.
[32] Itzkowitz SH. Inflammatory bowel disease and cancer. Gastroenterol Clin North Am 1997;26:129-39.
[33] Itzkowitz SH, Yio X. Inflammation and cancer IV. Colorectal cancer in inflammatory bowel disease: the role of inflammation. Am J Physiol Gastrointest Liver Physiol 2004;287:G7-17.
[34] Rhodes JM, Campbell BJ. Inflammation and colorectal cancer: IBD-associated and sporadic cancer compared. Trends Mol Med 2002;8:10-6.
[35] Bussey HJR. Historical developments in familial polyposis. In: Herrera L, editor. Familial adenomatous polyposis. New York (NY): Alan R. Liss; 1990. p. 1-7.
[36] Peltomaki P, De la Chapelle A. Mutations predisposing to hereditary nonpolyposis colorectal cancer. Adv Cancer Res 1997;71:93-119.
[37] Lynch HT, Smyrk TC, Watson P, Lanspa SJ, Lynch JF, Lynch PM, et al. Genetics, natural history, tumor spectrum, and pathology of hereditary nonpolyposis colorectal cancer: an updated review. Gastroenterology 1993;104:1535-49.
[38] Bonita R, Howe AL. Older women in an aging world: achieving health across the life course. World Health Stat Q 1996;49:134-41.
[39] Prior TW, Chadwick RB, Papp AC, Arcot AN, Isa AM, Pearl DK, et al. The I1307K polymorphism of the APC gene in colorectal cancer. Gastroenterology 1999;116:58-63.
[40] Rozen P, Shomrat R, Strul H, Naiman T, Karminsky N, Legum C, et al. Prevalence of the I1307K APC gene variant in Israeli Jews of differing ethnic origin and risk for colorectal cancer. Gastroenterology 1999;116:54-7.
[41] Menges M, Gartner B, Georg T, Fischinger J, Zeitz M. Cost-benefit analysis of screening colonoscopy in 40- to 50-year-old first-degree relatives of patients with colorectal cancer. Int J Colorectal Dis 2005;[Epub]:1-6.
[42] Lindberg J, Stenling R, Palmqvist R, Rutegard J. Efficiency of colorectal cancer surveillance in patients with ulcerative colitis: 26 years' experience in a patient cohort from a defined population area. Scand J Gastroenterol 2005;40:1076-80.
[43] Losi L, Di Gregorio C, Pedroni M, Ponti G, Roncucci L, Scarselli A, et al. Molecular genetic alterations and clinical features in early-onset colorectal carcinomas and their role for the recognition of hereditary cancer syndromes. Am J Gastroenterol 2005;100:2280-7.
[44] Hakama M, Hoff G, Kronborg O, Pahlman L. Screening for colorectal cancer. Acta Oncol 2005;44:425-39.

[45] Janssens JF. Faecal occult blood test as a screening test for colorectal cancer. Acta Gastroenterol Belg 2005;68:244-6.
[46] Yang SH, Chien CC, Chen CW, Li SY, Huang CJ. Potential of faecal RNA in diagnosing colorectal cancer. Cancer Lett 2005;226:55-63.
[47] Janssens JF. Flexible sigmoidoscopy as a screening test for colorectal cancer. Acta Gastroenterol Belg 2005;68:248-9.
[48] Atkin W. Options for screening for colorectal cancer. Scand J Gastroenterol Suppl 2003;13-6.
[49] Ouyang DL, Chen JJ, Getzenberg RH, Schoen RE. Noninvasive testing for colorectal cancer: a review. Am J Gastroenterol 2005;100:1393-403.
[50] Bromer MQ, Weinberg DS. Screening for colorectal cancer – now and the near future. Semin Oncol 2005;32:3-10.
[51] Autier P, Boyle P, Buyse M, Bleiberg H. Is FOB screening really the answer for lowering mortality in colorectal cancer? Recent Results Cancer Res 2003;163:254-63.
[52] Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2002: cancer incidence. Mortality and prevalence worldwide. IARC cancer base no. 5, version 2.0. Lyon (France): IARC Press; 2004.
[53] Slater G, Papatestas AE, Tartter PI, Mulvihill M, Aufses AH, Jr. Age distribution of right- and left-sided colorectal cancers. Am J Gastroenterol 1982;77:63-6.
[54] Vobecky J, Leduc C, Devroede G. Sex differences in the changing anatomic distribution of colorectal carcinoma. Cancer 1984;54:3065-9.
[55] Jensen OM. Different age and sex relationship for cancer of subsites of the large bowel. Br J Cancer 1984;50:825-9.
[56] Schub R, Steinheber FU. Rightward shift of colon cancer. A feature of the aging gut. J Clin Gastroenterol 1986;8:630-4.
[57] Jass JR. Subsite distribution and incidence of colorectal cancer in New Zealand, 1974-1983. Dis Colon Rectum 1991;34:56-9.
[58] Kee F, Wilson RH, Gilliland R, Sloan JM, Rowlands BJ, Moorehead RJ. Changing site distribution of colorectal cancer. BMJ 1992;305:158.
[59] Demers RY, Severson RK, Schottenfeld D, Lazar L. Incidence of colorectal adenocarcinoma by anatomic subsite. An epidemiologic study of time trends and racial differences in the Detroit, Michigan area. Cancer 1997;79:441-7.
[60] Ji BT, Devesa SS, Chow WH, Jin F, Gao YT. Colorectal cancer incidence trends by subsite in urban Shanghai, 1972-1994. Cancer Epidemiol Biomarkers Prev 1998;7:661-6.
[61] Bonithon-Kopp C, Benhamiche AM. Are there several colorectal cancers? Epidemiological data. Eur J Cancer Prev 1999;8:S3-12.
[62] Troisi RJ, Freedman AN, Devesa SS. Incidence of colorectal carcinoma in the U.S.: an update of trends by gender, race, age, subsite, and stage, 1975-1994. Cancer 1999;85:1670-6.
[63] Miller A, Gorska M, Bassett M. Proximal shift of colorectal cancer in the Australian Capital Territory over 20 years. Aust N Z J Med 2000;30:221-5.
[64] Mitry E, Benhamiche AM, Couillault C, Roy P, Faivre-Finn C, Clinard F, et al. Effect of age, period of diagnosis and birth cohort on large bowel cancer incidence in a well-defined French population, 1976-1995. Eur J Cancer Prev 2002;11:529-34.
[65] Cucino C, Buchner AM, Sonnenberg A. Continued rightward shift of colorectal cancer. Dis Colon Rectum 2002;45:1035-40.
[66] Takada H, Ohsawa T, Iwamoto S, Yoshida R, Nakano M, Imada S, et al. Changing site distribution of colorectal cancer in Japan. Dis Colon Rectum 2002;45:1249-54.
[67] Thygesen LC, Gronbaek M, Johansen C. Colorectal cancer in Denmark 1943-1997. Dis Colon Rectum 2004;47:1232-41.
[68] Rabeneck L, Davila JA, El Serag HB. Is there a true "shift" to the right colon in the incidence of colorectal cancer? Am J Gastroenterol 2003;98:1400-9.
[69] White JS, McCallion K, Gardiner KR, Watson RG, Collins JS, McKee F, et al. Changing patterns of colorectal cancer. Am J Gastroenterol 2004;99:766.
[70] Ministry of Health. Israel National Cancer Registry. 2005. Available at: http://www.health.gov.il/icr/. [Last Accessed: 1/06].
[71] Imperiale TF, Wagner DR, Lin CY, Larkin GN, Rogge JD, Ransohoff DF. Risk of advanced proximal neoplasms in asymptomatic adults according to the distal colorectal findings. N Engl J Med 2000;343:169-74.
[72] Maddox M. Older women and the meaning of health. J Gerontol Nurs 1999;25:26-33.
[73] 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.
[74] The World Bank. Data & statistics: country classification. 2006. Available at: http://www.worldbank.org/data/countryclass/classgroups.htm. [Last Accessed: 1/06].

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BACKGROUND

Incidence and Prevalence

Hepatocellular carcinoma (HCC), which is the main pathological subtype of liver cancer, is a major contributor to cancer incidence and mortality. There is wide variation in the global distribution of HCC. Countries in Asia and sub-Saharan Africa bear 80% of the burden. Because of its short survival and high fatality rates, the incidence, prevalence, and mortality rates for HCC are very close to one another.

For Asian males, the highest age-standardized incidence rate (ASR) published in *Cancer Incidence in Five Continents [1]* reached 95.7 per 100,000 in Quidong County, China. In countries other than those in East and Southeast Asia, rates as low as 1.4 among Israelis born in Israel were reported. The median ASR in Asia was 17.1, reported from Miyagi Prefecture, Japan (Table 5.1).

In other continents, the median ASR for males was 5.5 for Europe (Tyrol, Austria), 4.6 in North America (New Jersey, United States), 3.8 in Oceania (New Zealand), and 3.5 in South America (Villa Clara, Cuba). In Africa, unusually, the two populations ranked in the middle of the distribution had very different rates: In Harare, Zimbabwe, the rate was 27.9, and the next lowest rate was in Kyadondo, Uganda (6.5). Worldwide, the median ASR for all registries was 5.4, among Blacks in New Jersey, United States of America *[1]*. Independent of race and geography, rates in men are at least 2 to 3 times those in women. This sex ratio is more pronounced in high-risk regions *[2]*.

In the United States, the incidence of HCC has approximately doubled over the past 3 decades. Registry data in Canada and Western Europe show similar trends. In contrast, the incidence of HCC in Singapore and Shanghai, China, both high-risk regions, has declined steadily over the past 2 decades. Reasons for both trends are not completely understood, but are likely related to public health efforts to control hepatitis B virus (HBV) in Asia and the "new" risk factors such as hepatitis C virus (HCV) and, possibly, diabetes in low-risk countries *[3]*.

Risk Factors

In most countries where the risk is high for liver cancer, principal risk factors include infection with HBV and exposure to dietary aflatoxin. In contrast, HCV and alcohol consumption are more important risk factors in low-risk countries. In countries with low liver cancer ASRs, excessive alcohol intake, cigarette smoking, and oral contraceptive use also are risk factors for HCC *[4]*.

Hepatitis B virus. Chronic infection by HBV is by far the most important risk factor for HCC in humans. It is estimated that 80% of HCC worldwide is etiologically associated with HBV. In the United States, although the infection rate in the general population is low, HBV is estimated to account for one-fourth of HCC cases among non-Asians *[5]*.

In Egypt, the prevalence of HBV has not been adequately studied because of the attention paid to the increasing prevalence of HCV. Nonetheless, it could be assumed that what applies to HCV also applies to HBV – that is, that there has been a parallel increase in the incidence of HBV.

Hepatitis C virus. Chronic infection by HCV is an important risk factor for HCC in low-incidence countries like the United States. However, this virus is believed to play a relatively minor role in the development of HCC in Africa and Asia. In general, HCC develops only after 2 or more

decades of HCV infection, and the increased risk is restricted largely to patients with cirrhosis or advanced fibrosis.

Factors that predispose to HCC among HCV-infected persons include male sex, older age, HBV co-infection, heavy alcohol intake, and possibly diabetes and a transfusion-related source of HCV infection. Other viral factors apparently play a minor role. The likelihood of development of HCC among HCV-infected persons is estimated to be 1%-3% after 30 years. Once cirrhosis is established, however, HCC develops at an annual rate of 1% to 4% *[6]*.

The population of Egypt has a heavy burden of liver disease, mostly due to chronic infection with HCV. Overall prevalence of antibody to HCV in the general population is around 15%-20%.

Table 5.1. Liver and Intrahepatic Bile Duct Cancer: Age-Standardized Incidence Rates* for the Highest, Median, and Lowest Country within Continent, by Sex − 1993-1997

Continent		Male		Female	
		Country	Rate	Country	Rate
Total World	Highest	China, Qidong County	95.7	Thailand, Khon Kaen	35.4
	Median	Switzerland, Basel	5.5	France, Bas-Rhin	1.9
	Lowest	Algeria	0.9	India, Karunagappally	0.3
Africa	Highest	The Gambia	48.9	The Gambia	17.6
	Median	Zimbabwe, Harare	27.9	Zimbabwe, Harare	11.6
		Kyadondo, Uganda	6.5		
	Lowest	Algeria	0.9	Algeria	0.9
Asia	Highest	China, Qidong County	95.7	Thailand, Khon Kaen	35.4
	Median	Japan, Miyagi Prefecture	17.1	Singapore, Chinese	5.1
	Lowest	Israel, Jews born in Israel	1.4	India, Karunagappally	0.3
Europe	Highest	Italy, Parma Province	19.6	Italy, Parma Province	6.6
	Median	Austria, Tyrol	5.5	Austria, Tyrol	1.9
	Lowest	The Netherlands, Eindhoven	1.4	The Netherlands, Maastricht	0.6
North America	Highest	United States, California, Los Angeles, Korean	20.7	United States, California, Los Angeles, Korean	10.4
	Median	United States, New Jersey	4.6	United States, Michigan, Detroit, White	1.6
	Lowest	Canada, Prince Edward Island	1.0	Canada, Newfoundland	0.8
Oceania	Highest	United States, Hawaii, Hawaiian	10.0	United States, Hawaii, Chinese	4.8
	Median	New Zealand	3.8	United States, Hawaii, White	1.5
	Lowest	Australia, Tasmania	2.3	Australia, South	0.9
South America	Highest	Costa Rica	5.4	Ecuador, Quito	3.5
	Median	Cuba, Villa Clara	3.5	United States, Puerto Rico	2.5
	Lowest	Brazil, Compinas	1.5	Brazil, Compinas	0.6

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

Source: 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.

It was hypothesized that the risk factor for HCV transmission that specifically sets Egypt apart from other countries is a personal history of parenteral anti-schistosomal therapy (PAT). A review of the Egyptian PAT mass-treatment campaigns, discontinued only in the 1980s, shows a very high potential for transmission of bloodborne pathogens. A cohort-specific HCV prevalence was lower in children and young adults than in older cohorts. These lower prevalence rates coincided with the gradual and final replacement of PAT with oral anti-schistosomal drugs at different points in time. Egypt's mass campaigns of PAT may represent the world's largest iatrogenic transmission of bloodborne pathogens *[7]*.

Aflatoxin B1. Aflatoxin B1 is the most potent liver cancer-forming chemical known. It is a product of the mold Aspergillus flavus, found in food that has been stored in a hot and humid environment. This mold is found in such foods as peanuts, rice, soybeans, corn, and wheat. Aflatoxin B1 has been implicated in the development of HCC in southern China and Sub-Saharan Africa. It is thought to cause cancer by producing mutations in the p53 gene. These mutations work by interfering with the gene's important tumor-suppressing functions [8].

In Egypt, aflatoxin contamination of food products is rampant. Methods of grain storage are not controlled, and there is lack of awareness of the dangers of improper storage. A study was conducted in 2 districts in Upper Egypt to measure the presence of fungal population in silage. Aflatoxins showed the highest incidence rates of occurrence in 22.5% of all samples analyzed. Other mycotoxins were detected in all samples *[9]*.

Alcohol. Alcohol intake has also been incriminated as a risk factor for HCC. There is compelling epidemiologic data, supported by animal experiments, confirming the increased risk of cancer associated with alcohol consumption. Cancer of the liver associated with alcohol usually occurs in the setting of cirrhosis *[10]*.

Interactions among risk factors. Sylla et al. *[8]* expressed the importance of interactions between HBV infection and exposure to aflatoxins in the development of HCC. There is evidence from both epidemiological studies and animal models that the 2 factors can act synergistically to increase the risk of HCC. The cellular and molecular mechanism of the interaction is as yet undefined. However, one possible mechanism attested to by studies in HBV transgenic mice is that chronic liver injury alters the expression of specific carcinogen-metabolizing enzymes, thus modulating the binding of aflatoxin to DNA in hepatocytes *[8]*.

Co-infection with HBV and HCV could be considered a potential HCC risk, higher than the risk attributed to infection with either type of virus alone. A multivariate analysis done by Benvegnu and Alberti shows that the risk of HCC is significantly higher in HBV and HCV co-infected patients, compared with those with single HBV surface antigen or anti-HCV positivity. These results indicate different patterns of risk factors, morphogenesis, and incidence of HCC development in HBV- and HCV-associated cirrhosis, suggesting different mechanisms of carcinogenesis *[11]*.

Alcohol may act as a co-carcinogen, and it has strong synergistic effects with other risk factors, including HBV, HCV, aflatoxin, vinyl chloride, obesity, and diabetes mellitus. Alcohol enhances the effects of environmental carcinogens directly; it also enhances them indirectly by contributing to nutritional deficiency and impairing immunological tumor surveillance. Acetylaldehyde, the main metabolite of alcohol, causes hepatocellular injury and is an important factor in causing increased oxidant stress, which damages DNA *[10]*.

RESULTS

Statistics provided by MECC registries showed that the liver was not a common site of cancer, except for Egypt (Table 5.2). Liver cancer's relative frequency was below 2.0% in the other MECC registries and in the US SEER population. In Egypt, however, liver cancer accounted for 12.7% of male cancers, 3.4% of female

cancers, and 8.1% of both sexes together. Male predominance was marked in Egyptians, with a 3.8:1 male-to-female ratio. Next were Cypriots (3.1:1), Israeli Arabs (3.0:1), and Jordanians and Israeli Jews (1.6:1 and 1.4:1, respectively). In US SEER data, the male-to-female ratio was 2.2:1. It is important to note that the sex ratios for the MECC registries other than Egypt are based on small numbers; therefore, they are subject to considerable uncertainty.

Overall Incidence

According to Table 5.2, the ASRs reported from all MECC registries, except Egypt, did not exceed 3.0 for males or 1.6 for females (Israeli Jews). The rates of US SEER were 5.9 for males, 2.1 for females, and 4.2 for both sexes together – rates that were higher than all MECC registries except Egypt.

The ASR for Egypt was 20.6 for males, 5.2 for females, and 12.8 for both sexes together. The rate for Egyptian males was 7 times the second-highest MECC rate (Israeli Jews) and more than 3 times the corresponding US SEER rate. For females, the rate for Egyptians was more than 3 times the highest MECC registry rate (Israeli Jews) and more than twice the US SEER rate (Table 5.2).

A ranking of countries in the world according to their reported liver cancer ASR showed that Egypt occupied the 90th percentile. Its rate was exceeded only by countries in East and Southeast Asia and 3 countries in Africa (Gambia, Mali, and Zimbabwe) *[1]*.

Age

To avoid reporting rates calculated on small numbers of observations, age was grouped into 3 categories, and rates were calculated for these groups (Table 5.3). The table shows the relatively young age distribution of liver cancer patients in Arab populations, which is a reflection of the younger age distribution of these populations compared with Israeli Jews, Cypriots, and the US SEER population.

Table 5.2. Liver and Intrahepatic Bile Duct Cancer: Proportions of Total Cancers, Male-to-Female Ratios, and Age-Standardized Incidence Rates, 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
Percent relative to total cancers	Total	1.1%	0.9%	1.1%	8.1%	1.3%	1.2%
	Male	1.7%	1.1%	1.5%	12.7%	1.6%	1.6%
	Female	0.6%	0.7%	0.6%	3.4%	1.0%	0.8%
Male-to-female ratio		3.1:1	1.4:1	3.0:1	3.8:1	1.6:1	2.2:1
Age-standardized incidence rate†	Total	1.7	2.2	1.6	12.8	1.6	4.2
	Male	2.8	3.0	2.7	20.6	1.9	5.9
	Female	0.8	1.6	0.6	5.2	1.3	2.1

*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.

Liver cancer ASRs showed a progressive increase with age. Below the age of 50 years, the incidence was generally low. Egyptian males had the highest rate (3.4), which is 5 times the rates in the other MECC registries and 2.5 times the US SEER rate. In the 70 years-and-older age group, the ASR for Egyptian males was 107.3 – almost 4 times the rate for Israeli Jews and 2.5 times the US SEER rate. The same general pattern was observed for rates among females aged 70 and older, but at a much lower level. Again, Egypt had the highest rate for females in this age group (32.2), followed by Israeli Jews (15.7). The US SEER rate for females in this age group was 19.5.

Subsites

As shown in Table 5.4, cancer in the liver was much more frequent than in intrahepatic bile ducts. In the MECC countries, the highest frequencies of cancer in the liver were in Egyptians (97.9%), followed by Israeli Arabs (96.9%). The US SEER frequency was 87.2%. The frequency of cancer in intrahepatic bile ducts in the MECC populations was highest in Cypriots (13.0%), followed by Jordanians (12.0%). The US SEER frequency was 12.8%. The significance of these differences awaits further examination.

Across MECC countries, large differences were seen in the ASRs of cancer in the liver. Egypt had the highest rate for males (20.1), nearly 4 times the US SEER rate (5.8). For other MECC registries,

Table 5.3. Liver and Intrahepatic Bile Duct Cancer: Total Cases, Median Age, 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	69	52	17	900	525	375	64	48	16	848	671	177	233	143	90	6,581	4,463	2,118
Median age	67.1	67.7	64.5	71.4	70.6	72.5	56.4	58.7	40.0	59.4	59.3	60.2	59.5	59.5	59.7	67.0	64.8	71.4
Age Groups (Distribution)‡																		
<50 y	*11.6%*	*13.5%*	-	8.6%	9.7%	6.9%	39.1%	*29.2%*	*68.8%*	20.2%	19.4%	23.2%	25.8%	25.9%	25.6%	14.6%	16.2%	11.3%
50-69 y	36.2%	32.7%	*47.1%*	36.2%	37.7%	34.1%	45.3%	54.2%	*18.8%*	63.3%	65.1%	56.5%	53.6%	53.8%	53.3%	43.0%	46.9%	34.8%
70+ y	52.2%	53.8%	*47.1%*	55.2%	52.6%	58.9%	*15.6%*	*16.7%*	-	16.5%	15.5%	20.3%	20.6%	20.3%	21.1%	42.4%	37.0%	53.9%
Age Groups (Rates)§																		
Total rate	1.7	2.8	0.8	2.2	3.0	1.6	1.6	2.7	0.6	12.8	20.6	5.2	1.6	1.9	1.3	4.2	6.4	2.4
<50 y	*0.4*	*0.6*	-	0.3	0.4	0.2	0.5	*0.6*	*0.4*	2.3	3.4	1.1	0.3	0.4	0.3	0.9	1.3	0.5
50-69 y	4.9	6.8	*3.1*	7.0	9.3	5.0	5.6	10.3	*1.2*	51.8	84.9	19.3	5.7	6.7	4.7	14.7	22.6	7.4
70+ y	16.3	29.3	*6.2*	21.0	28.2	15.7	*7.7*	*13.8*	-	67.3	107.3	32.2	10.2	12.9	7.8	29.5	44.0	19.5

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.

the rates ranged between 1.7 for Jordanians and 2.7 for Israeli Jews. Rates for females were much lower compared with males; nevertheless, the Egyptian rate was still the highest (5.2). Rates for females in other MECC registries varied between 0.6 (Israeli Arabs) and1.4 (Israeli Jews). The US SEER rate (2.0) was a little higher than that of Israeli Jews.

Despite the marked variation in incidence rates of cancer in the liver across MECC registries, the rates of cancer of intrahepatic bile ducts were similar and very low. The highest rates were those of Egyptians and US SEER (0.3 and 0.5, respectively).

Histology

As shown in Table 5.5, microscopic proof of diagnosis varied between registries, possibly a reflection of diagnostic practices in different MECC countries. The frequency of histological or cytological diagnosis was remarkably high in Jordanians (98.0%), followed by Cypriots (90.0%). Next were Israeli Arabs and Jews (72.6% and 60.8%, respectively). The frequency was lowest in Egypt (40.5%). In the US SEER population, histological or cytological diagnosis was available for 72.0% of cases.

The most frequent histological diagnosis for both sexes was carcinoma, representing 98.6% in Egyptians, 98.4% in Cypriots,

Table 5.4. Liver and Intrahepatic Bile Duct Cancer: Distribution of Cases and Age-Standardized Incidence Rates,* by Subsite 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
Distribution							
Liver	Total	87.0%	89.0%	96.9%	97.9%	88.0%	87.2%
	Male	84.6%	91.2%	97.9%	97.6%	92.3%	89.9%
	Female	94.1%	85.9%	*93.8%*	98.9%	81.1%	81.4%
Intrahepatic bile ducts	Total	*13.0%*	11.0%	-	2.1%	12.0%	12.8%
	Male	*15.4%*	8.8%	-	2.4%	*7.7%*	10.1%
	Female	-	14.1%	-	-	18.9%	18.6%
Rates*							
Liver	Total	1.5	2.0	1.5	12.5	1.4	3.8
	Male	2.4	2.7	2.6	20.1	1.7	5.8
	Female	0.8	1.4	*0.6*	5.2	1.0	2.0
Intrahepatic bile ducts	Total	*0.2*	0.2	-	0.3	0.2	0.5
	Male	*0.4*	0.2	-	0.5	*0.1*	0.6
	Female	-	0.2	-	-	0.3	0.4

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

†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.

92.5% in Jordanians, 92.1% in Israeli Jews, and 72.3% in Israeli Arabs. The frequency in US SEER data was 96.9%. Differences in frequency between the sexes were minimal.

The frequency of hepatoblastoma was generally low in all registries except for Israeli Arabs – especially females (14.9% for both sexes, 9.1% for males, and 28.6% for females), a point that needs further confirmation, as the data are based on only 7 total hepatoblastoma cases.

The frequency of sarcoma was low (around 1%). Unspecified cancer was also infrequent; the only exception was Israeli Arabs (8.5% for both sexes), but again this is based on only unspecified cases.

In Egypt, the most frequent histological diagnosis was HCC (84.9%). In the US SEER population, the frequency of HCC was 72.4%. In other MECC registries, HCC was also the most common diagnosis, with frequencies that were variable but less than in Egypt and US SEER. The frequency of HCC in Israeli Jews was 69.1%, followed by Israeli Arabs (55.3%), Cypriots (53.2%), and Jordanians (41.7%).

Table 5.5. Liver and Intrahepatic Bile Duct Cancer: Total Cases Microscopically Confirmed, and Proportions of Microscopic Confirmation and Histologic Type, 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
Total cases microscopically confirmed	62	49	13	508	312	196	47	33	14	345	284	61	228	140	88	4,727	3,241	1,486
Microscopically confirmed	90.0%	93.2%	81.3%	60.8%	63.3%	57.1%	72.6%	68.1%	*86.7%*	40.5%	42.1%	34.3%	98.0%	97.7%	98.6%	72.0%	72.7%	70.2%
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	98.4%	98.0%	*100.0%*	92.1%	93.3%	90.3%	72.3%	78.8%	*57.1%*	98.6%	99.3%	95.1%	92.5%	93.6%	90.9%	96.9%	97.7%	95.3%
Hepatocellular carcinoma	53.2%	53.1%	*53.8%*	69.1%	75.6%	58.7%	55.3%	60.6%	*42.9%*	84.9%	85.9%	80.3%	41.7%	49.3%	29.5%	72.4%	78.0%	60.2%
Cholangiocarcinoma	33.9%	34.7%	*30.8%*	16.1%	12.2%	22.4%	*10.6%*	*12.1%*	-	6.4%	*5.3%*	*11.5%*	39.0%	32.1%	50.0%	17.4%	13.4%	26.2%
Unspecified carcinoma	*8.1%*	*6.1%*	-	3.5%	*3.2%*	*4.1%*	-	-	-	6.1%	*6.7%*	-	10.1%	11.4%	*8.0%*	2.8%	2.3%	3.7%
Other specified carcinomas	-	-	*0.0%*	3.3%	*2.2%*	*5.1%*	-	-	*0.0%*	*1.2%*	*1.4%*	*0.0%*	*1.8%*	-	*3.4%*	4.4%	3.9%	5.2%
Hepatoblastoma	*0.0%*	*0.0%*	*0.0%*	*1.4%*	*1.6%*	-	*14.9%*	*9.1%*	*28.6%*	*0.9%*	-	-	*3.5%*	*3.6%*	*3.4%*	1.1%	0.8%	2.0%
Sarcoma	-	-	*0.0%*	*1.8%*	-	*3.6%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*1.3%*	-	-	1.0%	0.9%	1.4%
Haemangiosarcoma	*0.0%*	*0.0%*	*0.0%*	*1.2%*	*1.0%*	*1.5%*	-	-	*0.0%*	-	*0.0%*	-	-	-	-	0.4%	*0.4%*	*0.5%*
Other sarcomas	-	-	*0.0%*	*1.8%*	-	*3.6%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*1.3%*	-	-	0.6%	*0.5%*	*0.9%*
Unspecified cancer	*0.0%*	*0.0%*	*0.0%*	3.5%	*3.5%*	*3.6%*	*8.5%*	-	-	-	-	*0.0%*	*1.8%*	-	-	0.8%	0.6%	1.1%
Other specified cancer	*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%*	*0.0%*	*0.1%*	-	*0.2%*

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). Where a percentage has been suppressed because it is based on only 1 or 2 cases, the remaining percentages will not sum to 100%.

Contrary to the low frequency of HCC in Jordan and Cyprus, the frequency of cholangiocarcinoma was higher in these countries than in the other registries, including US SEER (39.0% and 33.9% for Jordan and Cyprus, respectively). In US SEER series, the reported frequency was 17.4%, which was slightly higher than in Israeli Jews (16.1%), followed by Israeli Arabs (10.6%) and Egyptians (6.4%). The cause of carcinomas of the bile ducts remains speculative, and various genetic alterations are of potential importance *[12]*.

The frequency of unspecified carcinoma was also highest in Jordanians (10.1%) and Cypriots (8.1%) (Table 5.5). It seems likely that most of these unspecified carcinomas are really HCCs, where the medical notes are not specific enough to identify HCC.

Table 5.6 displays incidence rates for the different histological types. These rates were lower than those presented for total cases because they include only those patients with microscopic confirmation. Due to the wide variation among the registries in the percentage of cases that are microscopically confirmed (Table 5.5), comparisons of these rates across registries can be misleading. However, the table does show that the ASR of patients with a microscopic proof of HCC in Egypt was as high as 4.3, confirming the large magnitude of the liver cancer problem in Egypt.

SUMMARY AND CONCLUSIONS

The current results indicated a marked variation in incidence rates, with low incidence in all registries except Egypt. The ASR for Egyptians was 20.6 for males, 5.2 for females, and 12.8 for both sexes together. The Egyptian rates for males were 7 times the highest MECC rate, and more than 3 times the corresponding US SEER rate. For Egyptian females, the rate was more than 3 times the highest MECC rate and more than twice the US SEER rate. Compared with rates reported in *Cancer Incidence in Five Continents*, Egypt ranked next to East and Southeast Asian countries and 3 African countries.

The ASRs increased with age in all MECC registries, and reached 107.3 for males and 32.2 for females in Egypt in the 70+ age group.

Male predominance was evident, with male-to-female ratios between 3.8:1 and 1.4:1. The US SEER ratio was intermediate (2.1:1). The age distribution at diagnosis of patients in Arab populations was younger than that of Cypriot, Israeli Jewish, and US SEER patients. This difference could be attributed to the relatively young age structure of Arab populations.

Cancer in the liver was more frequent than in the intrahepatic bile ducts. Hepatocellular carcinoma was the most frequent histological diagnosis. The frequency of pathological confirmation of diagnosis varied between countries, possibly due to differences in diagnostic practice. This was reflected in the rates of microscopically confirmed cases.

Risk factors for HCC include HBV, HCV, aflatoxins, and alcohol. Except for alcohol, these are assumed to play an important role in the high incidence of HCC in Egypt. HBV vaccination of children and high-risk groups must be the priority in reducing the incidence of HCC. Measures to reduce food spoilage by fungi and the associated dietary exposure to aflatoxins are a desirable public health goal *[13]*.

Successful antiviral therapy of patients with HCV-related cirrhosis may reduce the future risk for HCC. Given the current prevalence of HCV infection among persons 30 to 50 years of age, the incidence and mortality rates of HCC are likely to rise over the next 10 to 20 years. Future research should focus on improving understanding of the incidence and risk factors for HCC, causes of HCV-related carcinogenesis, means of early detection, and better treatment for HCC.

Table 5.6. Liver and Intrahepatic Bile Duct Cancer: Age-Standardized Incidence Rates,* by Histological Diagnosis 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 rates*	1.5	2.6	*0.7*	1.3	1.8	0.9	1.1	1.7	*0.6*	5.1	8.6	1.7	1.6	1.9	1.2	3.1	4.7	1.8
Carcinoma	1.5	2.5	*0.7*	1.2	1.7	0.8	0.9	1.4	*0.4*	5.0	8.5	1.6	1.5	1.8	1.1	3.0	4.6	1.6
Hepatocellular carcinoma	0.8	1.4	*0.3*	0.9	1.4	0.5	0.7	1.1	*0.3*	4.3	7.4	1.3	0.7	1.0	0.4	2.3	3.7	1.0
Cholangiocarcinoma	0.5	0.8	*0.2*	0.2	0.2	0.2	*0.1*	*0.2*	-	0.3	*0.5*	*0.2*	0.6	0.6	0.7	0.5	0.6	0.4
Unspecified carcinoma	*0.1*	*0.1*	-	0.0	*0.0*	*0.0*	-	-	-	0.3	0.6	-	0.2	0.2	*0.1*	0.1	0.1	0.1
Other specified carcinomas	-	-	*0.0*	0.0	*0.0*	*0.0*	-	-	*0.0*	*0.1*	*0.1*	*0.0*	*0.0*	-	*0.0*	0.1	0.2	0.1
Hepatoblastoma	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	-	*0.1*	*0.1*	*0.1*	*0.0*	-	-	*0.0*	*0.0*	*0.0*	0.1	0.1	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
Haemangiosarcoma	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	-	-	*0.0*	-	*0.0*	-	-	-	-	0.0	*0.0*	*0.0*
Other sarcomas	-	-	*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*	*0.0*	*0.0*	0.0	*0.1*	*0.0*	*0.1*	-	-	-	-	*0.0*	*0.0*	-	-	0.0	0.0	0.0
Other specified cancer	*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*	*0.0*	*0.0*	-	*0.0*

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

†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.

Source: 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.

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REFERENCES

[1] 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.

[2] McGlynn KA, London WT. Epidemiology and natural history of hepatocellular carcinoma. Best Pract Res Clin Gastroenterol 2005;19:3-23.

[3] El Serag HB. Hepatocellular carcinoma: an epidemiologic view. J Clin Gastroenterol 2002;35:S72-S78.

[4] Stuver SO. Towards global control of liver cancer? Semin Cancer Biol 1998;8:299-306.

[5] Yu MC, Yuan JM, Govindarajan S, Ross RK. Epidemiology of hepatocellular carcinoma. Can J Gastroenterol 2000;14:703-9.

[6] El Serag HB. Hepatocellular carcinoma and hepatitis C in the United States. Hepatology 2002;36:S74-S83.

[7] Frank C, Mohamed MK, Strickland GT, Lavanchy D, Arthur RR, Magder LS, et al. The role of parenteral antischistosomal therapy in the spread of hepatitis C virus in Egypt. Lancet 2000;355:887-91.

[8] Sylla A, Diallo MS, Castegnaro J, Wild CP. Interactions between hepatitis B virus infection and exposure to aflatoxins in the development of hepatocellular carcinoma: a molecular epidemiological approach. Mutat Res 1999;428:187-96.

[9] El Shanawany AA, Mostafa ME, Barakat A. Fungal populations and mycotoxins in silage in Assiut and Sohag governorates in Egypt, with a special reference to characteristic Aspergilli toxins. Mycopathologia 2005;159:281-9.

[10] Voigt MD. Alcohol in hepatocellular cancer. Clin Liver Dis 2005;9:151-69.

[11] Benvegnu L, Alberti A. Patterns of hepatocellular carcinoma development in hepatitis B virus and hepatitis C virus related cirrhosis. Antiviral Res 2001;52:199-207.

[12] Tannapfel A, Wettekind C. Gallbladder and bile duct carcinoma, biology and pathology. Internist (Berl) 2004;45:33-41.

[13] Wild CP, Hall AJ. Primary prevention of hepatocellular carcinoma in developing countries. Mutat Res 2000;462:381-93.

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BACKGROUND

Worldwide, lung cancer is the most commonly diagnosed cancer and causes more deaths than any other cancer *[1,2]*. Its high mortality rate results from both a high incidence rate and a low survival rate, with only 14% of US lung cancer patients surviving 5 years after diagnosis *[3]*. Lung cancer is also the leading cause of cancer death in most countries *[4-6]*.

International variations in the incidence of lung cancer are striking, with age-standardized incidence rates (ASRs) per 100,000 below 10 in parts of Africa, China, and South America, and over 100 in some Black populations in the United States *[2,5]*.

Throughout all age groups, incidence of lung cancer rises sharply with age *[4]*. This pattern is sometimes complicated by cohort effects related to changes in tobacco consumption *[7-9]*.

Tobacco use is by far the most important risk factor in the development of lung cancer. In 1979, the US Surgeon General estimated that 90% of lung cancer deaths in males and 79% in females were due to cigarette smoking *[4]*. Smoking more than 20 cigarettes a day has been shown to confer a risk of between 15- and 25-fold relative to nonsmokers *[10-12]*. Both the duration and intensity of cigarette smoking increases the risk, as does the tar content and the lack of a filter *[13]*. The risk decreases with time after smoking cessation, with long-term ex-smokers approaching but not reaching the risk of nonsmokers *[14]*. Other types of tobacco smoking, such as pipe, cigar, and water-pipe smoking, are also linked to lung cancer, although the relative risks are not as high as for cigarette smoking *[4]*. Exposure to other persons' cigarette smoke (known as passive smoking or environmental tobacco smoke) is also related to an increased risk of lung cancer, although the relative risk is understandably much lower than in smokers.

Worldwide, the incidence of lung cancer among males is much higher than among females, due primarily to the lower prevalence of smoking among females. The sex difference in cigarette consumption has diminished, and in many countries lung cancer rates continue to increase among females.

Smoking is related to all the major types of lung cancer, including squamous cell carcinoma, small cell carcinoma, and adenocarcinoma. It used to be thought that adenocarcinoma was not caused by smoking, but in the United States, adenocarcinoma is now the most common type of lung cancer in smokers *[15]*.

Several other risk factors for lung cancer have been identified. Occupational exposures that increase the risk of lung cancer include asbestos *[16]*, which also causes an increase in the risk of mesothelioma, a cancer of the pleura *[17]*. Asbestos exposure and cigarette smoking act synergistically, together raising the risk of lung cancer multiplicatively *[18]*.

Other occupational exposures related to lung cancer include arsenic *[19]*, chromium *[20]*, polycyclic aromatic hydrocarbons *[21]*, and radon. The latter exposure was first discovered among underground miners in North America, Europe, and Asia *[22]*, but is now the source of concern for the general population because many household basements show relatively high levels of radon. It is estimated that in the United States, indoor radon may be the second most important risk factor for lung cancer after cigarette smoking *[23]*. Lung cancer is also one of the major effects of exposure to high doses of ionizing radiation, such as in medical and atomic radiation. Various pollutants in urban air are implicated in lung cancer incidence rates worldwide *[4]*.

Epidemiological investigations have shown associations between consumption of fresh vegetables and fruits and a low risk of lung cancer *[24]*. Investigations have focused on carotenoid intake and serum carotenoid levels *[4]*, both of which have also shown associations with low risk of lung cancer. However, several randomized trials of beta-carotene supplementation have yielded the unexpected result that among smokers, high doses of beta-carotene can increase the risk of lung cancer *[25,26]*. The biological explanation is as yet unclear.

There has been some evidence of lung cancer clustering in families, with suggestions that heritable factors may also play a part in lung cancer etiology *[4]*. Much effort has gone into discovering genetic susceptibility factors, and the P450 gene *CYP2D6*, which regulates debrisoquine metabolism, was at one time thought to be important, but later results have indicated that at most its effect is modest *[27]*. Reduced activity of glutathione S-transferase (GST) has also been linked to increased risk of lung cancer, and *GSTM1* deficiency is associated with a moderately elevated relative risk *[28]*.

RESULTS

Table 6.1 presents the total numbers and proportions by age group, incidence rates age-standardized to the world standard, and age- and sex-specific incidence rates for MECC populations and the US SEER population.

The total numbers of cases from each population were at least a few hundred, except for Cypriot, Egyptian, and Israeli Arab females. The proportions of cases over 70 years of age were around 50% in the US SEER and Israeli Jewish populations, 40% in Cypriots, and 20%-30% in Egyptians, Jordanians, and Israeli Arabs. These differences are largely due to differences in the population age distribution (Table 6.1).

The overall ASRs were much lower in the MECC populations than in US SEER. The rates in Israel (Jews and Arabs) were approximately half that of US SEER. In Cyprus, Jordan, and Egypt, rates were between one-third and one-fifth of the US SEER rate (Table 6.1).

Among males, the lung cancer ASR in MECC populations was highest in Israeli Arabs, followed by Israeli Jews, Cypriots, Jordanians, and Egyptians. The rate among Israeli Arab males was 34% higher than in Israeli Jewish males (Table 6.1).

Worldwide statistics *[2]* show that the lung cancer ASRs for males in other Middle Eastern populations, such as Algeria (17.1) and Kuwait (20.0), were close to that in Jordan (16.4), while the rate in other Western countries, such as Canada (59.0) and Ireland (42.3), were similar to that in the United States.

The lung cancer incidence rates in females were lower than in males. All the MECC female populations displayed rates far lower than in the US SEER female population. Among the MECC female populations, the highest rate was in Israeli Jews, but this was only one-third the rate in US SEER. All of the other MECC populations had rates less than half that of Israeli Jews, with Jordanians and Egyptians having the lowest rates. It is notable that the rate among Israeli Arab females was not much higher than the rates among Jordanian and Egyptian females, a reflection of the similarities in cultures and habits related to smoking among females in these 3 Arab populations. The female ASRs in Algerians (1.9) and Omanians (2.6) *[4]* were somewhat lower than in Jordanians (3.1), Egyptians (3.7), and Israeli Arabs (4.8), but Kuwaitis (5.3) had a slightly higher rate.

Table 6.1 also presents the age- and sex-specific incidence rates in 4 broad age groups. As expected, the rates increased with age, from the youngest age group (<50 years of age) to the oldest (age 70 years and older). One interesting aspect of the age-specific incidence rates is that the ratio of the MECC population rates to the US SEER rates

decreased with age. For example, the ratios of the rates in male Israeli Jews to those in the male US SEER population were 0.85 for <50 years of age, 0.64 for 50-60 years of age, 0.61 for 60-70 years of age, and 0.50 for age 70 years and older. For male Israeli Arabs, the ratios were 1.09 for <50 years of age, 1.08 for 50-60 years of age, 0.79 for 60-70 years of age, and 0.62 for age 70 years and older.

Such decreasing ratios are suggestive (but not conclusive) evidence of a cohort effect. It is possible that more recent generations in the Middle East have increasingly taken up cigarette smoking, which has caused the younger age groups to have lung cancer rates more like those seen in the US population. Unfortunately, there is little information about the history of smoking prevalence in the MECC populations, except for that in Israeli Jews. Figure 6.1 shows smoking prevalence from 1965 to 2000 in Israeli Jewish and US males, as well as the lung cancer ASRs in both populations from the mid-1970s onwards. It appears that in the latter part of the 1960s, approximately 30 years before the period covered by this monograph, the smoking prevalence in Israel was not very much lower than in the United States, and that by 1973, 25 years before the monograph's period, the smoking prevalence in Israel had surpassed that in the United States. Thus, although Figure 6.1 does indeed indicate that recent generations of males in Israel have smoked as much or more than their counterparts in the United States, the similarity of the smoking prevalence 25-30 years before this monograph's timeframe raises the question why Israeli rates of lung cancer are not already much closer to those of the United States. While further analysis is required, including an examination of past

Table 6.1. Lung 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*

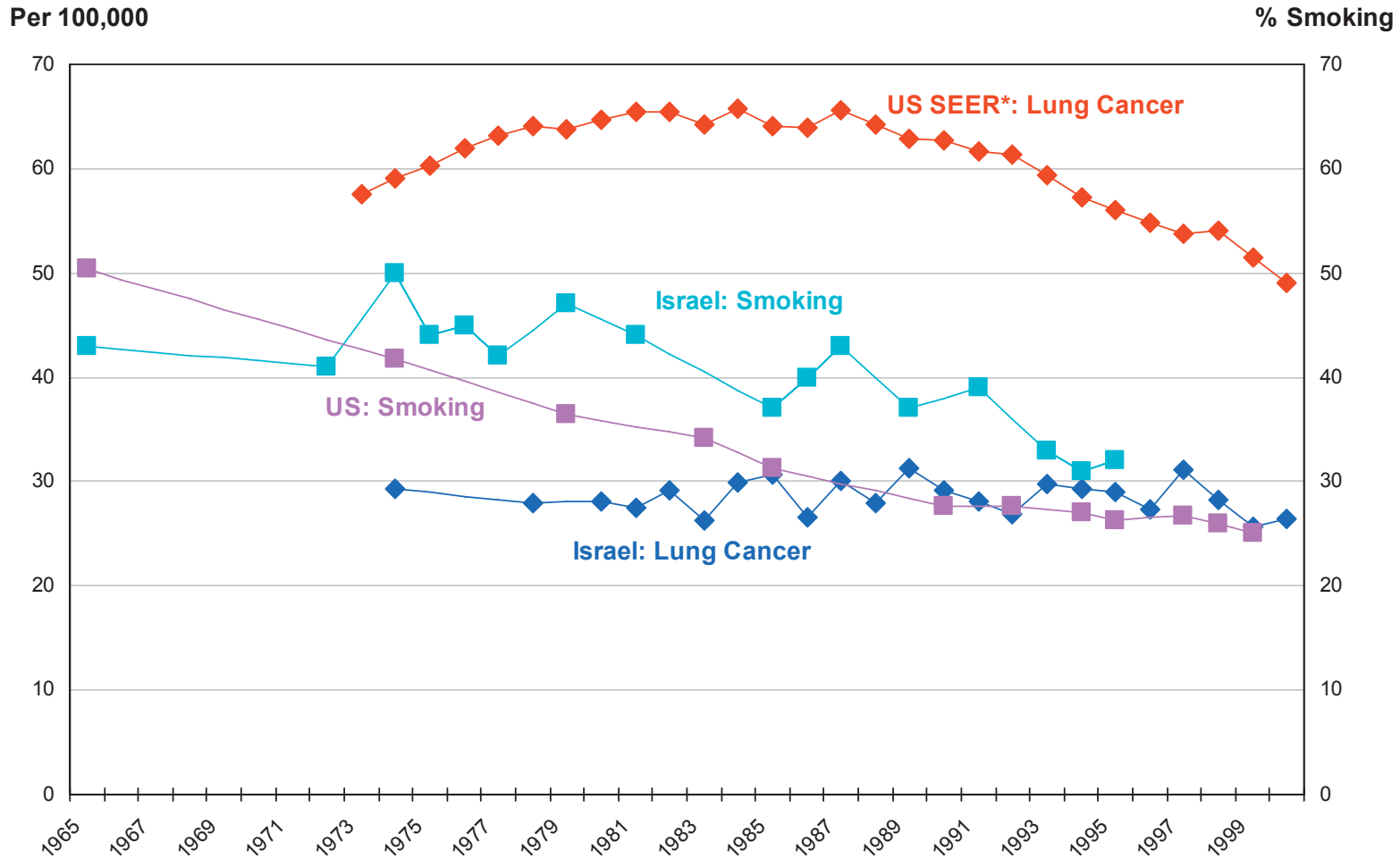
	Cyprus 1998-2001			Israel (Jews) 1996-2001			Israel (Arabs) 1996-2001			Egypt 1999-2001			Jordan 1996-2001			US SEER† 1999-2001		
	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female
Total cases	514	423	91	7,402	4,892	2,510	706	611	95	496	370	126	1,336	1,128	208	63,559	34,973	28,586
Age Groups (Distribution)																		
<50	8.4%	6.9%	*15.4%*	7.6%	6.9%	8.9%	13.5%	11.6%	25.3%	19.6%	16.2%	29.4%	15.3%	13.8%	23.1%	5.7%	5.5%	5.9%
50-59	19.1%	19.1%	18.7%	13.8%	13.5%	14.3%	24.5%	26.5%	*11.6%*	22.2%	22.7%	20.6%	26.0%	26.5%	23.1%	14.7%	14.9%	14.4%
60-69	31.7%	32.2%	29.7%	29.6%	31.9%	25.1%	31.7%	32.9%	24.2%	36.5%	39.5%	27.8%	37.0%	37.6%	33.7%	26.8%	27.7%	25.8%
70+	40.9%	41.8%	36.3%	49.1%	47.7%	51.7%	30.3%	29.0%	38.9%	21.8%	21.6%	22.2%	21.8%	22.1%	20.2%	52.8%	51.9%	54.0%
Age Groups (Rates)‡																		
Total rate	13.4	23.4	4.7	19.0	28.4	11.4	20.4	38.0	4.8	7.7	11.9	3.7	9.9	16.4	3.1	39.2	48.6	31.9
<50	1.7	2.3	*1.1*	2.3	2.8	1.8	2.3	3.6	1.0	1.3	1.6	1.0	1.4	2.1	0.6	3.1	3.3	2.9
50-59	32.0	53.4	11.1	40.4	55.1	27.0	49.7	92.9	*6.3*	17.7	26.6	8.4	23.7	39.2	6.9	75.1	86.2	64.5
60-69	75.0	132.2	24.2	105.0	165.5	55.1	109.8	213.2	21.0	42.9	70.9	16.1	59.5	95.7	18.1	223.3	271.1	181.1
70+	97.4	187.6	27.0	155.1	239.9	93.6	159.9	297.2	49.7	52.3	83.1	25.2	61.6	110.7	17.1	359.3	479.9	277.6

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 6.1. Lung Cancer: Age-Standardized Incidence Rates and Smoking Prevalence among Israeli and US White Males – 1965-2000



*SEER 13 Registries, Public Use Data Set, from data submitted November 2004.
Source: Reproduced with permission of Dr. Gad Rennert, who compiled the data from a variety of sources.

age-specific smoking prevalence and age-specific lung cancer rates, it is possible that genetic factors may explain some of the current differences between Israeli and US SEER rates.

The histological type of lung cancer is an important factor in the epidemiology, treatment, and prognosis of lung cancers. Table 6.2 shows data on the histology of lung and pleural cancers in the MECC and US SEER populations.

The percentage of microscopically confirmed cases varied widely among the registries, with a very high rate in Jordan (97.2%), a rate of around 90% in Cyprus and US SEER registries, and lower rates in Israel and Egypt. The high rate in Jordan indicates possible under-diagnosis of lung cancer in that country, whereas the low rates in Israel indicate that the registry may sometimes be missing details of diagnosis in the information provided by the hospitals. The low rate in Egypt may arise from patterns of care of the elderly population there.

Table 6.2 also indicates a remarkably high proportion of adenocarcinoma in the Cyprus population (54.4%), and a similarly remarkable proportion of large cell carcinoma in Egypt (25.6%). These findings, if confirmed, may provide new clues to the etiology of lung cancer.

Table 6.2. Lung Cancer: Number of Cases and Proportions of Microscopic Confirmation and Histologic Type, 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
Total cases microscopically confirmed	467	381	86	5,936	3,950	1,986	594	523	71	383	288	95	1,298	1,095	203	57,126	31,672	25,454
Microscopically confirmed	90.9%	90.1%	94.5%	80.2%	80.7%	79.1%	84.1%	85.6%	74.7%	77.2%	77.8%	75.4%	97.2%	97.1%	97.6%	89.9%	90.6%	89.0%
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	95.3%	94.8%	97.7%	96.3%	96.4%	96.1%	95.0%	95.2%	93.0%	94.8%	94.4%	95.8%	96.7%	96.9%	95.6%	98.8%	98.8%	98.8%
Squamous cell carcinoma	24.6%	27.0%	*14.0%*	24.8%	29.7%	15.0%	29.0%	31.4%	*11.3%*	21.1%	25.3%	*8.4%*	31.4%	33.9%	17.7%	21.0%	24.8%	16.3%
Adenocarcinoma	54.4%	49.1%	77.9%	36.6%	30.9%	47.8%	31.0%	28.5%	49.3%	29.5%	23.3%	48.4%	27.7%	24.7%	43.4%	37.2%	34.2%	40.9%
Small cell carcinoma	8.1%	9.4%	-	9.6%	10.8%	7.3%	14.8%	14.3%	*18.3%*	13.3%	15.3%	*7.4%*	13.4%	14.3%	8.4%	14.1%	13.1%	15.3%
Large cell carcinoma	*2.1%*	*2.4%*	-	3.9%	4.3%	3.1%	3.2%	3.6%	*0.0%*	25.6%	26.4%	23.2%	3.5%	3.5%	*3.9%*	6.2%	6.4%	5.9%
Other specified carcinomas	3.4%	*3.7%*	-	16.9%	16.0%	18.7%	13.0%	12.8%	*14.1%*	*2.4%*	*2.8%*	-	4.9%	4.6%	*6.9%*	8.3%	8.1%	8.6%
Unspecified carcinoma	*2.6%*	*3.2%*	*0.0%*	4.5%	4.7%	4.2%	4.0%	4.6%	*0.0%*	*2.9%*	*1.4%*	*7.4%*	15.8%	15.9%	15.3%	12.1%	12.3%	11.8%
Sarcoma	-	-	*0.0%*	0.5%	0.5%	*0.6%*	-	*0.0%*	-	*0.0%*	*0.0%*	*0%*	*0.4%*	*0.0%*	*2.5%*	0.2%	0.2%	0.2%
Mesothelioma	-	-	*0.0%*	0.3%	0.4%	*0.2%*	-	-	*0.0%*	-	-	*0.0%*	*0.3%*	*0.4%*	*0.0%*	0.1%	0.1%	*0.0%*
Unspecified cancer	4.1%	4.5%	-	2.5%	2.4%	2.8%	3.7%	4.0%	-	5.0%	*5.2%*	*4.2%*	2.3%	2.5%	*1.5%*	0.8%	0.8%	0.8%
Other specified types	*0.0%*	*0.0%*	*0.0%*	0.3%	*0.3%*	*0.4%*	*0.7%*	-	-	*0.0%*	*0.0%*	*0.0%*	*0.3%*	*0.3%*	-	0.2%	0.2%	0.2%

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%.

SUMMARY AND CONCLUSIONS

The data show that lung cancer incidence in the MECC populations was much lower than in the US SEER population. However, the younger age groups (under 60 years of age) in the Israeli Arab male population had rates comparable to those in US SEER, and it is possible that a cohort effect is in progress, whereby rates in the older age groups will also reach or surpass those in the United States. There is also a hint of a similar phenomenon among the Israeli Jewish male population, although from past smoking prevalence data one might expect to see higher rates than are currently being observed. It is possible that genetic factors may explain part of the difference currently seen between Israeli Jewish and US SEER rates. Apart from the Israeli Arabs, other Arab populations in MECC appear to have had low rates, although reports of higher smoking prevalence in these populations give reason for greater vigilance.

Unusual histological patterns in Cyprus, with a high proportion of adenocarcinoma, and in Egypt, with a high proportion of large cell carcinoma, deserve further examination.

REFERENCES

[1] Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2002: cancer incidence. Mortality and prevalence worldwide. IARC cancer base no. 5, version 2.0. Lyon (France): IARC Press; 2004.

[2] 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.

[3] Ries LAG, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg L, et al. SEER cancer statistics review, 1975-2002. 2003. Available at: http://seer.cancer.gov/csr/1975_2000/. [Last Accessed: 12/05].

[4] Blot WJ, Fraumeni JF, Jr. Cancers of the lung and pleura. In: Schottenfeld D, Fraumeni JF, Jr., editors. Cancer epidemiology and prevention, second edition. New York (NY): Oxford University Press; 1996. p. 637-65.

[5] Devesa SS, Bray F, Vizcaino AP, Parkin DM. International lung cancer trends by histologic type: male:female differences diminishing and adenocarcinoma rates rising. Int J Cancer 2005;117:294-9.

[6] Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74-108.

[7] Thun MJ, Henley SJ, Calle EE. Tobacco use and cancer: an epidemiologic perspective for geneticists. Oncogene 2002;21:7307-25.

[8] Jemal A, Chu KC, Tarone RE. Recent trends in lung cancer mortality in the United States. J Natl Cancer Inst 2001;93:277-83.

[9] Jemal A, Ward E, Thun MJ. Contemporary lung cancer trends among U.S. women. Cancer Epidemiol Biomarkers Prev 2005;14:582-5.

[10] Hammond EC. Smoking in relation to the death rates of one million men and women. Natl Cancer Inst Monogr 1966;19:127-204.

[11] Doll R, Peto R, Wheatley K, Gray R, Sutherland I. Mortality in relation to smoking: 40 years' observation on male British doctors. Br Med J 1994;309:901-11.

[12] McLaughlin JK, Hrubec Z, Blot WJ, Fraumeni JF, Jr. Smoking and cancer mortality among U.S. veterans: a 26-year follow-up. Int J Cancer 1995;60:190-3.

[13] Lubin JH, Blot WJ, Berrino F, Flamant R, Gillis CR, Kunze M, et al. Patterns of lung cancer risk according to type of cigarette smoked. Int J Cancer 1984;33:569-76.

[14] International Agency for Research on Cancer. Tobacco smoking: monographs on the evaluation of carcinogenic risk of chemicals to man, volume 38. Lyon (France): International Agency for Research on Cancer; 1986.

[15] U.S. Surgeon General and Centers for Disease Control and Prevention. The health consequences of smoking. A report of the Surgeon General. 7-12-2005. Available at: http://www.cdc.gov/tobacco/sgr/sgr_2004/index.htm. [Last Accessed: 1/06].

[16] McDonald JC, McDonald AD. Epidemiology of asbestos-related lung cancer. In: Antman K, Aisner J, editors. Asbestos related malignancy. Orlando (FL): Grune and Stratton; 1987. p. 57-9.

[17] McDonald AD, McDonald JC. Epidemiology of malignant mesothelioma. In: Antman K, Aisner J, editors. Asbestos related malignancy. Orlando (FL): Grune and Stratton; 1987. p. 31-55.

[18] Berry G, Newhouse ML, Antonis P. Combined effect of asbestos and smoking on mortality from lung cancer and mesothelioma in factory workers. Br J Ind Med 1985;42:12-8.

[19] Blot WJ, Fraumeni JF, Jr. Arsenic and lung cancer. In: Samet J, editor. The epidemiology of lung cancer. New York (NY): Marcell Dekker; 1994. p. 207-18.
[20] Alderson MR, Rattan NS, Bidstrup L. Health of workmen in the chromate-producing industry in Britain. Br J Ind Med 1981;38:117-24.
[21] International Agency for Research on Cancer. Polynuclear aromatic hydrocarbons: monographs on the evaluation of carcinogenic risk of chemicals to man, parts I-IV, volumes 32-35. Lyon (France): International Agency for Research on Cancer; 1985.
[22] Samet JM. Radon and lung cancer. J Natl Cancer Inst 1989;81:745-57.
[23] Lubin JH, Boice JD, Jr. Estimating Rn-induced lung cancer in the United States. Health Phys 1989;57:417-27.
[24] Colditz GA, Stampfer MJ, Willett WC. Diet and lung cancer. A review of the epidemiologic evidence in humans. Arch Intern Med 1987;147:157-60.
[25] The Alpha-Tocopherol, Beta Carotene (ATBC) Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. N Engl J Med 1994;330:1029-35.
[26] Omenn GS, Goodman GE, Thornquist MD, Balmes J, Cullen MR, Glass A, et al. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. N Engl J Med 1996;334:1150-5.
[27] Shaw GL, Falk RT, Deslauriers J, Frame JN, Nesbitt JC, Pass HI, et al. Debrisoquine metabolism and lung cancer risk. Cancer Epidemiol Biomarkers Prev 1995;4:41-8.
[28] McWilliams JE, Sanderson BJ, Harris EL, Richert-Boe KE, Henner WD. Glutathione S-transferase M1 (GSTM1) deficiency and lung cancer risk. Cancer Epidemiol Biomarkers Prev 1995;4:589-94.

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BACKGROUND

Cancer of the larynx may develop in the glottis (the central part of the larynx that includes the vocal cords), the supra glottis (the area above the glottis), or more rarely in the sub glottis (the area of connection of the larynx to the trachea). It is much more commonly diagnosed in males than females and in developed countries among those aged 60 years and older.

Incidence of laryngeal cancer among males is high in some parts of South America (Argentina, Uruguay, and Cuba), in southwestern Europe (Italy, Spain, and France), in parts of Central/Eastern Europe (Croatia, Slovakia, Yugoslavia, Poland, and Belarus) and in US Blacks. In all these populations, the age-standardized incidence rate (ASR) per 100,000 in males is above 10 per annum. Among females, the highest rates are in US Blacks, but these rates do not exceed 3 *[1]*.

The primary risk factors for laryngeal cancer are tobacco and alcohol. A careful review of several sources of epidemiological evidence concluded that there is a strong dose-response relationship between cigarette smoking and laryngeal cancer *[2]*. Estimates of relative risk for those reporting smoking over 20 cigarettes per day range from around 4 *[3]* to 30 *[4]*. Studies have also shown that the risk decreases with the numbers of years since smoking cessation *[5,6]*.

The evidence that alcohol exposure causes laryngeal cancer is strong, although its quantification is more difficult to pinpoint because researchers have used different measures for exposure. Most investigators have identified a four- to five-fold risk between heavy drinkers and nondrinkers, although the definition of a heavy drinker has varied *[7-11]*.

Many studies have shown that alcohol consumption and cigarette smoking have an independent multiplicative effect on risk. The most recent reports are those of Dosemeci et al. *[11]*, carried out in Turkey, and Schlecht et al. *[12]*, in Brazil. This means that a heavy smoker who also drinks heavily may have a risk 60 times that of someone who abstains from smoking and alcohol (fifteen-fold due to the smoking, multiplied by four-fold due to the alcohol). There are also some reports of synergism – in other words, higher relative risks for smoking among drinkers than among nondrinkers *[10,13]*, but this has not been seen in other studies *[14-16]*.

The fact that these risk behaviors are more common among males than females probably explains the approximately five-fold difference in the incidence of laryngeal cancer between men and women seen in many countries.

Poor eating habits are often associated with alcohol abuse and may be part of the reason that the incidence of laryngeal cancer is higher among heavy drinkers. In particular, low carotenoid intake, resulting from low consumption of fresh vegetables, has been associated with a greater risk of laryngeal cancer *[17]*. In a Phase II prevention trial, 13-cis retinoic acid was found to reduce the risk of second primary head and neck tumors *[18]*.

Occupational exposure studies have suggested links between laryngeal cancer and exposure to asbestos or chromium *[19]*; however, these suggested relationships have not been confirmed.

RESULTS

Table 7.1 presents the numbers, proportions by age group, incidence rates age-standardized to the world standard, and age-specific incidence rates for MECC populations and the US SEER population.

The total numbers of cases from each population were less than 150, except for Israeli Jews, Jordanians, and the US SEER population; therefore, extensive analysis was not possible. Numbers among females were particularly low, except in Israeli Jews and US SEER. The proportion of cases in persons over 60 years of age was around two thirds in US SEER, Israeli Jews, and Cypriots, and around one half in Egyptians, Jordanians, and Israeli Arabs. These differences are largely due to differences in the population age distribution.

Unlike lung cancer, the overall ASRs for laryngeal cancer were not much lower in the MECC populations than in the US SEER population. The rate in Israeli Arab males (6.0) appeared to exceed that in US SEER males (4.6). The rate in Israeli Jews, Jordanians, and Egyptians was similar to the SEER rate. The rate in Cypriots appeared lower than in the other MECC populations. The laryngeal cancer rates among females in MECC populations appeared to be very low, but estimates are based on such small numbers that the actual levels cannot be precisely determined. The exception is among Israeli Jewish females, who appeared to have a lower incidence rate (0.6) than that of US SEER females (1.0).

The MECC rates of laryngeal cancer in males appeared similar to that of Algeria (4.3), but higher than those reported in Kuwait (2.9) and Oman (1.6). The low MECC rates in females are similar to those in other Middle Eastern countries *[1]*.

Given that cigarette smoking is the major risk factor for both laryngeal cancer and lung cancer, the different patterns seen in the incidence rates are puzzling. One might expect the ratios of the ASRs between 2 countries to be similar, but as mentioned above, laryngeal cancer incidence in MECC populations is similar to that of SEER, whereas lung cancer incidence rates in MECC are much lower than in SEER. This difference cannot be explained by alcohol consumption. Levels of alcohol consumption are higher in the SEER

Table 7.1. Laryngeal 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	59	53	6	886	756	130	112	103	9	145	133	12	365	335	30	3,927	3,107	820
Age Groups (Distribution)																		
<60 y	28.8%	30.2%	-	30.5%	30.6%	30.0%	49.1%	50.5%	*33.3%*	51.7%	50.4%	*66.7%*	46.6%	46.0%	53.3%	33.2%	32.9%	34.4%
60+ y	71.2%	69.8%	*83.3%*	69.5%	69.4%	70.0%	50.9%	49.5%	*66.7%*	48.3%	49.6%	*33.3%*	53.4%	54.0%	*46.7%*	66.8%	67.1%	65.6%
Age Groups (Rates)‡																		
Total rate	1.6	3.0	*0.2*	2.4	4.6	0.6	3.1	6.0	*0.5*	2.2	4.2	*0.3*	2.7	4.8	0.4	2.7	4.6	1.0
<60 y	0.6	1.1	-	1.0	1.9	0.3	1.5	2.7	*0.2*	1.1	2.0	*0.2*	1.2	2.0	0.2	1.0	1.7	0.4
60+ y	9.5	18.7	*1.6*	13.7	26.9	3.4	16.5	32.0	*3.3*	11.3	22.2	*1.3*	15.1	27.4	*2.2*	15.8	28.3	5.8

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.

Table 7.2. Laryngeal and Lung Cancer: Age Distribution of Cases among US SEER* Males --1999-2001†

	Laryngeal Cancer 1999-2001	Lung Cancer 1999-2001
Total cases	3,107	34,973
<35 y	*0.2%*	0.2%
35-39 y	0.7%	0.5%
40-44 y	2.7%	1.6%
45-49 y	5.7%	3.1%
50-54 y	10.5%	5.9%
55-59 y	12.9%	9.0%
60-64 y	15.2%	12.6%
65-69 y	15.7%	15.1%
70-74 y	15.1%	18.5%
75+ y	21.1%	33.4%

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

†"*[Numeral]*" (italic) = 0 or 3-15 cases.

populations than in MECC, so one might expect an even larger difference between MECC and SEER in laryngeal cancer incidence than in lung cancer incidence – the opposite of the pattern observed.

Table 7.2 shows a comparison of the percentage of lung cancer cases and laryngeal cancer cases by age among males in the US SEER population. This shows that laryngeal cancer tends to develop at an earlier age than lung cancer. Other data show the same trend. One may therefore infer that the latent period to laryngeal cancer after smoking begins is shorter than for lung cancer. This being the case, the similarity of laryngeal cancer rates in MECC and SEER could be hypothesized to be due to the similarity in more recent years of the smoking prevalence in these populations (for example, see Figure 6.1). Conversely, lung cancer rates could be hypothesized to be different due to higher smoking prevalence in the SEER population in a period previous to that shown in Figure 6.1.

However, this hypothesis does not seem to hold on examination of the age-specific rates of laryngeal cancer in Israeli Jewish and US SEER males, by 5-year age groups (Table 7.3). If the above hypothesis were true, one would expect to see Israeli rates somewhat higher at younger ages and somewhat lower at older ages. Instead, one sees that rates are similar at all ages.

The great majority of registered cases of laryngeal cancers are microscopically confirmed. In the US SEER population, Cyprus, and Jordan, the percentage is over 98%. In Egypt and Israel, it is around 90% (see Table 1.2). Differences in microscopic confirmation rates between the registries are discussed in Chapter 1.

SUMMARY AND CONCLUSIONS

The incidence of laryngeal cancer in males in the MECC populations was comparable to that in US SEER, except that it appeared somewhat higher in Israeli Arabs and somewhat lower in Cypriots. One might expect that the MECC rates should be lower than in the US SEER population, similar to lung cancer, but this was not the case. Further investigation of the reasons seems indicated.

Table 7.3. Laryngeal and Lung Cancer: Age-Standardized and Age-Specific Incidence Rates* among Israeli Jewish and US SEER Males – 1996-2001

	Laryngeal Cancer Israel (Jews) 1996-2001	Laryngeal Cancer US SEER† 1999-2001	Lung Cancer Israel (Jews) 1996-2001	Lung Cancer US SEER† 1999-2001
Total rate	4.6	4.6	28.4	48.6
40-44 y	2.2	1.8	9.9	11.6
45-49 y	4.5	4.3	20.2	26.6
50-54 y	11.5	9.2	35.8	58.7
55-59 y	15.3	15.4	79.2	120.7
60-64 y	23.0	24.1	137.6	225.4
65-69 y	27.6	30.7	202.6	332.1
70-74 y	32.1	33.5	242.9	461.0
75+ y	28.5	27.8	236.8	498.9

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

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

Since cigarette smoking is the major known risk factor for laryngeal cancer, and alcohol consumption in the MECC populations is generally low, monitoring of smoking prevalence combined with programs for smoking cessation would be expected to help reduce the incidence of laryngeal cancer in MECC countries.

REFERENCES

[1] 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.

[2] Rothman KJ, Cann CI, Flanders D, Fried MP. Epidemiology of laryngeal cancer. Epidemiol Rev 1980;2:195-209.

[3] Maier H, Tisch M. Epidemiology of laryngeal cancer: results of the Heidelberg case-control study. Acta Otolaryngol Suppl 1997;527:160-4.

[4] Maier H, Dietz A, Gewelke U, Heller WD, Weidauer H. Tobacco and alcohol and the risk of head and neck cancer. Clin Investig 1992;70:320-7.

[5] Franceschi S, Talamini R, Barra S, Baron AE, Negri E, Bidoli E, et al. Smoking and drinking in relation to cancers of the oral cavity, pharynx, larynx, and esophagus in northern Italy. Cancer Res 1990;50:6502-7.

[6] Schlecht NF, Franco EL, Pintos J, Kowalski LP. Effect of smoking cessation and tobacco type on the risk of cancers of the upper aero-digestive tract in Brazil. Epidemiology 1999;10:412-8.

[7] Herity B, Moriarty M, Daly L, Dunn J, Bourke GJ. The role of tobacco and alcohol in the aetiology of lung and larynx cancer. Br J Cancer 1982;46:961-4.

[8] Brownson RC, Chang JC. Exposure to alcohol and tobacco and the risk of laryngeal cancer. Arch Environ Health 1987;42:192-6.

[9] Tuyns AJ, Esteve J, Raymond L, Berrino F, Benhamou E, Blanchet F, et al. Cancer of the larynx/hypopharynx, tobacco and alcohol: IARC international case-control study in Turin and Varese (Italy), Zaragoza and Navarra (Spain), Geneva (Switzerland) and Calvados (France). Int J Cancer 1988;41:483-91.

[10] Choi SY, Kahyo H. Effect of cigarette smoking and alcohol consumption in the aetiology of cancer of the oral cavity, pharynx and larynx. Int J Epidemiol 1991;20:878-85.

[11] Dosemeci M, Gokmen I, Unsal M, Hayes RB, Blair A. Tobacco, alcohol use, and risks of laryngeal and lung cancer by subsite and histologic type in Turkey. Cancer Causes Control 1997;8:729-37.

[12] Schlecht NF, Franco EL, Pintos J, Negassa A, Kowalski LP, Oliveira BV, et al. Interaction between tobacco and alcohol consumption and the risk of cancers of the upper aero-digestive tract in Brazil. Am J Epidemiol 1999;150:1129-37.

[13] Wynder EL, Covey LS, Mabuchi K, Mushinski M. Environmental factors in cancer of the larynx: a second look. Cancer 1976;38:1591-601.

[14] Baron AE, Franceschi S, Barra S, Talamini R, La Vecchia C. A comparison of the joint effects of alcohol and smoking on the risk of cancer across sites in the upper aerodigestive tract. Cancer Epidemiol Biomarkers Prev 1993;2:519-23.

[15] Zheng W, Blot WJ, Shu XO, Gao YT, Ji BT, Ziegler RG, et al. Diet and other risk factors for laryngeal cancer in Shanghai, China. Am J Epidemiol 1992;136:178-91.

[16] Falk RT, Pickle LW, Brown LM, Mason TJ, Buffler PA, Fraumeni JF, Jr. Effect of smoking and alcohol consumption on laryngeal cancer risk in coastal Texas. Cancer Res 1989;49:4024-9.

[17] McLaughlin JK, Gridley G, Block G, Winn DM, Preston-Martin S, Schoenberg JB, et al. Dietary factors in oral and pharyngeal cancer. J Natl Cancer Inst 1988;80:1237-43.

[18] Hong WK, Lippman SM, Itri LM, Karp DD, Lee JS, Byers RM, et al. Prevention of second primary tumors with isotretinoin in squamous-cell carcinoma of the head and neck. N Engl J Med 1990;323:795-801.

[19] Austin DF, Reynolds P. Laryngeal cancer. Cancer epidemiology and prevention, second edition. New York (NY): Oxford University Press; 1996.

Gad Rennert

BACKGROUND

Breast cancer is the most common cancer in women in developed Western countries *[1]* and is becoming ever more significant in many developing countries *[2]*. Although incidence rates are increasing, mortality rates are stable, representing an improved survival rate. This improvement can be attributed to effective means of early detection, mainly mammography, as well as to significant improvement in treatment options.

RISK FACTORS

Breast cancer should be largely viewed as a disease predominantly influenced by risk factors related to lifestyle, as only approximately 15% of all breast cancer cases can be attributed to familial and genetic influences *[3]*. Most known risk factors for breast cancer can be linked to hazardous effects of hormonal exposures *[4]*, although other risk factors such as exposure to ionizing radiation are also relevant in some populations *[5,6]*.

Reproduction-Related Exposures

Early age at menarche, late age at menopause *[4]*, small number of children and nulliparity, late age at first birth *[7]*, and little or no breastfeeding *[8,9]* have all been associated with an increased risk of developing breast cancer. Although several retrospective studies have suggested that induced abortion is related to an increased risk of this disease, this is not seen in prospective studies *[10]*, and its status as a breast cancer risk factor is unclear. The period of exposure to sex hormones before the first full-term pregnancy is a time when the breast tissue is especially susceptible to carcinogenesis. Long-term use of hormone replacement therapy, but apparently not long-term use of oral contraceptives, is also related to increased risk of breast cancer *[11-14]*. Despite the use of mega-doses of hormones in fertility treatments, there is no current evidence that these treatments are hazardous to the breast *[15,16]*. Of major interest are risk factors for which there is a potential to reduce risk at the population level. Use of external hormones and breastfeeding probably are the 2 best candidates. Recent meta-analyses have demonstrated that long-term breastfeeding can be linked with up to a 30% reduction in breast cancer risk.

Benign Breast Disease

History of benign breast disease is also related to increased risk of breast cancer *[17]*. The risk, however, is mostly restricted to women who underwent biopsies, and especially those in whom atypical hyperplasia was found in such biopsies *[18]*.

Nutritional Factors

The role of diet and nutrition in the etiology of breast cancer has been under debate for decades. Dietary fat has been the most investigated food constituent studied in this regard. It is currently believed that a high-fat diet is not directly related to the risk of breast cancer *[19,20]*. Overall caloric intake, and obesity in particular with certain weight-gain patterns, are related to increased breast cancer risk, with different effects between pre- and post-menopausal women *[21,22]*. This is also in line with a proven role of regular physical activity in reducing breast cancer risk *[23]*. High fruit and vegetable consumption is related to decreased breast cancer risk in most, but not all, studies *[24]*. Specifically, the consumption of cruciferous vegetables has been shown in vitro and in vivo to be related to such protection *[25]*. Of all food items studied, regular alcohol consumption, even at moderate levels, has consistently been

found to be related to a mild increase in breast cancer risk in women *[26,27]*.

Other Lifestyle and Environmental Risk Factors

Active and passive smoking have recently been shown to be related to breast cancer risk *[27,28]*. Ionizing radiation has been shown to increase the risk of breast cancer in studies following cohorts exposed to the A-bomb as well as in studies of women exposed to medical radiation *[5,6]*.

Numerous studies have failed to show that environmental hazards, such as exposure to specific pollutants, are substantially related to breast cancer risk. Some have suggested that exposure to polychlorinated biphenyls (known as PCBs) and organochlorines carries increased risk of breast cancer, but these suggestions have not been substantiated in well-designed studies *[29-31]*.

High Breast Density

High breast density, as reflected on mammography films, has been shown to be one of the most significant markers of breast cancer risk *[32]*. Dense breast tissue probably reflects high hormonal exposure and is typical of young women, women using hormone replacement therapy, and those who are *BRCA* gene carriers.

Genetic Factors

An established proportion of all breast cancer cases is caused by mutations in specific genes, mainly the *BRCA* genes. This proportion differs between different ethnic groups, and is especially high among Jewish women of Ashkenazi and Iraqi origin *[33-38]*. In the latter group, up to 10% of all newly diagnosed breast cancers are due to mutations in these genes. In addition to *BRCA* gene mutations, other genes such as *AT* and *p53* are also involved in the development of breast cancer *[3]*. A variety of single nucleotide polymorphisms in genes encoding phase I and phase II enzymes, as well as other enzymes involved in the hormonal metabolism, are thought to interact with hormonal, nutritional, and radiological exposures to increase the risk of breast cancer.

Risk Factor Summary

Differences in prevalence of exposure to these lifestyle and genetic risk factors among women from different countries in the Middle East are probably responsible for the variability in breast cancer incidence seen between countries in this area *[39,40]*. Time trends in the prevalence of the lifestyle risk factors can be directly correlated with time trends in breast cancer incidence. Delay in time of first pregnancy, decrease in number of children and in breastfeeding, increase in use of external hormones, and a move toward high-calorie Western diets are all responsible for the current trends in breast cancer incidence in the developed as well as the developing countries in the Middle East.

RESULTS

Overall Incidence

Breast cancer was the leading tumor in females in all cancer registries involved in this analysis, accounting for as high as 37.6% of all reported tumors in Egyptian females to as low as 27.7% of all reported tumors in Israeli Arab females (Table 8.1). Age-standardized incidence rates (ASRs) per 100,000 females were highest among Israeli Jews (93.1), similar to the rates reported in US SEER females (97.2). These rates were significantly higher than those reported in Cypriot (57.7), Egyptian (49.6), Jordanian (38.0), and Israeli Arab (36.7) females. The high incidence rates described in Israeli Jews were similar to those described in North American and West European countries, while the lower rates in the other

Middle Eastern groups were more similar to rates in Mediterranean Europe, Eastern Europe, and some of Asia and Africa *[41]*.

Male breast cancer was a relatively rare disease, responsible for only 0.2%-0.5% of all malignancies in males in all registries (MECC and US SEER) (see Table 1.6). Nevertheless, the age-standardized rate in Israeli Jewish males (1.1) was almost 40% higher than the rates reported by the US SEER program or the Egyptian registry (0.8) (see Table 1.7).

Age

Marked differences are noted between age-specific breast cancer rates in participating registries. Age-specific rates in almost all age groups were highest in the Israeli Jewish population (Table 8.2). These rates were higher than the US SEER rates in the age groups 35-54 years and were similar to or slightly lower than the US rates for the older age groups. Age-specific rates in females 25-34 years were highest in the Egyptian registry and substantially lower in the Jordanian and Israeli Arab populations. While between 57% and 68% of all breast cancers in the Arab populations of Egypt, Jordan, and Israel were diagnosed before the age of 55 years, only about 44% of the breast cancers among Cypriots and 37% among Israeli Jews were diagnosed in that age group. The Israeli Jewish figure was again much closer to the US SEER figure of 35% (Figure 8.1).

Histology

As shown in Table 8.3, microscopic confirmation was available for the vast majority of the registered malignancies, ranging from 92.0% to 99.4%, with small differences between the participating countries. Classification of tumors into specific histological subgroups was available for 98.6% of the tumors with microscopic diagnosis in Cypriots, 94.2% in Israeli Jews, 91.5% in Israeli Arabs, 91.3% in Egyptians, and 90.7% in Jordanians, as compared with 98.7% of the tumors in the SEER program. Thus, in all of the MECC registries, less than 10% of the microscopically confirmed breast cancers were identified as neoplasm or carcinoma only.

The leading tumor histology in all registries was infiltrating duct carcinoma, followed by lobular carcinoma (Table 8.3). In the SEER program, more infiltrating duct carcinomas were registered with a

Table 8.1. Breast Cancer: Female Breast Cancer Indicators 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
Number of incident female breast cancer cases	1,066	17,325	762	1,945	2,930	78,802
Breast cancer as proportion of all reported tumors in females	35.4%	31.5%	27.7%	37.6%	32.5%	32.3%
Female breast cancer age-standardized incidence rates†	57.7	93.1	36.7	49.6	38.0	97.2

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

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

lobular component than in the MECC region registries. Between-country differences were noted mainly in the proportion of lobular carcinomas and adenocarcinomas.

DISCUSSION

The main finding in these data is the high incidence rate of breast cancer in Israeli Jews, compared with a low rate in Arab populations and an intermediate rate in Cypriots. While the proportion of all cases occurring in younger ages was higher among the Arabs, the age-specific rates in practically all age groups were highest in the Israeli Jewish population. A younger age distribution of the cases in Arab populations is a reflection of the younger demographic profile. The use of age-specific rates corrects for this demographic difference. It is of interest, however, that the rates in the very young age groups in Egyptians, but not in Jordanians or Israeli Arabs, were similar to the rates in Israeli Jews, which are among the highest in

Table 8.2. Breast Cancer: Age-Standardized and Age-Specific Incidence Rates among Females 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 rate‡	57.7	93.1	36.7	49.6	38.0	97.2
Age Groups (Rates)§						
00-04 y	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*
05-09 y	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*
10-14 y	*0.0*	-	*0.0*	*0.0*	*0.0*	*0.1*
15-19 y	*0.0*	*0.3*	*0.0*	-	-	*0.2*
20-24 y	-	1.7	*0.0*	*1.4*	*0.8*	1.3
25-29 y	*4.9*	9.5	8.7	9.8	5.7	7.1
30-34 y	27.2	27.8	11.8	28.9	20.8	25.2
35-39 y	43.5	69.5	35.2	63.6	47.1	61.7
40-44 y	96.3	124.4	53.4	96.7	73.6	117.5
45-49 y	148.8	205.9	93.5	144.9	82.6	192.1
50-54 y	185.8	275.3	104.2	171.5	129.3	253.1
55-59 y	166.7	310.1	124.0	181.2	114.6	332.4
60-64 y	198.3	346.8	144.0	144.2	134.8	386.8
65-69 y	195.1	359.1	136.8	105.0	131.1	431.1
70-74 y	225.4	405.1	118.7	94.1	103.0	458.7
75+ y	203.7	379.9	96.4	99.6	77.6	458.7

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.

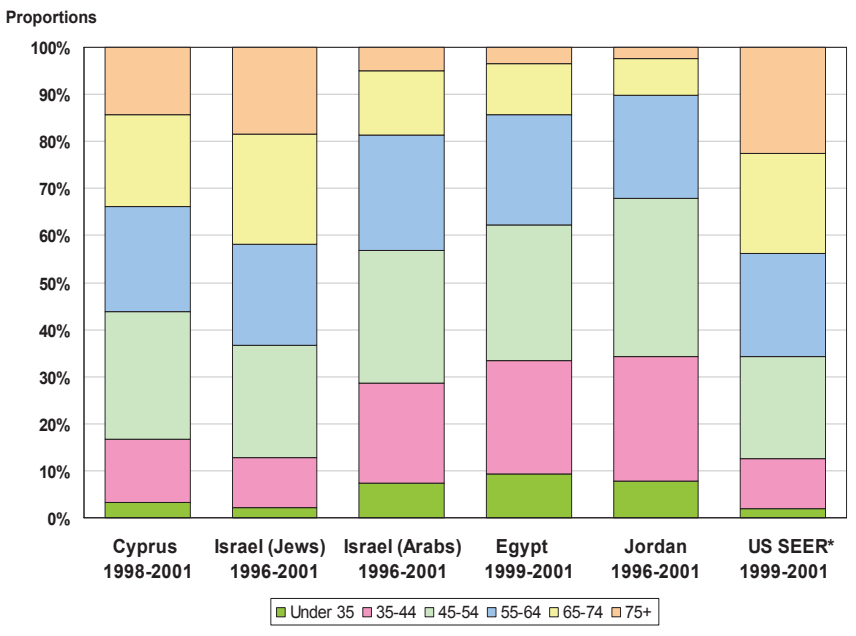
‡Rates are per 100,000 females and are age-standardized to the World Standard Million.

§Rates are per 100,000 females.

the world. Given the fact that the Egyptian registry covers only part of the Egyptian population, a remote possibility that some of these rates reflect a selection into the study cohort of younger women cannot be ignored. Nevertheless, a study of immigrants from the Middle East to Australia did indicate that the Egyptian women had the highest breast cancer rates of all Middle Eastern immigrants *[42]*.

These differences in incidence rates provide an example of the potential role of lifestyle and genetic factors in breast cancer etiology. As the Arab and Jewish populations differ dramatically with respect to most of the important hormonal risk factors (number of children, total length of breastfeeding, age at first birth, use of external hormones) as well as with respect to diet *[43]*, it is not surprising that such large differences in incidence are evident. Studies comparing the etiology of breast and colon cancers in Jewish and Arab women in Israel have shown major differences in the number of births and prevalence of breastfeeding between the 2 demographic groups and between cases and controls within each of the groups. A major cohort effect has also been observed, with the Israeli Arab population moving toward the behaviors of the Israeli Jewish population (lower number of children and less breastfeeding in the younger cohort). Still, breastfeeding in the Arab populations is highly prevalent and is seen as required by Islam *[44]*. A study in Jordan has indicated that obesity was the only risk factor, of those studied, that was significantly different between women with breast cancer and healthy controls *[45]*. The Mediterranean diet – with high consumption of fruits, vegetables, and olive oil, and low consumption of red meat – is the staple of most Arab populations and is usually correlated with reduced risk of several types of cancer, among them breast cancer *[46-49]*.

Figure 8.1. Breast Cancer: Proportions of New Cases by Age Group 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.

About 10% of all breast cancers in the large Ashkenazi Jewish population carry founder mutations in the *BRCA* genes. The high prevalence of these mutations in the Jewish population is at least partially responsible for the exceptionally high incidence rates in the younger Jewish age groups. It is also potentially responsible for the slightly higher proportion of lobular tumors as well as for the higher breast cancer rate in Jewish males (due to the founder mutation 6174delT in *BRCA2*). Such high-prevalence founder mutations have not been described in the Arab population *[50-52]*. Mutations described in the Cypriot population are rare *[53]*.

Another possible contributing factor to the observed differences in breast cancer rates between Jordan and Egypt and Israel is the difference in screening practices between the countries, although the impact of such a difference is only temporary. Israel has been employing a nationwide, full-coverage mammography screening

program in women over the age of 50 since 1996. Organized screening usually results in a temporary increase in incidence rates. Given the length of time it took to achieve a high screening prevalence, this temporary effect could have an impact for a period of about 10 years.

SUMMARY AND CONCLUSIONS

Breast cancer rates in the Middle East registries included in this analysis express a unique picture of the Israeli Jewish population having one of the highest rates worldwide, and the neighboring Arab populations having some of the lower world rates. Such a major difference between populations living in a relatively small area

Table 8.3. Breast Cancer: Proportions of Microscopic Confirmation and Histologic Type of Female Breast Cancers 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 cases microscopically confirmed	1,062	16,104	718	1,842	2,956	78,489
Microscopically confirmed	98.7%	92.0%	92.9%	99.4%	93.5%	98.9%
Distribution of Microscopically Confirmed Cases						
Histologic distribution†	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
Unspecified: Neoplasm, carcinoma[1]	1.4%	5.8%	8.5%	8.7%	9.3%	1.3%
Specified histologic type	98.6%	94.2%	91.5%	91.3%	90.7%	98.7%
Distribution of Microscopically Confirmed and Specified Cases						
Microscopically confirmed and specified	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
Infiltrating duct carcinoma[2]	80.7%	77.5%	78.1%	84.7%	81.8%	70.2%
Lobular carcinoma[3]	7.3%	9.7%	8.5%	5.3%	7.4%	8.4%
Infiltrating duct and lobular carcinoma[4]	2.3%	2.7%	3.7%	2.8%	1.8%	8.8%
Adenocarcinoma[5]	7.4%	5.3%	3.5%	1.3%	4.7%	6.9%
Medullary carcinoma[6]	0.3%	1.1%	0.9%	1.0%	1.5%	0.7%
All other	2.0%	3.7%	5.3%	4.9%	2.8%	5.0%

ICD-O-3 codes
[1]8000,8001,8010,8020,8021,8230
[2]8500,8521,8541
[3]8520
[4]8522
[5]8050,8140,8211,8260,8401,8480,8481,8490,8503
[6]8510

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

†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 will not sum to 100%.

emphasizes the importance of both lifestyle and genetic factors in the causation of breast cancer. It is very important to evaluate the prevalence of risk habits in the area populations and to correlate these exposures with noted differences in incidence. This will allow for a better understanding of the optimal way to combat breast cancer in low- and high-incidence populations.

REFERENCES

[1] Althuis MD, Dozier JM, Anderson WF, Devesa SS, Brinton LA. Global trends in breast cancer incidence and mortality 1973-1997. Int J Epidemiol 2005;34:405-12.

[2] Yang L, Parkin DM, Ferlay J, Li L, Chen Y. Estimates of cancer incidence in China for 2000 and projections for 2005. Cancer Epidemiol Biomarkers Prev 2005;14:243-50.

[3] Martin AM, Weber BL. Genetic and hormonal risk factors in breast cancer. J Natl Cancer Inst 2000;92:1126-35.

[4] ESHRE Capri Workshop Group. Hormones and breast cancer. Hum Reprod Update 2004;10:281-93.

[5] Ronckers CM, Erdmann CA, Land CE. Radiation and breast cancer: a review of current evidence. Breast Cancer Res 2005;7:21-32.

[6] Carmichael A, Sami AS, Dixon JM. Breast cancer risk among the survivors of atomic bomb and patients exposed to therapeutic ionising radiation. Eur J Surg Oncol 2003;29:475-9.

[7] Albrektsen G, Heuch I, Hansen S, Kvale G. Breast cancer risk by age at birth, time since birth and time intervals between births: exploring interaction effects. Br J Cancer 2005;92:167-75.

[8] Lipworth L, Bailey LR, Trichopoulos D. History of breast-feeding in relation to breast cancer risk: a review of the epidemiologic literature. J Natl Cancer Inst 2000;92:302-12.

[9] Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. Lancet 2002;360:187-95.

[10] Beral V, Bull D, Doll R, Peto R, Reeves G, Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and abortion: collaborative reanalysis of data from 53 epidemiological studies, including 83,000 women with breast cancer from 16 countries. Lancet 2004;363:1007-16.

[11] Beral V, Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet 2003;362:419-27.

[12] Bergkvist L, Adami HO, Persson I, Hoover R, Schairer C. The risk of breast cancer after estrogen and estrogen-progestin replacement. N Engl J Med 1989;321:293-7.

[13] Hulley S, Furberg C, Barrett-Connor E, Cauley J, Grady D, Haskell W, et al. Noncardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). JAMA 2002;288:58-66.

[14] Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. Lancet 1996;347:1713-27.

[15] Gauthier E, Paoletti X, Clavel-Chapelon F. Breast cancer risk associated with being treated for infertility: results from the French E3N cohort study. Hum Reprod 2004;19:2216-21.

[16] Burkman RT, Tang MT, Malone KE, Marchbanks PA, McDonald JA, Folger SG, et al. Infertility drugs and the risk of breast cancer: findings from the National Institute of Child Health and Human Development Women's Contraceptive and Reproductive Experiences Study. Fertil Steril 2003;79:844-51.

[17] Wang J, Costantino JP, Tan-Chiu E, Wickerham DL, Paik S, Wolmark N. Lower-category benign breast disease and the risk of invasive breast cancer. J Natl Cancer Inst 2004;96:616-20.

[18] Vogel VG. Atypia in the assessment of breast cancer risk: implications for management. Diagn Cytopathol 2004;30:151-7.

[19] Cho E, Spiegelman D, Hunter DJ, Chen WY, Stampfer MJ, Colditz GA, et al. Premenopausal fat intake and risk of breast cancer. J Natl Cancer Inst 2003;95:1079-85.

[20] Velie E, Kulldorff M, Schairer C, Block G, Albanes D, Schatzkin A. Dietary fat, fat subtypes, and breast cancer in postmenopausal women: a prospective cohort study. J Natl Cancer Inst 2000;92:833-9.

[21] Key TJ, Appleby PN, Reeves GK, Roddam A, Dorgan JF, Longcope C, et al. Body mass index, serum sex hormones, and breast cancer risk in postmenopausal women. J Natl Cancer Inst 2003;95:1218-26.

[22] Harvie M, Howell A, Vierkant RA, Kumar N, Cerhan JR, Kelemen LE, et al. Association of gain and loss of weight before and after menopause with risk of postmenopausal breast cancer in the Iowa women's health study. Cancer Epidemiol Biomarkers Prev 2005;14:656-61.
[23] Patel AV, Callel EE, Bernstein L, Wu AH, Thun MJ. Recreational physical activity and risk of postmenopausal breast cancer in a large cohort of US women. Cancer Causes Control 2003;14:519-29.
[24] Zhang S, Hunter DJ, Forman MR, Rosner BA, Speizer FE, Colditz GA, et al. Dietary carotenoids and vitamins A, C, and E and risk of breast cancer. J Natl Cancer Inst 1999;91:547-56.
[25] Fares FA, Ge X, Yannai S, Rennert G. Dietary indole derivatives induce apoptosis in human breast cancer cells. Adv Exp Med Biol 1998;451:153-7.
[26] McDonald JA, Mandel MG, Marchbanks PA, Folger SG, Daling JR, Ursin G, et al. Alcohol exposure and breast cancer: results of the women's contraceptive and reproductive experiences study. Cancer Epidemiol Biomarkers Prev 2004;13:2106-16.
[27] Collaborative Group on Hormonal Factors in Breast Cancer. Alcohol, tobacco and breast cancer–collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. Br J Cancer 2002;87:1234-45.
[28] Reynolds P, Hurley S, Goldberg DE, Anton-Culver H, Bernstein L, Deapen D, et al. Active smoking, household passive smoking, and breast cancer: evidence from the California Teachers Study. J Natl Cancer Inst 2004;96:29-37.
[29] Engel LS, Hill DA, Hoppin JA, Lubin JH, Lynch CF, Pierce J, et al. Pesticide use and breast cancer risk among farmers' wives in the agricultural health study. Am J Epidemiol 2005;161:121-35.
[30] Coyle YM. The effect of environment on breast cancer risk. Breast Cancer Res Treat 2004;84:273-88.
[31] Calle EE, Frumkin H, Henley SJ, Savitz DA, Thun MJ. Organochlorines and breast cancer risk. CA Cancer J Clin 2002;52:301-9.
[32] Kerlikowske K, Shepherd J, Creasman J, Tice JA, Ziv E, Cummings SR. Are breast density and bone mineral density independent risk factors for breast cancer? J Natl Cancer Inst 2005;97:368-74.
[33] Szabo CI, King MC. Population genetics of BRCA1 and BRCA2. Am J Hum Genet 1997;60:1013-20.
[34] Struewing JP, Hartge P, Wacholder S, Baker SM, Berlin M, McAdams M, et al. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. N Engl J Med 1997;336:1401-8.
[35] Anglian Breast Cancer Study Group. Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases. Br J Cancer 2000;83:1301-8.
[36] Hopper JL, Southey MC, Dite GS, Jolley DJ, Giles GG, McCredie MR, et al. Population-based estimate of the average age-specific cumulative risk of breast cancer for a defined set of protein-truncating mutations in BRCA1 and BRCA2. Australian Breast Cancer Family Study. Cancer Epidemiol Biomarkers Prev 1999;8:741-7.
[37] Ford D, Easton DF, Stratton M, Narod S, Goldgar D, Devilee P, et al. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. Am J Hum Genet 1998;62:676-89.
[38] Rennert G, Dishon S, Rennert HS, Fares F. Phenotypic characteristics of families with BRCA1 and BRCA2 mutations in Israel. Eur J Cancer Prev 2005;14:357-61.
[39] Chlebowski RT, Chen Z, Anderson GL, Rohan T, Aragaki A, Lane D, et al. Ethnicity and breast cancer: factors influencing differences in incidence and outcome. J Natl Cancer Inst 2005;97:439-48.
[40] Bernstein L, Teal CR, Joslyn S, Wilson J. Ethnicity-related variation in breast cancer risk factors. Cancer 2003;97:222-9.
[41] 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.
[42] McCredie M, Coates M, Grulich A. Cancer incidence in migrants to New South Wales (Australia) from the Middle East, 1972-91. Cancer Causes Control 1994;5:414-21.
[43] Shakour SK, Almog R, Gruber SB, Low M, Pinchev M, Reisfeld D, et al. Reproductive risk factors for breast and colorectal cancers in the Arab population in Israel (abstract). Cairo (Egypt): Conference on Cancer in Developing Countries; 2005.
[44] Hawwas AW. Breast feeding as seen by Islam. Popul Sci 1987;7:55-8.
[45] Atoum MF, Al Hourani HM. Lifestyle related risk factors for breast cancer in Jordanian females. Saudi Med J 2004;25:1245-8.
[46] Trichopoulou A, Lagiou P, Kuper H, Trichopoulos D. Cancer and Mediterranean dietary traditions. Cancer Epidemiol Biomarkers Prev 2000;9:869-73.

[47] Alarcon de la Lastra C, Barranco MD, Motilva V, Herrerias JM. Mediterranean diet and health: biological importance of olive oil. Curr Pharm Des 2001;7:933-50.

[48] Menendez JA, Vellon L, Colomer R, Lupu R. Oleic acid, the main monounsaturated fatty acid of olive oil, suppresses Her-2/neu (erbB-2) expression and synergistically enhances the growth inhibitory effects of trastuzumab (Herceptin) in breast cancer cells with Her-2/neu oncogene amplification. Ann Oncol 2005;16:359-71.

[49] Nelson R. Oleic acid suppresses overexpression of ERBB2 oncogene. Lancet Oncol 2005;6:69.

[50] Atoum MF, Al Kayed SA. Mutation analysis of the breast cancer gene BRCA1 among breast cancer Jordanian females. Saudi Med J 2004;25:60-3.

[51] El Harith e, Abdel-Hadi MS, Steinmann D, Dork T. BRCA1 and BRCA2 mutations in breast cancer patients from Saudi Arabia. Saudi Med J 2002;23:700-4.

[52] Bedwani R, Abdel-Fattah M, El Shazly M, Bassili A, Zaki A, Seif HA, et al. Profile of familial breast cancer in Alexandria, Egypt. Anticancer Res 2001;21:3011-4.

[53] Hadjisavvas A, Charalambous E, Adamou A, Neuhausen SL, Christodoulou CG, Kyriacou K. Hereditary breast and ovarian cancer in Cyprus: identification of a founder BRCA2 mutation. Cancer Genet Cytogenet 2004;151:152-6.

Charitini Komodiki

BACKGROUND

Cervical Cancer

Cervical uterine cancer – referred to in this chapter as cervical cancer – is the second most common form of cancer among women worldwide, with an estimated 493,000 new cases (as compared with 1.15 million new cases of breast cancer) and 274,000 deaths (as compared with 411,000 deaths from breast cancer) in 2002. In general terms, cervical cancer is much more common in developing countries, in which it accounts for 15% of all new female cancers, whereas in developed countries it accounts for only 3.6% of such cases *[1]*.

In parts of Asia, Africa, and South America, cervical cancer is the most common form of malignant disease in females and is becoming a major cause of morbidity and mortality throughout the developing world. In the United Kingdom, Europe, North America, and Japan, cancers of the female reproductive system in general are less frequent than breast and gastrointestinal malignancies.

The worldwide differences in cervical cancer incidence are due, at least in part, to socioeconomic and behavioral differences across nations. Substantial declines in incidence and mortality of cervical cancer in Western countries have resulted mainly from comprehensive screening programs that have been implemented in the developed countries over the last decades.

Corpus Cancer

Corpus uterine cancer (sometimes referred to as endometrial cancer, and referred to in this chapter as corpus cancer) has a similar geographic distribution to that of ovarian cancer. The highest incidence is found in North America, with age-standardized incidence rates (ASRs) of around 18 per 100,000 in US Whites and around 15 in Canadians. ASRs are also quite high in Europe, particularly in Eastern European countries such as the Czech Republic, Slovakia, and Latvia, where rates are comparable to those in US Whites. Rates are low (generally less than 6) in southern and eastern Asia (including Japan) and in most of Africa *[2]*.

Corpus cancer appears more important as a cause of morbidity (199,000 new cases per annum, or 3.9% of cancers in women) than as a cause of mortality (50,000 deaths per annum, or 1.7% of cancer deaths in women) *[1]*. This is because corpus cancer carries a relatively favorable prognosis. Survival rates are rather high and slightly higher than for breast cancer – 89% for corpus cancer versus 81% for breast cancer in the United States, and 83% versus 74%, respectively, in Western Europe. The proportion of corpus cancer patients surviving up to 5 years in developing countries is lower than in developed countries (for example, 70% in South America and 69% in Eastern Europe), but still somewhat higher than for breast cancer patients (67% and 58%, respectively) *[1]*.

Part of the reason for these worldwide differences is that corpus cancer risk is related to prolonged high estrogen hormone levels, and these are more prevalent in developed countries, where women bear fewer children and are more likely to take hormone replacement therapy (HRT).

Etiology

Cervical Cancer

The risk of developing cervical cancer is associated with human papillomavirus (HPV) infections. Different types of HPV have been associated with different histologies, such as HPV type 16 with squamous cell carcinoma, and type 18 with adenocarcinoma.

In the 1990s, extensive research showed that HPV infection causes virtually all cases of cervical cancer. Bosch et al. *[3]* found HPV DNA in nearly all cervical cancers. Schiffman et al. *[4]* concentrated on precursors of cervical cancer. To confirm the strong association between oncogenic HPV and cervical cancer, a number of prospective studies were completed, including a 20,000-woman cohort in Oregon *[5]*, a 10,000-woman cohort in Costa Rica *[6]*, and similarly large studies in England *[7]*, Brazil *[8]*, Denmark *[9]*, and California *[10]*.

Currently, epidemiological studies have revealed not only that women without HPV do not develop cervical cancer, but also that neither do most women with HPV. A new generation of biomarkers should be investigated *[11]*.

Early onset of sexual activity, multiple sexual partners, smoking, and low socioeconomic status are associated with development of cervical cancer. A number of studies conducted in Denmark *[12]* showed that possible risk factors for cervical neoplasia in HPV-positive women included smoking, non-use of barrier contraceptives, and larger number of children born. According to results of a case control study *[13]* in Sweden, smoking appeared to be the most significant environmental risk factor for cervical cancer.

Smith et al. *[14]* suggested that herpes simplex virus-2 may act in the presence of HPV infection to increase the risk of invasive cervical carcinoma.

Corpus Cancer

Risk factors for corpus cancer can be classified as (1) endogenous, with prolonged high estrogen levels, and (2) exogenous.

Endogenous risk factors include obesity, early menarche, late menopause, low parity, polycystic ovary syndrome, estrogen-secreting tumors, and family history, particularly the Lynch type II syndrome. The data are inconclusive for diabetes mellitus and immune deficiency.

Exogenous risk factors include noncyclical estrogen replacement therapy, tamoxifen therapy, sequential oral contraception, diet, and previous radiation therapy.

The most well-established risk factors are associated with prolonged high estrogen levels, either due to natural causes, like nulliparity, or to artificial causes, such as postmenopausal estrogens. Beral et al. *[15]* in their review reported that almost 100 epidemiological studies found a relationship between the use of HRT and the risk of cancer of the female reproductive organs, namely the breast, uterus, or ovary. The risk increases with increasing duration of use. Bakken et al. *[16]* in their study in a Norwegian cohort of women found no significant increase in risk of corpus cancer. Factors that raise endogenous estrogen levels, such as obesity and consumption of processed meat and fish, are also associated with increased risk.

Combined oral contraception, cigarette smoking, and high parity are considered as protective factors against corpus cancer *[17]*.

RESULTS

Cervical Cancer

Among the MECC countries, the highest ASR of cervical cancer was observed in Israeli Jews (5.3), followed by Cypriots (3.7), Egyptians (2.7), Jordanians (2.6), and Israeli Arabs (2.5). The US SEER rate (7.0) was higher than for any MECC registry (Table 9.1). This could be attributed mainly to differences in sexual activity. The implementation of successful cervical cancer screening programs in most developed countries may, in the short term, reveal more cases, but would not in the long term account for a higher incidence.

The higher incidence rate observed in Israeli Jews was similar to that observed in Japan (Miyaki), Kuwait, Italy (Ragusa Province, Sassari, Umbria, Venetian region), Switzerland (Geneva), and Spain (Saragosa), while the low rate observed in Israeli Arabs was similar to that observed in some parts of China (Beijing, Shanghai, Tianjin). It is interesting to note that the highest rates of cervical cancer – observed in Zimbabwe, Harare (55.04) and Uganda (41.73) – are both far in excess of the rates reported in the MECC populations. On the other hand, in some parts of China (Changie, Cixion) no cases have been found *[2]*.

Corpus Cancer and Uterine Cancer Not Otherwise Specified

Among the MECC countries, the highest rate for corpus cancer and uterine cancer not otherwise specified (NOS) was observed in Israeli Jews (13.8), followed by Cypriots (11.8), Israeli Arabs (8.7), Jordanians (5.8), and Egyptians (3.5). In US SEER, the rate was much higher (17.6) (Table 9.1). The disparity between the rates in these populations could be attributed to differences in socioeconomic and behavioral factors, such as the number of children born and the use of HRT.

The higher ASRs observed in Israeli Jews and Cypriots were similar to those observed in other countries, such as New Zealand, Australia, Canada, Uruguay, Austria (Tyrol), France, Netherlands, Denmark, Switzerland, United Kingdom, Spain, and parts of Italy. In Asian countries like India, China, Thailand, Oman, Kuwait, and parts of Japan, ASRs below 5.0 were observed, similar to those observed in Jordan and Egypt *[2]*.

It should be noted that rates of corpus cancer were higher than for cervical cancer for all the registries in this MECC report.

Table 9.1. Cervical and Corpus Uterine Cancer: Number of Cases, Age Distribution, and Age-Standardized Incidence Rates,* by Age, among Females 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 cases - Cervical cancer	70	922	54	96	194	5,284
Total cases - Corpus cancer and uterine cancer, NOS§	225	2,645	161	124	405	14,129
	Age Groups (Distribution)					
Cervical cancer						
<30 y	-	2.5%	-	-	*2.1%*	6.4%
30-49 y	37.1%	44.8%	46.3%	36.5%	44.3%	48.4%
50-69 y	30.0%	33.0%	42.6%	52.1%	41.8%	30.2%
70+ y	30.0%	19.7%	*9.3%*	*9.4%*	11.9%	15.0%
Corpus cancer and uterine cancer, NOS§						
<50 y	9.3%	11.6%	13.7%	33.1%	26.4%	15.5%
50-59 y	25.8%	21.6%	34.2%	27.4%	28.9%	24.4%
60-69 y	34.2%	30.7%	32.3%	29.0%	31.6%	25.5%
70+ y	30.7%	36.2%	19.9%	*10.5%*	13.1%	34.6%
	Age Groups (Rates)*					
Cervical cancer						
Total rate	3.7	5.3	2.5	2.7	2.6	7.0
<30 y	-	0.3	-	-	*0.0*	1.2
30-49 y	6.4	10.9	3.9	3.1	4.0	14.0
50-69 y	8.0	12.4	8.3	9.6	7.6	15.4
70+ y	18.2	13.4	*6.6*	*8.4*	9.7	14.2
Corpus cancer and uterine cancer, NOS§						
Total rate	11.8	13.8	8.7	3.5	5.8	17.6
<50 y	1.6	2.4	1.0	1.1	1.4	3.7
50-59 y	37.6	42.8	31.7	10.9	16.7	53.7
60-69 y	68.4	72.5	47.5	16.3	32.7	89.7
70+ y	58.6	72.3	43.2	*12.5*	21.5	88.3

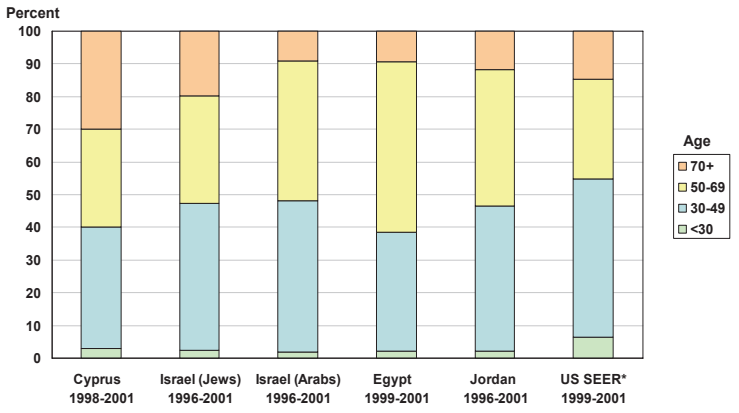
*Rates are per 100,000 females and are age-standardized to the World Standard Million.

†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.

§NOS indicates "not otherwise specified."

Figure 9.1. Cervical Cancer: Age Distribution by Country 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.

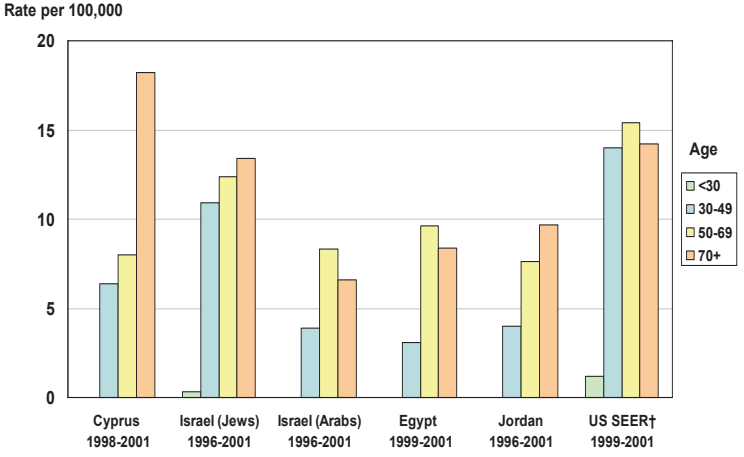
Overall Age Distribution

Cervical Cancer

In all MECC countries and US SEER, the proportion of cervical cancer diagnosed under the age of 30 years was low. However, the proportion in the MECC registries (about 2%) did appear to be lower than in US SEER (6.4%). This may be explained by the well-established cervical cancer screening program in the United States, which contributes to the diagnosis of cases at an earlier age. The highest percentages of cases were in the age group 30-49 years, except in Egypt, where over half the cases were in females aged 50-69 years, compared with 36.5% of those aged 30-49 years. In Cyprus, a higher percentage of cases occurred in those aged 70 years and above (30.0%), compared with the other registries (Table 9.1 and Figure 9.1).

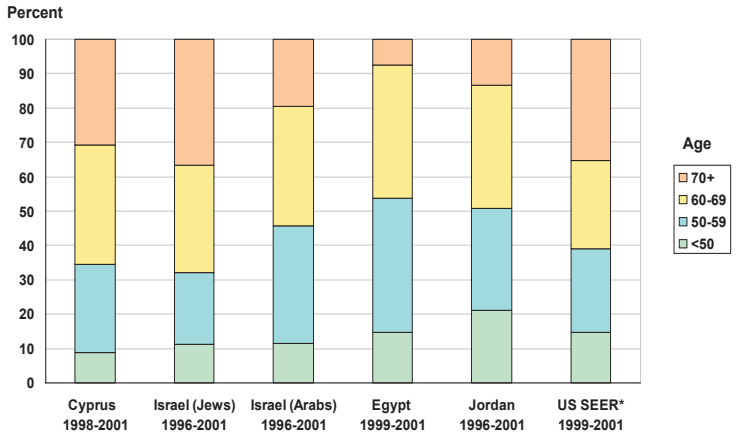
Just as the percentage of cervical cancer cases below the age of 30 years was very low, so were the incidence rates in this age group (Table 9.1). In Cypriots, Israeli Jews, and Jordanians, the ASR was highest for ages 70 and above, while in Egyptians, Israeli Arabs, and the US SEER population, the rate was highest in the age group 50-69 years. In the age group 70 years and above, the rate was highest in Cypriots (Table 9.1 and Figure 9.2).

Figure 9.2. Cervical Cancer: Age-Standardized Incidence Rates* by Country and Age in Cyprus, Israel (Jews and Arabs), Egypt, Jordan, and US SEER – 1996-2001



*Rates are per 100,000 and are age-standardized to the World Standard Million.
† SEER 13 Registries, Public Use Data Set, from data submitted November 2004.

Figure 9.3. Corpus Cancer: Age Distribution by Country 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.

Corpus Cancer and Uterine Cancer Not Otherwise Specified

The percentage of cases below the age of 50 years for corpus cancer and uterine cancer NOS was highest in Egyptians (33.1%) and Jordanians (26.4%). In Israeli Arabs, the disease was most commonly diagnosed in the age group 50-59 years; in Cypriots, Egyptians, and Jordanians, in the age group 60-69 years; and in Israeli Jews and US SEER, in the age group 70 years and above. Higher percentages of cases in this age group were found in Israeli Jews (36.2%), Cypriots (30.7%), and US SEER (34.6%) (Table 9.1 and Figure 9.3).

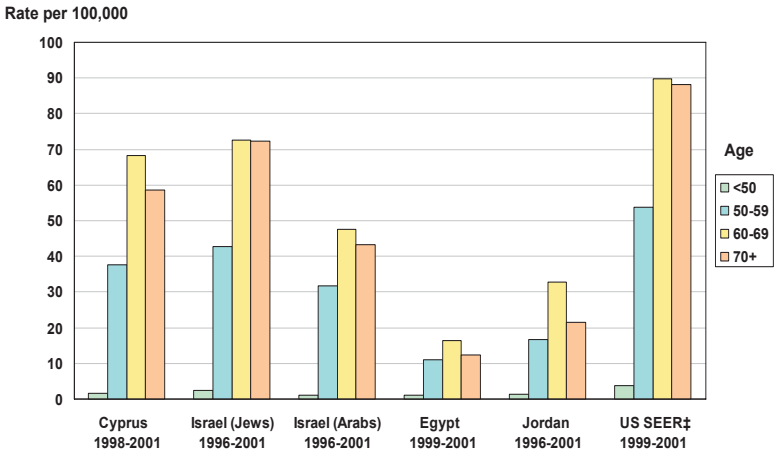
In each age group, incidence rates were highest in US SEER, followed by those in Israeli Jews and in Cypriots (Table 9.1 and Figure 9.4).

Histology of the Microscopically Confirmed Cases

Cervical Cancer

The majority of cervical cancers in all the registries were squamous cell carcinoma, with the lowest percentage (67.8%) in Israeli Jews and the highest percentage (82.6%) in Cypriots. Almost one-fifth of cases (ranging from 15.8% in Egypt to 22.9% in US SEER) were found to be adenocarcinoma (Table 9.2).

Figure 9.4. Corpus Cancer and Uterine Cancer NOS*: Age-Standardized Incidence Rates† by Country and Age in Cyprus, Israel (Jews and Arabs), Egypt, Jordan, and US SEER‡ – 1996-2001



*NOS indicates not otherwise specified.
†Rates are per 100,000 and are age-standardized to the World Standard Million.
‡SEER 13 Registries, Public Use Data Set, from data submitted November 2004.

Corpus Cancer and Uterine Cancer Not Otherwise Specified

The majority of corpus cancers in all the registries were adenocarcinoma, with the lowest percentage (76.7%) in Jordanians and the highest percentage (88.6%) in US SEER (Table 9.2). Uterine cancers NOS were also mostly adenocarcinoma, except among the relatively small numberof such cases in the US SEER population.

SUMMARY AND CONCLUSIONS

Cervical Cancer

Cervical cancer is now known to be caused by infection with various types of HPV. Early onset of sexual activity, multiple sexual partners, smoking, and low socioeconomic status are all associated with the disease.

The highest incidence rates of cervical cancer were found in US SEER, followed by Israeli Jews and Cypriots.

Table 9.2. Cervical and Corpus Uterine Cancer: Number of Cases and Proportions of Histologic Distribution among Females 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 cases - Cervical cancer	69	854	47	95	193	5,222
Total cases - Corpus cancer	217	2,169	136	53	215	13,768
Total cases - Uterine cancer, NOS‡	7	336	16	50	186	205
Cervical Cancer						
Adenocarcinoma	*15.9%*	22.6%	*17.0%*	*15.8%*	20.7%	22.9%
Squamous cell carcinoma	82.6%	67.8%	76.6%	71.6%	68.4%	70.0%
Other histologies	-	9.6%	*6.4%*	*12.6%*	10.9%	7.0%
Corpus Cancer						
Adenocarcinoma	87.1%	87.5%	88.2%	83.0%	76.7%	88.6%
Squamous cell carcinoma	*2.3%*	0.9%	-	*0%*	*1.9%*	0.4%
Other histologies	10.6%	11.7%	*10.3%*	*17.0%*	21.4%	10.9%
Uterine Cancer, NOS‡						
Adenocarcinoma	*42.9%*	60.7%	*75.0%*	50.0%	50.0%	22.9%
Squamous cell carcinoma	*0%*	*3.9%*	*0%*	-	*6.5%*	*3.4%*
Other histologies	*57.1%*	35.4%	*25.0%*	48.0%	43.5%	73.7%

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.

‡NOS indicates "not otherwise specified."

The proportion of cases diagnosed below age 30 years was very low – around 2% in MECC countries, compared with 6.4% in US SEER. This may be explained by the well-established cervical cancer screening program in the United States, which contributes to the diagnosis of cases at an earlier age. Most of the cases in MECC countries and US SEER were diagnosed in the age group 30-49 years, except in Egypt, where most of the cases were diagnosed in the age group 50-69 years.

In Cypriots, Israeli Jews, and Jordanians, the ASR was highest for ages 70 and above, while in Egyptians, Israeli Arabs, and US SEER, the rate was highest in the age group 50-69 years.

Corpus Cancer

Risk factors for corpus cancer are associated with prolonged high estrogen levels. Factors such as low parity and the use of HRT were more commonly found in the United States than in MECC countries. Corpus cancer was most commonly diagnosed in women older than 50 years at the time of diagnosis.

Incidence rates of corpus cancer were higher than those for cervical cancer in all of the registries in this study. In each age group, ASRs for corpus cancer were highest in US SEER, followed by those in Israeli Jews and in Cypriots. The highest rates for corpus cancer were observed in the age group 60-69 years in all of the registries.

REFERENCES

[1] Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74-108.

[2] 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.

[3] Bosch FX, Manos MM, Munoz N, Sherman M, Jansen AM, Peto J, et al. Prevalence of human papillomavirus in cervical cancer: a worldwide perspective. International biological study on cervical cancer (IBSCC) Study Group. J Natl Cancer Inst 1995;87:796-802.

[4] Schiffman MH, Bauer HM, Hoover RN, Glass AG, Cadell DM, Rush BB, et al. Epidemiologic evidence showing that human papillomavirus infection causes most cervical intraepithelial neoplasia. J Natl Cancer Inst 1993;85:958-64.

[5] Liaw KL, Glass AG, Manos MM, Greer CE, Scott DR, Sherman M, et al. Detection of human papillomavirus DNA in cytologically normal women and subsequent cervical squamous intraepithelial lesions. J Natl Cancer Inst 1999;91:954-60.

[6] Herrero R, Hildesheim A, Bratti C, Sherman ME, Hutchinson M, Morales J, et al. Population-based study of human papillomavirus infection and cervical neoplasia in rural Costa Rica. J Natl Cancer Inst 2000;92:464-74.

[7] Deacon JM, Evans CD, Yule R, Desai M, Binns W, Taylor C, et al. Sexual behaviour and smoking as determinants of cervical HPV infection and of CIN3 among those infected: a case-control study nested within the Manchester cohort. Br J Cancer 2000;83:1565-72.

[8] Franco EL, Villa LL, Sobrinho JP, Prado JM, Rousseau MC, Desy M, et al. Epidemiology of acquisition and clearance of cervical human papillomavirus infection in women from a high-risk area for cervical cancer. J Infect Dis 1999;180:1415-23.

[9] Kjaer SK, van den Brule AJ, Bock JE, Poll PA, Engholm G, Sherman ME, et al. Human papillomavirus – the most significant risk determinant of cervical intraepithelial neoplasia. Int J Cancer 1996;65:601-6.

[10] Moscicki AB, Hills N, Shiboski S, Powell K, Jay N, Hanson E, et al. Risks for incident human papillomavirus infection and low-grade squamous intraepithelial lesion development in young females. JAMA 2001;285:2995-3002.

[11] Schiffman MH, Castle P. Epidemiologic studies of a necessary causal risk factor: human papillomavirus infection and cervical neoplasia. J Natl Cancer Inst 2003;95:E2.

[12] Kjaer SK. Risk factors for cervical neoplasia in Denmark. APMIS Suppl 1998;80:1-41.

[13] Kjellberg L, Hallmans G, Ahren AM, Johansson R, Bergman F, Wadell G, et al. Smoking, diet, pregnancy and oral contraceptive use as risk factors for cervical intra-epithelial neoplasia in relation to human papillomavirus infection. Br J Cancer 2000;82:1332-8.

[14] Smith JS, Herrero R, Bosetti C, Munoz N, Bosch FX, Eluf-Neto J, et al. Herpes simplex virus-2 as a human papillomavirus cofactor in the etiology of invasive cervical cancer. J Natl Cancer Inst 2002;94:1604-13.

[15] Beral V, Banks E, Reeves G, Appleby P. Use of HRT and the subsequent risk of cancer. J Epidemiol Biostat 1999;4:191-210.

[16] Bakken K, Alsaker E, Eggen AE, Lund E. Hormone replacement therapy and incidence of hormone-dependent cancers in the Norwegian Women and Cancer study. Int J Cancer 2004;112:130-4.

[17] Souhami RL, Tannock I, Hohenberger P, Horiot JC, editors. Oxford textbook of oncology, second edition. Oxford (UK): Oxford University Press; 2001.

Charitini Komodiki

BACKGROUND

The incidence of ovarian cancer is higher in the highly industrial countries of the world, particularly in Western and Northern Europe and North America *[1]*. The median age at diagnosis is 62 years. Some 85% to 90% of ovarian cancers are epithelial, and more than two thirds are diagnosed at an advanced stage. Epithelial ovarian cancer is the leading cause of death in females with pelvic malignancies.

The etiology of ovarian cancer is poorly understood *[2]*. The risk of ovarian cancer is reduced in women with high parity and in women who use oral contraceptives. Full-term and complete pregnancy protects against the development of ovarian cancer *[3,4]*. Oral contraceptives that reduce or suppress ovulation, used for 5 years or longer, reduce the risk of this cancer by about half. Other factors that are associated with a reduced risk are a history of breastfeeding, tubal ligation, and hysterectomy *[5]*.

Factors associated with an increased risk for invasive epithelial ovarian cancer include older age, race (White), nulliparity, family history of ovarian cancer, and a history of endometrial or breast cancer *[5]*.

Engeland et al. *[6]* found a positive association between height and risk of ovarian cancer. Riman et al. *[7]* revealed an increased risk of epithelial ovarian cancer with the use of hormone replacement therapy with sequentially added progestin and estrogen.

Women who are single and have low parity and a history of breast cancer are at higher risk. The risk of ovarian cancer is usually found to be higher in White, affluent, and better-educated societies *[5]*.

The familial risk of ovarian cancer is also well documented *[5,8]*. Patients with *BRCA1* and *BRCA2* gene mutations have an increased risk of ovarian cancer *[5]*.

Childhood infections (such as mumps and rubella), obesity, diet, and exposure to radiation and to talc have been linked to ovarian cancer, but results are inconsistent *[9]*.

RESULTS

Overall Incidence

As shown in Table 10.1, among the MECC countries, the highest age-standardized incidence rate (ASR) of ovarian cancer was observed in female Israeli Jews (9.4) (the US SEER rate was 10.0). These rates were followed by Cypriots (7.7), Egyptians (5.4), Jordanians (4.6), and Israeli Arabs (3.6). In the under-50 age group, the rate of ovarian cancer was highest in Israeli Jews and US SEER (3.2), followed by Egyptians (2.5), Cypriots and Jordanians (2.1), and Israeli Arabs (1.4).

In the age group 50-69 years, the rate was highest in US SEER (33.5), followed by Israeli Jews (32.3), Cypriots (27.8), Egyptians (17.7), Jordanians (14.1), and Israeli Arabs (10.5) (Figure 10.1).

In the 70+ age group, the rate was highest in US SEER (52.7), followed by Israeli Jews (40.9), Cypriots (38.2), Israeli Arabs (19.3), Jordanians (17.3), and Egyptians (14.9). The incidence rates increased as age increased, with the exception of Egypt, where the rate was highest for 50- to 69-year-olds (Figure 10.1).

The differences in these rates conform to the pattern of ovarian cancer risk, whereby the cancer more commonly occurs among

females in developed industrial countries than in less developed countries. The highest MECC incidence rate, observed in Israeli Jews, can be compared to those rates found in some parts of Canada, Austria, France, Poland, Spain, and Italy. The lowest incidence rate, in Israeli Arabs, can be compared to rates observed in some parts of China, India, and Thailand *[10]*.

Among MECC countries, the higher incidence rates observed among Israeli Jews and Cypriots can be explained by the similar socioeconomic and cultural environment of the 2 countries, while the similar rates among Egyptians, Jordanians, and Israeli Arabs can be explained by the similar cultural, ethnic, and genetic characteristics in these countries.

Age

For Cypriots, Israeli Jews, and the US SEER population, the highest proportions of ovarian cancer cases were in the 50-69 year age group. For Jordanians, Egyptians, and Israeli Arabs, however, the highest percentages were in below-50 age group (Figure 10.2).

In US SEER and among Israeli Jews and Cypriots, the percentage of cases in the 70+ age group was quite high, while in Egyptians, Jordanians, and Israeli Arabs, it was much lower (Figure 10.2).

Histology

As shown in Table 10.2, proportions of microscopic confirmation varied widely (from 77.3% to 99.2%) among the registries. Comparisons of incidence rates by histology type are therefore unreliable. Instead, we compare the distribution of cases by histology subtype among microscopically confirmed cases. Carcinoma was the most commonly observed type of ovarian cancer in all registries, accounting for between 77.8% and 93.2% of the cancers. Serous carcinoma was the most commonly observed specific type of ovarian carcinoma in all MECC countries. The highest percentage of serous carcinoma was observed in Israeli Jews (44.9%), which was very close to the percentage in US SEER (42.1%), followed by Cypriots (40.6%), Israeli Arabs (36.2%), Jordanians (28.7%), and Egyptians (27.2%).

The most common form of ovarian carcinoma, after serous carcinoma, was adenocarcinoma. The percentages of adenocarcinoma were similar across all registries, ranging from 14.4% to 18.8%.

The proportion of mucinous carcinoma was higher in Egyptians (16.1%) and Jordanians (11.7%) than in the other registries, where percentages ranged from 6.0% to 8.7%.

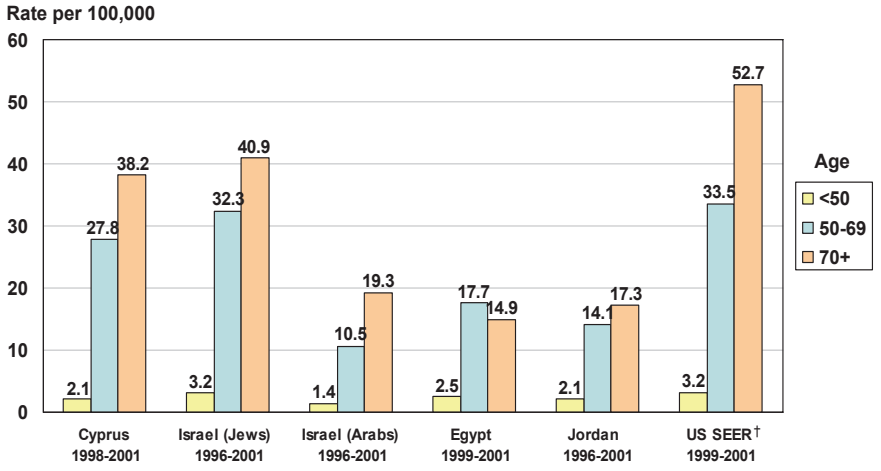
Table 10.1. Ovarian Cancer: Age-Standardized Incidence Rates* by Age among Females in Cyprus, Israel (Jews and Arabs), Egypt, Jordan, and US SEER – 1996-2001

	Cyprus 1998-2001	Israel (Jews) 1996-2001	Israel (Arabs) 1996-2001	Egypt 1999-2001	Jordan 1996-2001	US SEER† 1999-2001
Total rate	7.7	9.4	3.6	5.4	4.6	10.0
<50 y	2.1	3.2	1.4	2.5	2.1	3.2
50-69 y	27.8	32.3	10.5	17.7	14.1	33.5
70+ y	38.2	40.9	*19.3*	14.9	17.3	52.7

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

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

Figure 10.1. Ovarian Cancer: Age-Standardized Incidence Rates* by Country and Age in Cyprus, Israel (Jews and Arabs), Egypt, Jordan, and US SEER – 1996-2001



*Rates are per 100,000 and are age-standardized to the World Standard Million.
†SEER 13 Registries, Public Use Data Set, from data submitted November 2004.

The proportion of endometroid carcinoma was higher in the Israeli Jewish (15.0%) and US SEER populations (12.2%) than in the other registries, where percentages ranged from 7.8% to 10.9%.

The proportion of clear cell carcinoma cases was low in Cypriots, US SEER, and Israeli Jews, and almost non-existent in the Arab populations.

The percentages of other histological types of ovarian cancer were rather low. Germ-cell tumors accounted for a larger proportion of ovarian cancers in the Arab populations (7.2%-12.1%) than among the US SEER, Cypriot, and Israeli Jewish populations (2.2%-3.1%).

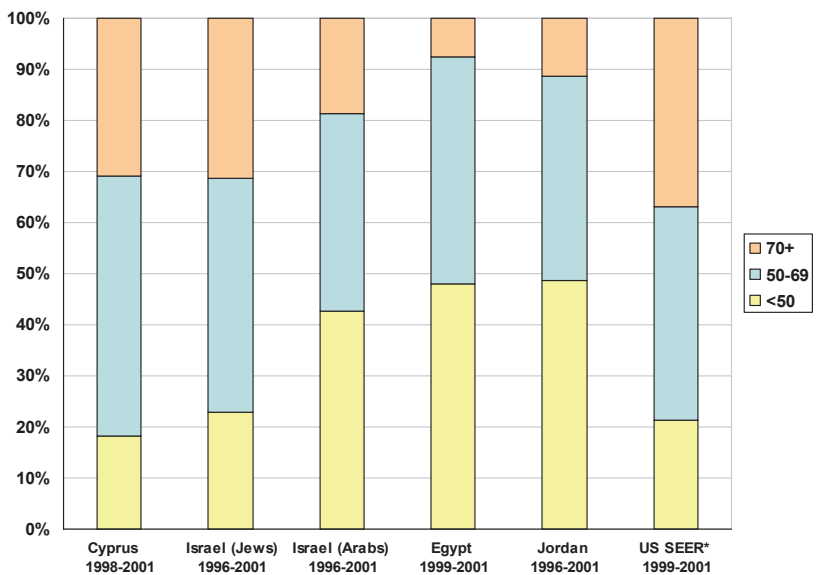
The percentage of sex cord-stromal tumors was very low in all populations, but particularly in Israeli Arabs and Jews.

SUMMARY AND CONCLUSIONS

US, Israeli Jewish, and Cypriot women had the highest incidence of ovarian cancer, while Egyptian, Jordanian, and Israeli Arab women had the lowest incidence for the same period. This could be attributed to differences in socioeconomic status of the countries, which no doubt relate to differences across these populations in parity, a major protective factor for ovarian cancer. The incidence rate among Israeli Jewish women was 9.4, almost 3 times the rate among Israeli Arab women.

In all MECC countries, the most common histological type of ovarian cancer was carcinoma of the ovary.

Figure 10.2. Ovarian Cancer: Age Distribution by Country 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.

The majority of ovarian cancer cases diagnosed in the age group 50-69 years were in US SEER, Cypriots, and Israeli Jews. On the other hand, the majority of ovarian cancer cases diagnosed in women below the age of 50 were in Egyptians, Jordanians, and Israeli Arabs. Among women over 50 years, the incidence rate in US SEER, Cypriots, and Israeli Jews was, on average, approximately twice that in Egyptians, Jordanians, and Israeli Arabs.

Among women younger than the age of 50, the incidence rate was between 2.1 and 3.2 in all populations under study, except in Israeli Arabs (1.4). This could imply a cohort effect, with women in newer generations of these populations having more similarities in their lifestyle. However, further observation is needed before drawing this conclusion.

Table 10.2. Ovarian Cancer: Proportions of Microscopic Confirmation and Histologic Type among Females 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 cases microscopically confirmed	138	1511	58	180	369	7706
Microscopically confirmed	96.5%	86.4%	77.3%	85.7%	99.2%	93.6%
Distribution						
Histologic distribution‡	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
Carcinoma	88.4%	93.2%	84.5%	77.8%	81.0%	91.8%
Serous carcinoma	40.6%	44.9%	36.2%	27.2%	28.7%	42.1%
Mucinous carcinoma	*8.7%*	6.0%	*6.9%*	16.1%	11.7%	7.5%
Endometroid carcinoma	*10.9%*	15.0%	*8.6%*	*7.8%*	10.6%	12.2%
Clear-cell carcinoma	*4.3%*	2.2%	-	-	*0.8%*	5.1%
Adenocarcinoma, NOS§	18.8%	16.0%	*17.2%*	14.4%	16.3%	16.7%
Other specified carcinomas	*3.6%*	3.0%	*5.2%*	*2.2%*	*1.9%*	4.7%
Unspecified carcinoma	-	6.2%	*8.6%*	8.9%	11.1%	3.4%
Sex cord-stromal tumors	*5.1%*	*0.5%*	*0.0%*	*6.1%*	*4.1%*	1.3%
Germ-cell tumors	*2.2%*	3.1%	*12.1%*	*7.2%*	10.8%	3.0%
Unspecified cancer	-	1.4%	-	*4.4%*	*0.8%*	0.7%
Other specified types	*2.9%*	2.1%	-	*4.4%*	*3.5%*	3.5%

The symbols "-" = 1-2 cases; "[numeral]*" (italics) = 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). However, where a percentage has been suppressed because it is based on only 1 or 2 cases, the remaining percentages may not sum to 100%.

§NOS indicates "not otherwise specified."

REFERENCES

[1] Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74-108.

[2] Tortolero-Luna G, Mitchell MF. The epidemiology of ovarian cancer. J Cell Biochem Suppl 1995;23:200-7.

[3] Zhang M, Lee AH, Binns CW. Reproductive and dietary risk factors for epithelial ovarian cancer in China. Gynecol Oncol 2004;92:320-6.

[4] Daly M, Obrams GI. Epidemiology and risk assessment for ovarian cancer. Semin Oncol 1998;25:255-64.

[5] Holschneider CH, Berek JS. Ovarian cancer: epidemiology, biology, and prognostic factors. Semin Surg Oncol 2000;19:3-10.

[6] Engeland A, Tretli S, Bjorge T. Height, body mass index, and ovarian cancer: a follow-up of 1.1 million Norwegian women. J Natl Cancer Inst 2003;95:1244-8.

[7] Riman T, Dickman PW, Nilsson S, Correia N, Nordlinder H, Magnusson CM, et al. Hormone replacement therapy and the risk of invasive epithelial ovarian cancer in Swedish women. J Natl Cancer Inst 2002;94:497-504.

[8] Riman T, Persson I, Nilsson S. Hormonal aspects of epithelial ovarian cancer: review of epidemiological evidence. Clin Endocrinol (Oxf) 1998;49:695-707.

[9] Souhami RL, Tannock I, Hohenberger P, Horiot JC, editors. Oxford textbook of oncology, second edition. Oxford (UK): Oxford University Press; 2001.

[10] 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.

Amal Samy Ibrahim, Hussein M. Khaled

BACKGROUND

Urinary bladder (or bladder) cancer is one of the most common cancers worldwide, with the highest incidence in industrialized countries. Age-standardized incidence rates (ASR) higher than 40 per 100,000 for males were reported from Europe (Belgium, 42.5; Italy, 41.0). In most European countries, the United States, and Canada, rates are between 20 and 30. Bladder cancer incidence is lowest in Asia and South America, approximately 70% lower than in Western industrialized countries.

As shown in Table 11.1, the lowest median bladder cancer ASR for males was in Asia (5.9), and the highest in Europe (23.9). Rates for females were much lower, but followed the same geographical pattern as for males.

Marked variation in bladder cancer incidence occurs not only between but also within countries. Italy, which had one of the highest rates for males worldwide (41.1 in Genua province), also had a rate of 27.9 in Ragusa province. Nonetheless, because of its high recurrence rate, the actual prevalence of active bladder cancer is estimated to be about 10 times the number of new cases *[1]*.

Histological Types

Two main histological types of bladder cancer are identified: the transitional cell carcinomas (TCC), related to cigarette smoking and most prevalent in Western and industrialized countries, and the squamous cell carcinomas (SCC), which are more frequently seen in some Middle Eastern and African countries, where urinary schistosomiasis is an endemic disease. Rare types of bladder cancer include small cell carcinoma, carcinosarcoma, primary lymphoma, and sarcoma *[2]*.

In industrialized Western countries, transitional cell tumors comprise 90%-95% of bladder tumors; 3%-7% are squamous cell, and 1%-2% are adenocarcinomas. Transitional cell carcinomas may show evidence of squamous or adenocarcinomatous differentiation. Well-differentiated tumors tend to recur, and the poorly differentiated tumors not only recur but also tend to invade locally and may metastasize *[3]*.

In developing countries in certain locations, up to 75% of cases are squamous cell carcinomas associated with *Schistosoma haematobium* infestation. They most often form in the setting of a chronic inflammation, such as in patients with long-term catheters, or are the *haematobium* type of schistosomiasis and tend to be of high grade. These squamous cell carcinomas are highly malignant, with poor prognosis. Success in treating these cancers relies heavily on early detection and aggressive surgical management *[4]*.

Etiology and Risk Factors

Cigarettes. Cigarette smoking, including exposure to secondhand smoke, is estimated to account for two-thirds of bladder cancers in males and one-third in females. There is strong correlation between the number of pack-years and the risk of developing bladder cancer. Quitting smoking decreases the risk, but the risk never returns to that of a nonsmoker. This situation is not unexpected, given the average 20-year latency between carcinogen exposure and bladder cancer development *[5]*.

In the Middle East region, cigarette smoking could be considered a time bomb. According to the World Health Organization (WHO) statistics shown in Table 11.2, Middle East Cancer Consortium (MECC) countries had a higher percentage of male smokers in 1998-1999, ranging from between 33.0% in Israel to 48.0% in Jordan, compared with 25.7% in the United States. Except for Israel

(24.0%), the frequency of female smokers in MECC countries is generally low, opening a promising avenue for prevention. The number of cigarettes consumed in the MECC countries is still lower than in the United States, except for Israel, where annual cigarette consumption per person (2,162) is near US consumption (2,255) *[6]*. The bomb will explode due to long latency of the disease, increase in consumption, increase in female smokers, and exposure of more youth to the habit.

Table 11.1. Bladder Cancer: Age-Standardized Incidence Rates* for the Highest, Median, and Lowest Country within Continent, by Sex – 1993-1997†

Continent		Male		Female	
		Country	Rate	Country	Rate
Africa	Highest	France, La Reunion	12.0	Zimbabwe, Harare	8.3
	Median	Algeria	10.7	Algeria	2.3
	Median	Zimbabwe, Harare	8.3	France, La Reunion	1.3
	Lowest	The Gambia	1.3	The Gambia	0.5
South America	Highest	Uruguay, Montevideo	22.6	Uruguay, Montevideo	4.3
	Median	United States, Puerto Rico	9.8	Brazil, Goiania	2.7
	Lowest	France, Martinique	3.6	Ecuador, Quito	1.3
North America	Highest	United States, New Jersey, White	28.0	United States, Connecticut, White	8.0
	Median	United States, New Mexico, Non-Hispanic, White	19.4	United States, Louisiana, Central Region, White	5.2
	Median	United States, California, Los Angeles	19.0	United States, Louisiana, New Orleans	5.1
	Lowest	United States, New Mexico, American Indian	4.1	United States, New Mexico, American Indian	0.7
Asia	Highest	Israel, Jews born in Europe or United States	27.8	Israel, Jews born in Europe or United States	6.0
	Median	China, Beijing	5.9	Singapore	1.7
	Lowest	India, Trivandrum	2.0	India, Karunagappally	0.3
Europe	Highest	Belgium, Limburg	42.5	Scotland	8.1
	Median	England, South and Western Regions	23.9	Czech Republic	4.6
	Median	England, Merseyside and Cheshire	23.7	France, Doubs	4.5
	Lowest	Slovenia	11.1	Belarus	1.6
Australia	Highest	United States, Hawaii, White	23.9	Australia, South	6.2
	Median	United States, Hawaii	13.4	United States, Hawaii, Japanese	3.4
	Lowest	United States, Hawaii, Hawaiian	6.8	United States, Hawaii, Filipino	2.2
Total World	Highest	Belgium, Limburg	42.5	Zimbabwe, Harare	8.3
	Median	United States, Louisiana, Central Region	16.6	Spain, Navarra	3.9
	Lowest	The Gambia	1.3	India, Karunagappally	0.3

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

†Years vary slightly between countries.

Source: 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.

Schistosomiasis. Schistosomiasis, also known as Bilharzias, is a parasitic disease caused by infection with *schistosome* blood flukes. Four *schistosome* species are parasitic in humans: *S. haematobium*, *S. mansoni*, *S. Japonicum*, and *S. intercalatum*. Of these, *S. haematobium*, also called urinary schistosomiasis, is the one related to bladder cancer. The disease is common in northeast Africa, southwest Asia, and Madagascar *[7]*.

The *S. Haematobium* adult mature worms inhabit the mesenteric and pelvic veins of humans, where they mate and reproduce. The females deposit eggs that eventually rupture the venules and discharge into the surrounding tissues. Eggs are mainly carried to the bladder wall and excreted in urine. With their terminal spine, the eggs injure the bladder wall, leading to hematuria, calcification, and cystitis. When the excreted eggs reach fresh water, the miracidia hatch and infect water snails. Within the snails, mature sporocytes produce cercariae, which are expelled into the water, waiting for the human host. People who make contact with such water, mainly male farmers, get the disease. Children and adolescents are also at high risk, due to bathing and swimming in canals with infected snails *[8]*.

Schistosomiasis is one of the oldest known parasitic diseases. Paleopathologic examination of mummified tissues detected schistosomal eggs in gastrointestinal and urinary tracts of mummies belonging to the 20th dynasty (1250-1200 BC) (Figure 11.1). Medical papyri show that ancient Egyptians knew not only the etiology of the disease and its main symptom (hematuria), but also recommended antimony as a line of treatment. Prevention was proposed through refraining from polluting water, and farmers and others with prolonged exposure to canal water were advised to wear penile sheaths to prevent the worms from entering their bodies. Furthermore, it was said that the deceased had to sign in the book of the dead that they had not polluted water during their lifetime *[9,10]*.

The prevalence and severity of schistosomiasis tend to rise sharply with opportunities for exposure. In Egypt, the disease prevalence increased dramatically after installation of the High Dam, which created perennial irrigation. Thus, the peculiar agricultural setting of the Nile Valley singled out Egypt for a dose-response relationship not encountered in other parts of Africa *[11]*. Over the last 2 decades, Egypt succeeded in lowering the prevalence of schistosomiasis from 35% in 1983 to 1.7% in 2003, with complete eradication in certain districts *[12]* (Figure 11.2).

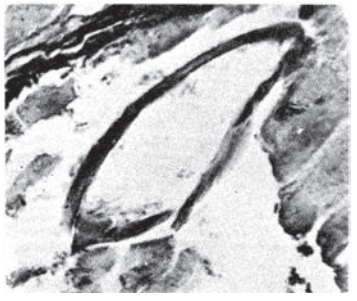
Table 11.2. Bladder Cancer: Adult and Youth Smoking Prevalence, Cigarettes Smoked, and Quit Rate in Cyprus, Israel (Jews and Arabs), Egypt, Jordan, and the United States − 1998-2000

Countries	Population (in thousands)	Adult Smoking Prevalence			Youth Smoking Prevalence			Cigarettes Smoked Annually (per capita)	Quit Rate (among those who have ever smoked)
		Total	Male	Female	Total	Male	Female		
Cyprus	784	29.0%	38.5%	7.6%	-	-	-	-	11.0%
Israel	6,040	28.5%	33.0%	24.0%	-	-	-	2,162	10.0%
Egypt	67,884	18.3%	35.0%	1.8%	-	-	-	1,275	50.0%
Jordan	4,913	29.0%	48.0%	10.0%	20.6%	27.0%	13.4%	1,832	-
United States	283,230	23.6%	25.7%	21.5%	25.8%	27.5%	24.2%	2,255	42.0%

Source: Mackay J and Eriksen M. The tobacco atlas. Geneva (Switzerland): World Health Organization; 2002.

There is a plethora of literature incriminating *S. haematobium* infestation as a risk factor for bladder cancer, but explanation for this association remains speculative *[13]*. Evidence that supports the association between schistosomiasis and bladder cancer includes the geographical correlation between the 2 conditions, the distinctive patterns of sex and age at diagnosis, the clinicopathological identity of schistosome-associated bladder cancer (SABC), and extensive evidence in experimentally infected animals *[14]*. Due to the previous lack of population-based registries in Egypt, data published so far have been mostly retrospective relative frequencies, with their inherent limitations. An age-standardized mortality rate for bladder cancer of 10.8 in males placed Egypt at the top of the list of the 54 countries that provided data for the 1987 WHO database, and supported the hypothesis that *S. haematobium* infection predisposes to malignant bladder neoplasms *[15]*. This population-based study documents, for the first time, the effect of changes in schistosomiasis control on bladder cancer incidence.

Figure 11.1. Bladder Cancer: Egg of *S. Haematobium* Found in Tissues of an Egyptian Mummy



Photograph used with permission from Prof. Nabil El-Bolkainy, Professor of Pathology and Dean Emeritus, National Cancer Institute, Cairo University, Cairo, Egypt.

Egyptian literature describes a special profile for SABC, with marked male predominance, relatively young age at diagnosis, predominance of squamous cell carcinoma (75% or more), severe urinary tract infection and calcification, and special predilection to farmers. The early onset of this type of bladder cancer might reflect the latent period of carcinogenesis that takes 20-30 years after the peak of schistosomal infestation in the third decade of life. In Egyptian hospital series, the mean age at diagnosis of SABC was 41 years, about 5 years younger than patients with non-schistosomal bladder cancer, with a male-to-female ratio that ranged from 5:1 to 9:1 *[16]*.

Other risk factors. Certain organic chemicals – particularly aromatic (aryl)-amines such as naphthalene, benzidine, aniline dyes, and 4-aminobiphenyl – are known bladder carcinogens and have helped identify high-risk occupations, including petroleum chemical/rubber workers, hairdressers, painters, textile workers, truck drivers, and aluminum electroplaters. Bladder cancer may also result from pelvic radiotherapy, phenacetin use, and cyclophosphamide exposure, resulting in a four- to five-fold relative risk increase, particularly when exposure is in a chronic low-dose form *[17,18]*.

Age and sex are additional risk factors. Bladder cancer is 2 to 3 times more common in males. People over the age of 70 years develop the disease 2 to 3 times more often than those aged 55-69 years, and 15 to 20 times more often than those aged 30-54 years. The highest incidence occurs in males over age 60 years and females over age 70; however, even teenage males have a finite chance of bladder cancer, while it is very rare to see bladder cancer in a female under the age of 40 *[19]*.

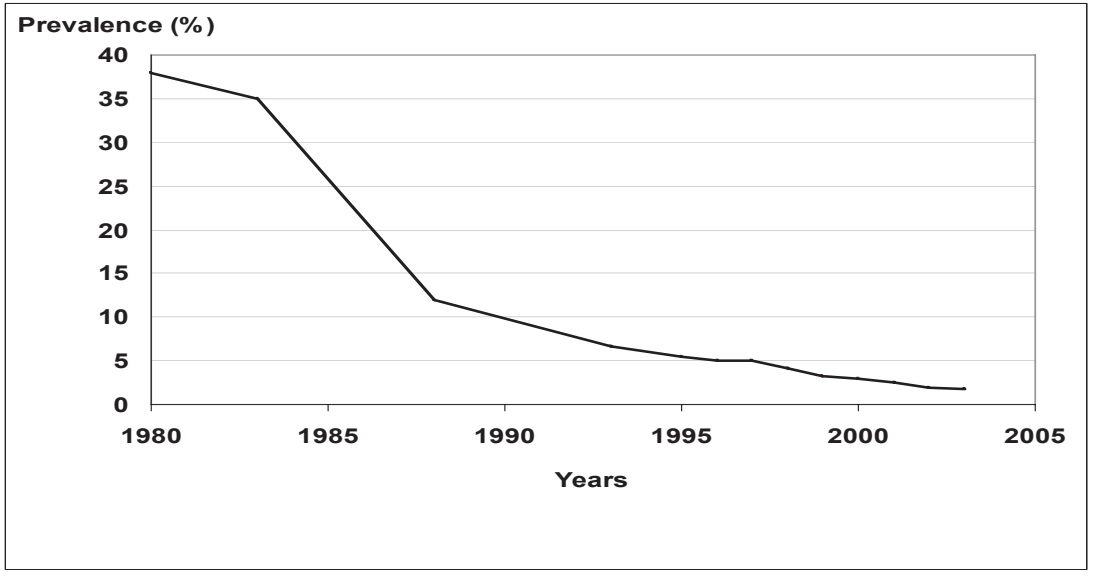
A diet high in saturated fat and consumption of Aristolochia fangchi (an herb used in some weight-loss formulas) have been incriminated as risk factors for bladder cancer. There is also a strong racial/ethnic disparity, with disease much more common in Caucasians than in those of African, Latino, or Asian descent *[20]*.

Genetic Background

The major differences in the clinicopathologic features observed between the Western type of bladder cancer and SABC probably reflect underlying alternate tumor biology and carcinogenic pathways.

Chromosomal studies. Several studies attempted to characterize the chromosomal aberrations of SABC, including both SCC and TCC subtypes. Data were compared with those of the Western world. Some studies revealed that deletions of chromosome 9p where a tumor suppressor gene (*CDKN2*) resides were more frequent in SCC (92%) than in TCC (39%). Allelic losses in chromosome 17p, where the *p53* gene resides, were less frequent in SCC (38%) than TCC (60%) *[21]*. It was also demonstrated that the histopathologic subtype rather than the schistosomal impact itself determines the pattern of chromosomal changes. Aberrations of chromosomes 7, 9, and 17 showed reciprocal patterns in TCC and SCC, whether associated with schistosomiasis or not *[22]*. The predominantly male development of SABC has been explained by the high frequency of loss of chromosome Y. Using the

Figure 11.2. Bladder Cancer: Change in Prevalence of *S. Haematobium* in Egypt after Schistosomiasis Control Program – 1980-2003



Source: Department of Endemic Diseases, Ministry of Health and Population, Egypt (2004).

FISH technique, Khaled and Aly demonstrated that 41% of cases of SABC showed loss of chromosome Y *[23]*.

Cancer genes. Oncogenes and tumor suppressor genes have been implicated in a variety of human cancers. Many studies have attempted to identify molecular events associated with specific genes that underlie neoplastic progression in the development of SABC. These include the inactivation of *p53 [24,25]*, activation of *H-ras [26]*, and inactivation of the retinoblastoma gene *[27]*. Studies indicate that Egyptian bladder cancers show *p53* mutations in both the squamous and transitional types. These mutations are known to be related to lymph node metastasis and a greater propensity to progression, and in the Egyptian studies *[24,25]* were associated with advanced stage of disease. Excess mutations might be due to high levels of urinary nitrates in bilharzial patients producing nitric oxide by inflammatory cells. In these cases, there is usually an overexpression of *MDM2* as well. The *ras* oncogene does not seem to be strongly implicated in the differential process of carcinogenesis in SABC, judging from studies in different countries. An incidence of 10% of *H-ras* mutations was seen in bladder cancer in Japan and the United States, similar to the Egyptian cases.

Habuchi et al. *[28]* suggested that cigarette smoking might have a significant impact on the mutations of the *p53* gene in urothelial cancers. Urothelial carcinogenesis in the presence of schistosomiasis seems to proceed along pathways different from those linked to smoking, since cigarette smoking appears to have a significant impact on the mutation of the *p53* gene with A:T to G:C transitions, which are not observed in SABC.

RESULTS

As shown in Table 11.3, bladder cancer was one of the more common cancers in the MECC countries – especially Egypt, where it ranked first in males, representing 16.2% of male cancers. Among Egyptian females, its frequency was 4.0%, by far exceeded by breast cancer (37.6% of female malignancies). For both sexes together, the frequency of bladder cancer was 10.1%, nearly the same as non-Hodgkin lymphoma (10.5%) and next in frequency to breast cancer (18.9%) (see Table 1.6).

Other MECC registries reported relative frequencies of bladder cancer in males of 12.3% for Cypriots, 10.0% for Israeli Jews, 9.9% for Jordanians, and 8.1% for Israeli Arabs. The proportions in females were much lower, and bladder cancer was not among the 10 most frequent types of cancer in females in these registries. For both sexes together, relative frequencies in other MECC countries were all lower than for Egypt, ranging from 7.5% down to 5.0%. The relative frequency in the United States was lower than in MECC countries for males, and similar to MECC countries for females (Table 11.3).

Among the MECC registries and US SEER, the male-to-female ratio for bladder cancer incidence was highest in Jordanians (7.4:1), followed by Israeli Arabs (6.9:1) and Cypriots (5.3:1). Ratios in Egyptians and Israeli Jews were very close to one another (4.2:1 and 4.1:1, respectively). The US SEER ratio was the lowest (2.9:1). This male predominance could be attributed to cigarette smoking, which is more common among males than females. Nonetheless, previous reports from Egypt indicated a higher male-to-female ratio as one of the features of SABC. The lower ratio observed for Egypt in the current results favors the transition from SABC to the Western type, TCC, which is mostly related to cigarette smoking.

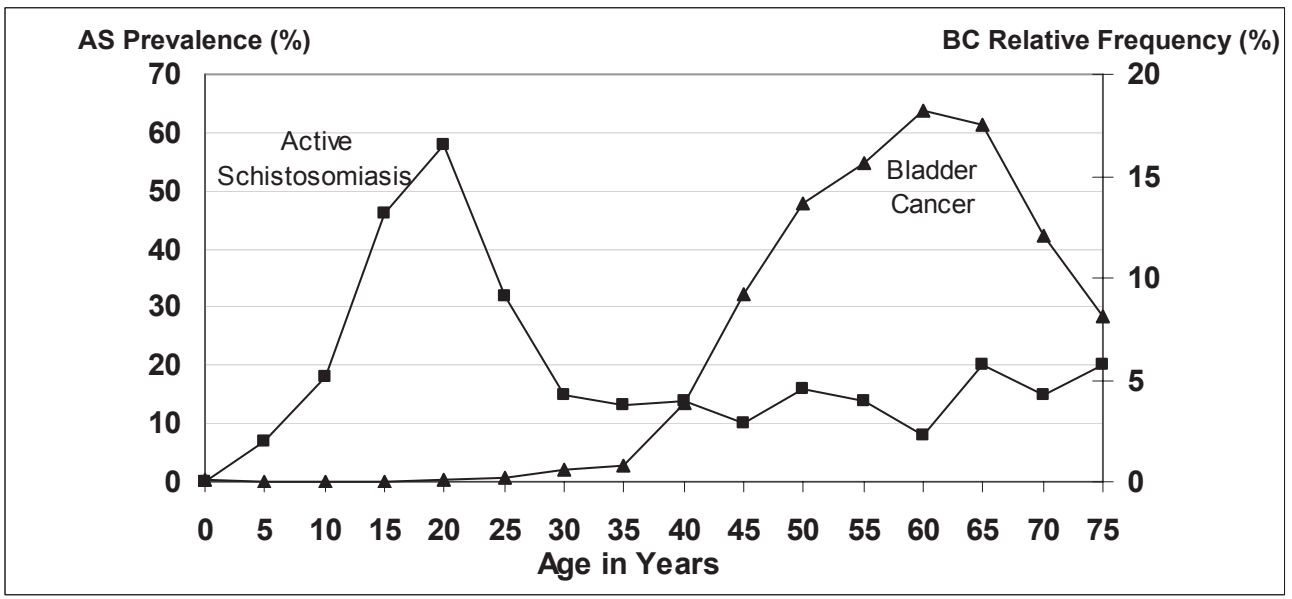
The relatively high frequency of bladder cancer in Egypt supports the etiological relationship to urinary schistosomiasis. Despite the marked decrease in prevalence of endemic schistosomiasis over the last 2 decades, Egypt is still paying the toll of the previously high prevalence of the disease. Comparison of the frequency of active urinary schistosomiasis previously reported during the era of high prevalence of the disease *[8]* and the age-specific incidence rate indicates a strong cohort effect (Figure 11.3). It could be anticipated that in the near future, there will be a marked decrease in SABC in Egypt as a sequel to schistosomiasis control. The potential risk is

the rise in incidence of bladder cancer related to other risk factors, especially smoking.

Overall Incidence

Results, based for the first time on population data, show that Egypt had a serious problem of bladder cancer. The highest ASR for both sexes together was that of Egyptians (16.6), followed by Israeli Jews (15.1), Cypriots (11.2), and Israeli Arabs (8.6). Jordanians had

Figure 11.3. Bladder Cancer: Prevalence of of Active Schistosomiasis (AS) by Age and Age Distribution of Bladder Cancer (BC) in Egypt



Source: Data on prevalence of schistosomiasis from Khozam and El Ayayisha villages, Upper Egypt 1975. Higashi GI, Aboul-Enein MI. Diagnosis and epidemiology of schistosoma haematobium infections in Egypt. In: El-Bolkainy MN, Chu E editors. Detection of bladder cancer associated with schistosomiasis. Cairo (Egypt): Al-Ahram Press; 1992. p. 47-69. Data on age distribution of bladder cancer (1999-2001) from Table 11.5 in this chapter.

the lowest ASR (7.6), with less than half the rates of Egyptians and Israeli Jews. The US SEER rate was 12.2 (Table 11.3).

Egyptians and Israeli Jews had the highest ASR for males (27.5), followed by Cypriots (20.5) and Israeli Arabs (16.0). Jordanians had the lowest rate (13.2). The SEER ASR was 20.9. For females, the same pattern was observed at a much lower level. Egyptians ranked first (6.3), followed very closely by Israeli Jews (5.1), then by Cypriots (3.3), Israeli Arabs (2.1), and Jordanians (1.8). The SEER ASR for females was 5.5.

Comparison of male ASRs in Egypt with rates worldwide *[29]* showed that Egypt occupied the 86th percentile, with rates surpassed only by those in some West European countries. The high rates in Israel could be attributed to smoking. Egypt is still paying the double toll of the increasing exposure to smoking and the effect of the previously high prevalence of schistosomiasis as an endemic disease, an effect that will possibly persist for 2 to 3 decades to come.

Age

As shown in Table 11.3, the median age of bladder cancer patients showed marked variation between countries, with a range of 11.3 years, US SEER included. For both sexes, the youngest median age was that of Egyptians (61.6 years), followed by Jordanians (62.2 years) and Israeli Arabs (65.3 years). Median ages in Cypriots, Israeli Jews, and US SEER were all in the 70s. Median ages followed the same pattern for all registries, without too much difference between the sexes. This could be a reflection of the age

Table 11.3. Bladder Cancer: Summary Table of Cancer Statistics for 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
Bladder cancer cases	Total	460	6,215	299	1,057	1,038	21,355
	Male	387	4,991	261	852	915	15,893
	Female	73	1,224	38	205	123	5,462
Bladder cancer as a proportion of all cancers	Total	7.5%	5.9%	5.0%	10.1%	5.7%	4.3%
	Male	12.3%	10.0%	8.1%	16.2%	9.9%	6.2%
	Female	2.4%	2.2%	1.4%	4.0%	1.4%	2.2%
	Male-to-female ratio	5.3:1	4.1:1	6.9:1	4.2:1	7.4:1	2.9:1
Median age	Total	71.0	71.7	65.3	61.6	62.2	72.9
	Male	70.7	71.3	65.2	61.8	62.3	72.5
	Female	72.1	73.3	66.0	60.6	62.0	74.1
Age-standardized incidence rate‡	Total	11.2	15.1	8.6	16.6	7.6	12.2
	Male	20.5	27.5	16.0	27.5	13.2	20.9
	Female	3.3	5.1	2.1	6.3	1.8	5.5
Microscopically confirmed	Total	99.3%	94.5%	95.7%	88.7%	99.9%	98.7%
	Male	99.2%	94.5%	96.2%	89.2%	100.0%	98.9%
	Female	100.0%	94.3%	92.1%	86.8%	99.2%	98.2%

Table 11.3. continued

		Cyprus 1998-2001	Israel (Jews) 1996-2001	Israel (Arabs) 1996-2001	Egypt 1999-2001	Jordan 1996-2001	US SEER† 1999-2001
Distribution of Microscopically Confirmed Cases							
Histologic distribution§		100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
Carcinoma	Total	99.6%	98.6%	98.3%	98.0%	99.6%	99.4%
	Male	99.5%	98.5%	98.0%	98.4%	99.7%	99.5%
	Female	100.0%	99.0%	100.0%	96.1%	99.2%	99.2%
Squamous cell carcinoma	Total	-	0.7%	-	25.5%	1.8%	1.5%
	Male	-	0.7%	0.0%	21.7%	1.6%	100.0%
	Female	0.0%	1.1%	-	41.6%	3.3%	2.8%
Transitional cell carcinoma	Total	96.5%	93.8%	92.0%	62.9%	90.8%	94.9%
	Male	96.4%	94.0%	92.8%	67.1%	91.9%	95.6%
	Female	97.3%	92.6%	85.7%	44.9%	82.8%	93.0%
Adenoca	Total	1.3%	1.5%	3.5%	5.7%	3.8%	1.2%
	Male	100.0%	1.4%	2.8%	5.0%	3.1%	1.1%
	Female	2.7%	1.9%	8.6%	8.4%	9.0%	1.7%
Other specified carcinoma	Total	-	0.4%	-	-	-	0.6%
	Male	-	0.4%	-	-	-	0.6%
	Female	0.0%	0.5%	0.0%	0.0%	0.0%	0.5%
Unspecified carcinoma	Total	1.3%	2.2%	1.4%	3.8%	3.1%	1.2%
	Male	1.6%	2.0%	1.6%	4.5%	3.0%	1.2%
	Female	0.0%	2.8%	0.0%	-	4.1%	1.2%
Sarcoma	Total	0.0%	0.1%	0.0%	0.4%	-	0.2%
	Male	0.0%	0.1%	0.0%	-	-	0.1%
	Female	0.0%	-	0.0%	1.7%	0.0%	0.2%
Unspecified cancer	Total	0.0%	0.1%	1.7%	1.5%	0.3%	0.2%
	Male	0.0%	1.1%	2.0%	1.4%	-	0.2%
	Female	0.0%	0.5%	0.0%	1.7%	-	0.3%
Other histologies	Total	-	0.3%	0.0%	-	0.0%	0.2%
	Male	-	0.2%	0.0%	0.0%	0.0%	0.2%
	Female	0.0%	0.3%	0.0%	-	0.0%	0.3%

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.

§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 will not sum to 100%.

structure of the populations studied. As described in the "Overview and Summary Data" chapter of this monograph, MECC countries showed 2 different age structures. Arab populations (Egyptians, Jordanians, and Israeli Arabs) were relatively young compared with Israeli Jews and Cypriots. This relatively low median age for Arab populations, with 50% younger than age 60 years, has serious public health implications due to productive years of life lost due to bladder cancer.

Table 11.4. Bladder Cancer: Number of Cases and Age Distribution, by 5-Year and Broader Age Groups and 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
Total cases	460	387	73	6,215	4,991	1,224	229	261	38	1,057	852	205	1,038	915	123	21,355	15,893	5,462
5-Year Age Groups (Distribution)																		
00-04 y	0.0%	0.0%	0.0%	-	0.0%	-	0.0%	0.0%	0.0%	-	-	0.0%	-	-	-	0.0%	-	0.1%
05-09 y	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%
10-14 y	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%	-	-
15-19 y	0.0%	0.0%	0.0%	0.1%	-	-	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.4%	0.3%	-	0.0%	0.0%	-
20-24 y	0.7%	-	-	0.2%	0.2%	0.3%	0.0%	0.0%	0.0%	-	-	0.0%	0.6%	0.4%	-	0.1%	0.1%	0.1%
25-29 y	0.9%	1.0%	0.0%	0.3%	0.2%	0.7%	1.3%	1.5%	0.0%	-	-	-	1.0%	0.9%	-	0.1%	0.1%	0.2%
30-34 y	-	-	0.0%	0.5%	0.5%	0.5%	2.0%	1.9%	-	0.6%	-	2.0%	1.6%	1.7%	-	0.3%	0.3%	0.5%
35-39 y	0.9%	-	-	0.8%	0.8%	0.7%	2.0%	1.5%	-	0.8%	0.9%	0.0%	2.9%	3.0%	2.4%	0.8%	0.8%	0.9%
40-44 y	1.7%	2.1%	0.0%	1.5%	1.6%	1.0%	4.3%	4.2%	-	3.9%	3.5%	5.4%	3.9%	3.9%	4.1%	1.6%	1.7%	1.5%
45-49 y	3.7%	3.9%	-	3.2%	3.2%	3.1%	6.4%	6.9%	-	9.2%	8.6%	11.7%	6.5%	6.7%	4.9%	3.0%	3.1%	2.8%
50-54 y	5.9%	5.4%	8.2%	5.3%	5.5%	4.7%	7.4%	7.7%	-	13.7%	13.5%	14.6%	11.4%	10.3%	19.5%	5.1%	5.1%	5.0%
55-59 y	8.0%	8.5%	5.5%	6.5%	6.8%	5.6%	10.0%	10.3%	7.9%	15.6%	16.1%	13.7%	14.2%	14.9%	8.9%	7.2%	7.5%	6.3%
60-64 y	8.9%	8.8%	9.6%	10.2%	11.0%	7.4%	15.4%	15.3%	15.8%	18.2%	18.7%	16.1%	16.6%	16.9%	13.8%	9.5%	9.9%	8.5%
65-69 y	15.2%	16.3%	9.6%	14.9%	15.3%	12.8%	17.1%	15.7%	26.3%	17.5%	17.4%	18.0%	16.3%	16.1%	17.9%	12.3%	12.6%	11.7%
70-74 y	19.3%	18.9%	21.9%	19.0%	18.9%	19.4%	11.4%	12.3%	-	12.1%	12.6%	10.2%	12.3%	13.0%	7.3%	16.5%	17.0%	15.0%
75+ y	34.3%	33.9%	37.0%	37.4%	35.9%	43.5%	22.7%	22.6%	23.7%	8.1%	8.2%	7.8%	12.2%	11.8%	15.4%	43.3%	41.9%	47.4%
Broader Age Groups (Distribution)																		
Total cases	460	387	73	6,215	4,991	1,224	299	261	38	1,057	852	205	1,038	915	123	21,355	15,893	5,462
<40 y	2.8%	2.3%	5.5%	2.0%	1.8%	2.5%	5.4%	5.0%	7.9%	1.7%	1.5%	2.4%	6.6%	6.4%	8.1%	1.5%	1.3%	1.8%
40-59 y	19.3%	19.9%	16.4%	16.6%	17.1%	14.4%	28.1%	29.1%	21.1%	42.4%	41.7%	45.4%	35.9%	35.7%	37.4%	16.9%	17.3%	15.6%
60-69 y	24.1%	25.1%	19.2%	25.1%	26.3%	20.2%	32.4%	31.0%	42.1%	35.7%	36.0%	34.1%	32.9%	33.0%	31.7%	21.9%	22.5%	20.2%
70+ y	53.7%	52.7%	58.9%	56.4%	54.8%	62.9%	34.1%	34.9%	28.9%	20.2%	20.8%	18.0%	24.6%	24.8%	22.8%	59.8%	58.9%	62.4%

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.

The age structure of bladder cancer patients in 5-year age groups is shown in Table 11.4. To avoid reporting incidence rates on small numbers of certain age groups, age was empirically grouped into 4 categories: <40, 40-59, 60-69, and 70+ years. In Egypt and Jordan, the most frequent age group among bladder cancer patients was 40-59 years (42.4% and 35.9% of total cases in the two countries, respectively), with decreasing frequency in successive age groups. The other registries reported a progressive increase in frequency to a peak in older age groups, although this trend was less marked among Israeli Arabs.

Table 11.5 shows the age-specific incidence rates. It may be seen that rates in Egypt were highest in the age groups up to 70 years, but in those aged 70 years and older, incidence rates in Israel and the United States were higher than in Egypt. It is possible that this is due to underdiagnosis of elderly patients in Egypt, or it may point to a difference in the etiologies of SABC and tobacco-related bladder cancer.

Histology

Reports from all registries except Egypt showed a very low frequency of squamous cell carcinoma. In Egypt, SCC represented 21.7% and 41.6% of male and female bladder cancers, respectively (Table 11.3). Previous reports from Egypt indicated a higher frequency of SCC that reached 75% of bladder malignancies. This lower frequency of SCC relative to previous reports supports the etiological relationship to urinary schistosomiasis in Egypt and the effect of successful control measures of the endemic disease. The increase in frequency of TCC and decrease in frequency of SCC relative to previous reports indicate a transition phase from the SABC to the Western type of bladder cancer related to smoking.

For TCC, the ASR for both sexes together showed marked variation between registries (Table 11.6). The highest rate was that of Israeli Jews (13.5), almost double the lowest rate (Jordanians, 6.9). Next to Israeli Jews were Cypriots (10.7), Egyptians (9.3), and Israeli Arabs (7.6). The US SEER rate was 11.5.

The same ranking of TCC incidence rates was observed for males and females. The highest rates were those of Israeli Jews (24.6 and 4.5), followed by Cypriots (19.5 and 3.2), Egyptians (16.4 and 2.4), Israeli Arabs (14.3 and 1.7), and Jordanians (12.1 and 1.5), for males and females, respectively – another point underlining the serious effects of the uncontrolled smoking epidemic. The corresponding US SEER rates were 19.8 for males and 5.0 for females. For all registries, rates showed progressive increases with aging.

Comparison of incidence rates of SCC was possible for Egypt and US SEER only, due to small numbers and very low rates in other registries (Table 11.6). ASRs for Egypt, both sexes, were almost 12-25 times the rates of US SEER, which were the same for males and females. US SEER rates showed a progressive increase with age. In Egypt, rates increased to a much higher peak that occurred among the age group 60-69 years (21.0, 31.6, and 10.8, for both sexes, males, and females, respectively). This observation supports the relationship between bladder cancer and schistosomiasis. The TCC to SCC ratio that was reversed relative to previous reports indicates that Egypt is in a transition phase between SABC and the Western cigarette-related type of bladder cancer.

SUMMARY AND CONCLUSIONS

Bladder cancer is one of the more common cancers in the Middle East countries under study. Egypt had both the highest frequency and incidence rates and had a different histological pattern than other countries. This could be attributed to the relationship between bladder cancer and *S. haematobium*, a parasitic disease that used to be endemic in Egypt, and which is currently under control, with complete eradication in certain districts. In the present study, this relationship was supported for the first time by population-based data. Egypt was the only country that showed a high frequency and incidence of squamous cell carcinoma, which is the histologic type related to schistosomiasis. Egypt also showed an earlier peak of age-specific incidence rates, possibly due to the early age at schistosomal infection and the latent time needed for carcinogenesis.

Nevertheless, the profile of bladder cancer in Egypt was not typical of that described in earlier reports about the disease. Male predominance was marked but was not specific for Egypt. The frequency of squamous cell carcinoma, though relatively high, was lower than that usually seen with schistosomal-associated bladder cancer. The profile seemed to be one of a transition toward tobacco-related bladder cancer, possibly due to decreasing prevalence of schistosomiasis during the last 2 decades.

Table 11.5. Bladder Cancer: Age-Specific Incidence Rates,* by 5-Year and Broader Age Groups and 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
5-Year Age Groups (Rates)																		
Total Rate	11.2	20.5	3.3	15.1	27.5	5.1	8.6	16.0	2.1	16.6	27.5	6.3	7.6	13.2	1.8	12.2	20.9	5.5
00-04 y	0.0	0.0	0.0	-	0.0	-	0.0	0.0	0.0	-	-	0.0	-	-	-	0.1	-	0.1
05-09 y	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
10-14 y	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	-	-
15-19 y	0.0	0.0	0.0	0.2	-	-	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.2	-	0.1	0.1	-
20-24 y	1.5	-	-	0.5	0.7	0.3	0.0	0.0	0.0	-	-	0.0	0.2	0.2	-	0.2	0.4	0.1
25-29 y	2.1	4.3	0.0	0.9	1.0	0.7	0.7	1.3	0.0	-	-	-	0.4	0.6	-	0.4	0.4	0.3
30-34 y	-	-	0.0	1.8	3.0	0.6	1.2	1.9	-	0.8	-	1.1	0.9	1.5	-	0.8	0.9	0.6
35-39 y	1.9	-	-	2.7	4.6	1.0	1.4	1.8	-	1.1	2.3	0.0	2.1	3.7	0.4	1.8	2.6	1.0
40-44 y	3.9	7.9	0.0	5.0	9.0	1.3	4.0	6.7	-	6.9	9.9	3.7	3.9	6.8	1.0	3.7	5.7	1.8
45-49 y	9.4	16.8	-	10.5	17.6	3.9	7.7	14.7	-	19.3	27.5	10.1	7.7	13.9	1.4	7.7	11.9	3.6
50-54 y	16.4	25.8	7.2	21.8	37.3	7.2	11.5	21.0	-	40.1	64.0	16.5	15.2	23.4	6.4	15.0	22.9	7.4
55-59 y	26.5	47.8	5.6	38.4	67.3	12.4	19.3	34.4	3.9	61.2	98.9	21.3	21.7	38.4	3.4	28.6	45.5	12.5
60-64 y	35.3	60.4	11.7	59.6	111.2	15.6	38.9	70.7	9.7	76.5	133.4	25.1	34.4	58.4	7.2	49.8	80.6	21.7
65-69 y	70.8	138.2	13.1	94.4	176.0	28.9	59.2	105.9	21.1	106.4	169.7	42.7	50.5	81.7	14.2	76.2	125.6	34.1
70-74 y	107.7	197.8	35.0	130.5	243.7	46.0	58.0	128.5	-	109.7	194.2	34.1	57.7	110.8	7.9	110.0	192.0	45.7
75+ y	119.1	229.4	35.7	162.4	303.9	63.2	92.1	171.5	22.8	100.1	175.9	34.7	50.5	92.0	14.2	148.0	286.3	65.4
Broader Age Groups (Rates)																		
Total Rate	11.2	20.5	3.3	15.1	27.5	5.1	8.6	16.0	2.1	16.6	27.5	6.3	7.6	13.2	1.8	12.2	20.9	5.5
<40 y	0.7	1.0	0.4	0.6	0.9	0.3	0.3	0.5	0.1	0.2	0.3	0.1	0.4	0.6	0.1	0.3	0.4	0.2
40-59 y	12.8	22.3	3.4	16.9	29.3	5.6	9.7	17.7	1.8	28.7	44.8	12.0	11.1	18.8	2.8	12.3	19.2	5.7
60-69 y	50.5	93.7	12.3	74.5	139.0	21.3	47.6	85.8	14.6	89.3	149.0	32.6	41.3	68.4	10.2	61.1	99.9	27.0
70+ y	113.4	213.6	35.4	146.4	273.8	54.6	75.1	150.0	14.4	104.9	185.1	34.4	54.1	101.4	11.0	129.0	239.1	55.5

*Rates are per 100,000, and for the broad age groups are age-standardized to the World Standard Million.

†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.

Table 11.6. Bladder Cancer: Age-Standardized Incidence Rates,* by Histological Type 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
Transitional Cell Carcinoma																		
Total rate	10.7	19.5	3.2	13.5	24.6	4.5	7.6	14.3	1.7	9.3	16.4	2.4	6.9	12.1	1.5	11.5	19.8	5.0
<40 y	0.6	1.0	0.3	0.5	0.8	0.2	0.3	0.5	0.1	0.1	0.2	-	0.3	0.5	0.1	0.3	0.4	0.2
40-59 y	12.8	22.3	3.4	15.5	26.8	5.0	8.6	16.1	1.2	15.9	26.8	4.5	10.0	17.2	2.3	11.6	18.3	5.2
60-69 y	46.3	85.0	12.3	67.7	126.4	19.3	42.7	77.3	12.7	50.3	88.7	13.8	38.1	63.9	8.5	58.1	95.5	25.3
70+ y	109.3	205.2	34.7	127.9	239.1	47.6	63.9	130.0	10.6	58.2	110.7	11.9	48.9	92.5	9.2	120.6	224.9	50.9
Squamous Cell Carcinoma																		
Total rate										3.7	5.1	2.3				0.2	0.2	0.1
<40 y										0.1	0.1	-				0.0	-	0.0
40-59 y										7.5	10.2	4.7				0.2	0.2	0.2
60-69 y										21.0	31.6	10.8				0.7	0.8	0.6
70+ y										14.3	16.8	12.2				1.9	2.6	1.4

*Rates are per 100,000, and rates for the broad age groups are age-standardized to the World Standard Million.

†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.

Other risk factors, mainly smoking, are responsible for the high incidence of bladder cancer in other countries in the region. The economic burden of the disease is greater in Arab populations, particularly Egypt, where the median age of diagnosis is younger than in the West. Efforts toward smoking control and respecting the rights of nonsmokers must be intensified. Smoking rates appear to be higher in the Middle East region than in the United States, although the amount of cigarettes smoked in the Middle East may be lower.

A prospective study could be of value to document the change in the bladder cancer profile in Egypt during the current post-schistosomal control era, with transition from schistosome-related SCC to the smoking-related TCC common in Western countries.

REFERENCES

[1] Stein JP, Lieskovsky G, Cote R, Groshen S, Feng AC, Boyd S, et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. J Clin Oncol 2001;19:666-75.

[2] Sengupta N, Siddiqui E, Mumtaz FH. Cancers of the bladder. J R Soc Health 2004;124:228-9.

[3] Messing EM, Young TB, Hunt VB, Gilchrist KW, Newton MA, Bram LL, et al. Comparison of bladder cancer outcome in men undergoing hematuria home screening versus those with standard clinical presentations. Urology 1995;45:387-96.

[4] El Sebaie M, Zaghloul MS, Howard G, Mokhtar A. Squamous cell carcinoma of the bilharzial and non-bilharzial urinary bladder: a review of etiological features, natural history, and management. Int J Clin Oncol 2005;10:20-5.

[5] Peterson RO, editor. Urologic pathology, second edition. Philadelphia (PA): J.B. Lippincott; 1992.
[6] Mackay J and Eriksen M. The tobacco atlas. Geneva (Switzerland): World Health Organization; 2002.
[7] Vaishnav VP. Schistosomiasis induced squamous cell carcinoma of the urinary bladder. Indian J Pathol Microbiol 2003;46:148-9.
[8] Higashi GI, Aboul-Enein MI. Diagnosis and epidemiology of schistosoma haematobium infections in Egypt. In: El-Bolkainy MN, Chu E, editors. Detection of bladder cancer associated with schistosomiasis. Cairo (Egypt): Al-Ahram Press; 1992. p. 47-69.
[9] Badr MM. The history of urology in ancient Egypt. J Int Coll Surg 1963;39:404-13.
[10] Badr MM. Schistosomiasis in ancient Eqypt. In: El-Bolkainy MN, Chu E, editors. Detection of bladder cancer associated with schistosomiasis. Cairo (Egypt): Al-Ahram Press; 1992. p. 124-8.
[11] Mostafa MH, Sheweita SA, O'Connor PJ. Relationship between schistosomiasis and bladder cancer. Clin Microbiol Rev 1999;12:97-111.
[12] Ministry of Health and Population. Prevalence of schistosomiasis on Egypt. Report of the Department of Endemic Disease (personal communication). (Egypt): Ministry of Health and Population; 2002.
[13] Cheever AW. Schistosomiasis and neoplasia. J Natl Cancer Inst 1978;61:13-8.
[14] Badawi AF, Mostafa MH, Probert A, O'Connor PJ. Role of schistosomiasis in human bladder cancer: evidence of association, aetiological factors, and basic mechanisms of carcinogenesis. Eur J Cancer Prev 1995;4:45-59.
[15] World Health Organization. Evaluation of carcinogenic risk to humans: schistosomes, liver flukes and Helicobactor pylori. IARC Monograph 1994;61:45-119.
[16] Shokeir AA. Squamous cell carcinoma of the bladder: pathology, diagnosis and treatment. BJU Int 2004;93:216-20.
[17] Gordon O, Carel RS, Kordish E. The role of occupational exposures in the etiology of bladder cancer [Hebrew]. Harefuah 2004;143:772-4, 840.
[18] Travis LB, Curtis RE, Glimelius B, Holowaty EJ, van Leeuwen FE, Lynch CF, et al. Bladder and kidney cancer following cyclophosphamide therapy for non-Hodgkin's lymphoma. J Natl Cancer Inst 1995;87:524-30.
[19] Cohen SM, Shirai T, Steineck G. Epidemiology and etiology of premalignant and malignant urothelial changes. Scand J Urol Nephrol Suppl 2000;105-15.
[20] Negri E, La Vecchia C. Epidemiology and prevention of bladder cancer. Eur J Cancer Prev 2001;10:7-14.
[21] Gonzalez-Zulueta M, Shibata A, Ohneseit PF, Spruck CH, III, Busch C, Shamaa M, et al. High frequency of chromosome 9p allelic loss and CDKN2 tumor suppressor gene alterations in squamous cell carcinoma of the bladder. J Natl Cancer Inst 1995;87:1383-93.
[22] Pycha A, Mian C, Posch B, Haitel A, El Baz M, Ghoneim MA, et al. Numerical aberrations of chromosomes 7, 9 and 17 in squamous cell and transitional cell cancer of the bladder: a comparative study performed by fluorescence in situ hybridization. J Urol 1998;160:737-40.
[23] Khaled HM, Aly MS, Magrath IT. Loss of Y chromosome in bilharzial bladder cancer. Cancer Genet Cytogenet 2000;117:32-6.
[24] Weintraub M, Khaled HM, Abdel-Rahman Z, Bahnasi A, Eissa S, Venzon DJ, et al. p53 mutations in Egyptian bladder cancer. Int J Oncol 1995;7:1269-74.
[25] Osman I, Scher HI, Zhang ZF, Pellicer I, Hamza R, Eissa S, et al. Alterations affecting the p53 control pathway in bilharzial-related bladder cancer. Clin Cancer Res 1997;3:531-6.
[26] Fujita J, Nakayama H, Onoue H, Rhim JS, el Bolkainy MN, el Aaser AA, et al. Frequency of active ras oncogenes in human bladder cancers associated with schistosomiasis. Jpn J Cancer Res 1987;78:915-20.
[27] El-Mawla NG, El-Bolkainy MN, Khaled HM. Bladder cancer in Africa: update. Semin Oncol 2001;28:174-8.
[28] Habuchi T, Takahashi R, Yamada H, Ogawa O, Kakehi Y, Ogura K, et al. Influence of cigarette smoking and schistosomiasis on p53 gene mutation in urothelial cancer. Cancer Res 1993;53:3795-9.
[29] 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.

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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

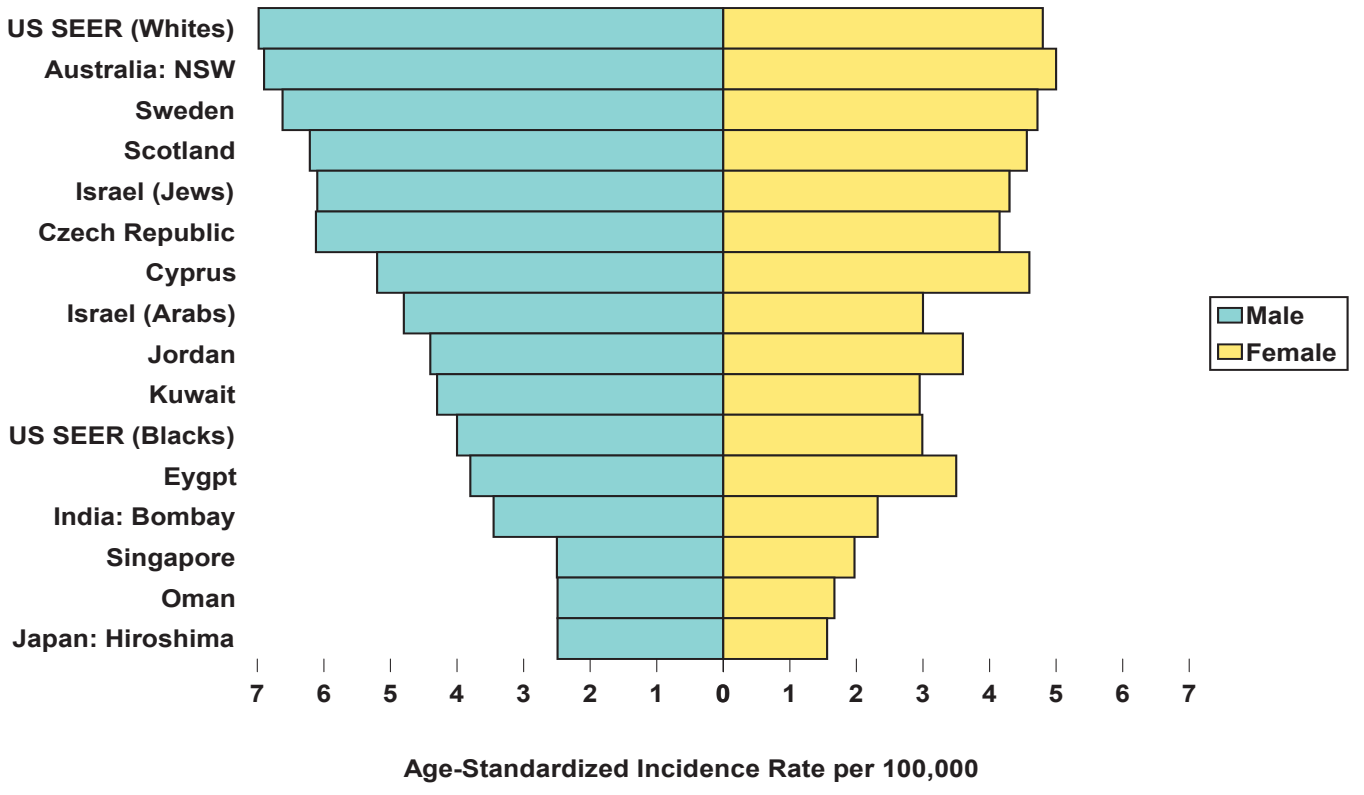
The symbols "-" = 1-2 cases; and "[numeral]*" (italic) = 0 or 3-15 cases.

†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

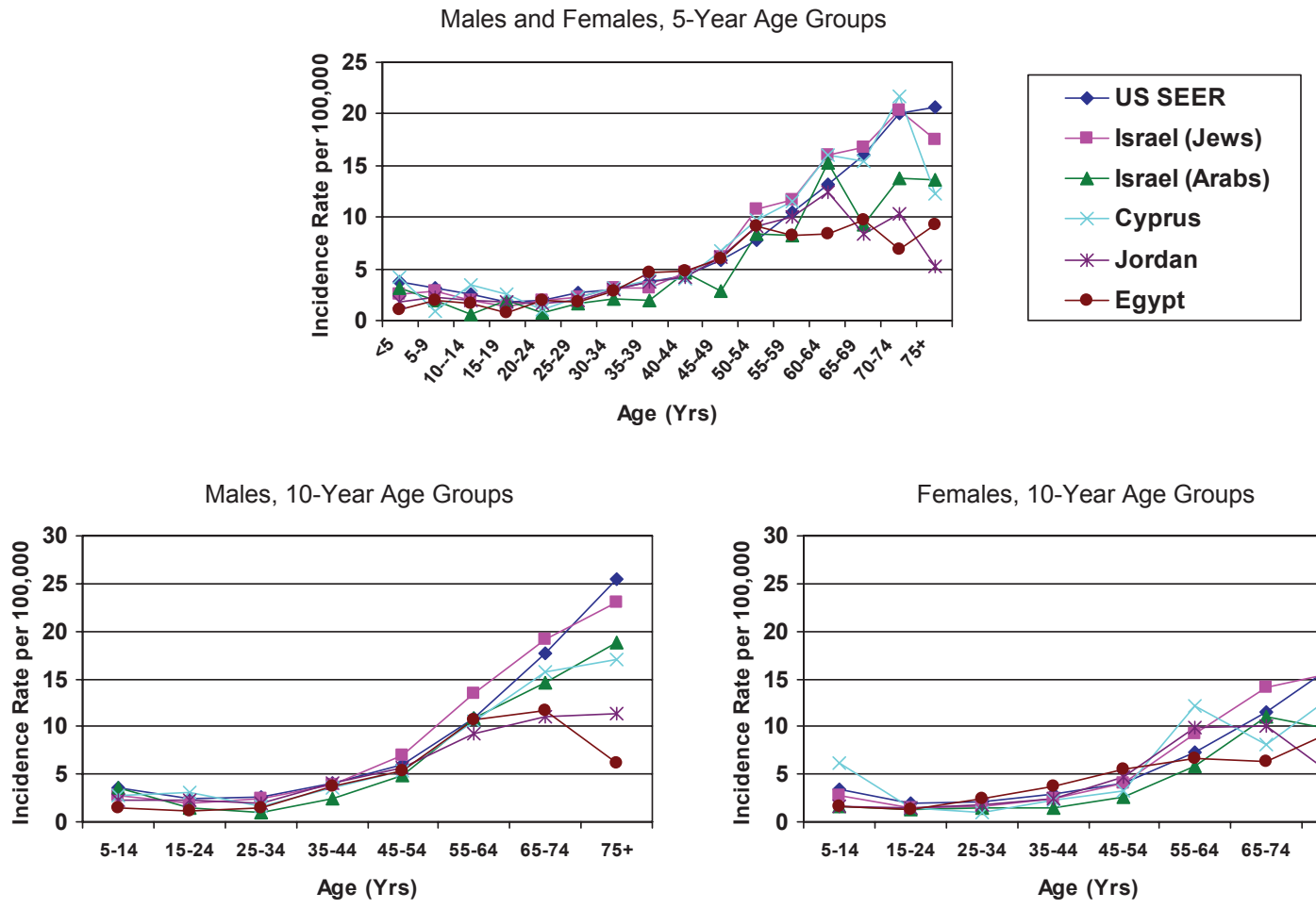


Table 12.3. Brain and Other Central Nervous System Cancer: Number of Cases, Age Distribution, and Age-Standardized Incidence Rates, by Age and Sex, in Cyprus, Israel (Jews and Arabs), Egypt, Jordan, and US SEER − 1996-2001*

	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.

REFERENCES

[1] Russell DS, Rubenstein LJ. Pathology of tumours of the nervous system. Baltimore (MD): Williams and Wilkins; 1989.

[2] Inskip PD, Linet MS, Heineman EF. Etiology of brain tumors in adults. Epidemiol Rev 1995;17:382-414.

[3] Preston-Martin S, Mack WJ. Neoplasms of the nervous system. In: Schottenfeld D, Fraumeni JF, Jr., editors. Cancer epidemiology and prevention. New York (NY): Oxford University Press; 1996. p. 1231-81.

[4] Wrensch M, Minn Y, Chew T, Bondy M, Berger MS. Epidemiology of primary brain tumors: current concepts and review of the literature. Neuro-Oncol 2002;4:278-99.

[5] Malkin D, Jolly KW, Barbier N, Look AT, Friend SH, Gebhardt MC, et al. Germline mutations of the p53 tumor-suppressor gene in children and young adults with second malignant neoplasms. N Engl J Med 1992;326:1309-15.

[6] Hisada M, Garber JE, Fung CY, Fraumeni JF, Jr., Li FP. Multiple primary cancers in families with Li-Fraumeni syndrome. J Natl Cancer Inst 1998;90:606-11.

[7] Eng C, Maher ER. Dominant genes and phakomatoses associated with multiple primary cancers. In: Neugut AI, Meadows AT, Robinson E, editors. Multiple primary cancers. Philadelphia (PA): Williams and Wilkins; 1999. p. 165-95.

[8] Nichols KE, Malkin D, Garber JE, Fraumeni JF, Jr., Li FP. Germ-line p53 mutations predispose to a wide spectrum of early-onset cancers. Cancer Epidemiol Biomarkers Prev 2001;10:83-7.

[9] Narod SA, Stiller C, Lenoir GM. An estimate of the heritable fraction of childhood cancer. Br J Cancer 1991;63:993-9.

[10] Ron E, Modan B, Boice JD, Jr., Alfandary E, Stovall M, Chetrit A, et al. Tumors of the brain and nervous system after radiotherapy in childhood. N Engl J Med 1988;319:1033-9.

[11] Neglia JP, Meadows AT, Robison LL, Kim TH, Newton WA, Ruymann FB, et al. Second neoplasms after acute lymphoblastic leukemia in childhood. N Engl J Med 1991;325:1330-6.
[12] Karlsson P, Holmberg E, Lundell M, Mattsson A, Holm LE, Wallgren A. Intracranial tumors after exposure to ionizing radiation during infancy: a pooled analysis of two Swedish cohorts of 28,008 infants with skin hemangioma. Radiat Res 1998;150:357-64.
[13] Little MP, de Vathaire F, Shamsaldin A, Oberlin O, Campbell S, Grimaud E, et al. Risks of brain tumour following treatment for cancer in childhood: modification by genetic factors, radiotherapy and chemotherapy. Int J Cancer 1998;78:269-75.
[14] Preston DL, Ron E, Yonehara S, Kobuke T, Fujii H, Kishikawa M, et al. Tumors of the nervous system and pituitary gland associated with atomic bomb radiation exposure. J Natl Cancer Inst 2002;94:1555-63.
[15] Sadetzki S, Chetrit A, Freedman L, Stovall M, Modan B, Novikov I. Long-term follow-up for brain tumor development after childhood exposure to ionizing radiation for tinea capitis. Radiat Res 2005;163:424-32.
[16] Inskip PD, Tarone RE, Hatch EE, Wilcosky TC, Shapiro WR, Selker RG, et al. Cellular-telephone use and brain tumors. N Engl J Med 2001;344:79-86.
[17] Kleinerman RA, Linet MS, Hatch EE, Tarone RE, Black PM, Selker RG, et al. Self-reported electrical appliance use and risk of adult brain tumors. Am J Epidemiol 2005;161:136-46.
[18] Modan B, Wagener DK, Feldman JJ, Rosenberg HM, Feinleib M. Increased mortality from brain tumors: a combined outcome of diagnostic technology and change of attitude toward the elderly. Am J Epidemiol 1992;135:1349-57.
[19] Legler JM, Ries LA, Smith MA, Warren JL, Heineman EF, Kaplan RS, et al. Brain and other central nervous system cancers: recent trends in incidence and mortality. J Natl Cancer Inst 1999;91:1382-90.
[20] Preston-Martin S. Descriptive epidemiology of primary tumors of the brain, cranial nerves and cranial meninges in Los Angeles County. Neuroepidemiology 1989;8:283-95.
[21] Inskip PD, Tarone RE, Hatch EE, Wilcosky TC, Fine HA, Black PM, et al. Sociodemographic indicators and risk of brain tumours. Int J Epidemiol 2003;32:225-33.
[22] Lutz WK, Fekete T. Endogenous and exogenous factors in carcinogenesis: limits to cancer prevention. Int Arch Occup Environ Health 1996;68:120-5.
[23] 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.
[24] Hatch EE, Linet MS, Zhang J, Fine HA, Shapiro WR, Selker RG, et al. Reproductive and hormonal factors and risk of brain tumors in adult females. Int J Cancer 2005;114:797-805.
[25] Wrensch M, Lee M, Miike R, Newman B, Barger G, Davis R, et al. Familial and personal medical history of cancer and nervous system conditions among adults with glioma and controls. Am J Epidemiol 1997;145:581-93.
[26] Schlehofer B, Blettner M, Preston-Martin S, Niehoff D, Wahrendorf J, Arslan A, et al. Role of medical history in brain tumour development. Results from the international adult brain tumour study. Int J Cancer 1999;82:155-60.
[27] Wrensch M, Weinberg A, Wiencke J, Miike R, Barger G, Kelsey K. Prevalence of antibodies to four herpesviruses among adults with glioma and controls. Am J Epidemiol 2001;154:161-5.
[28] Brenner AV, Linet MS, Fine HA, Shapiro WR, Selker RG, Black PM, et al. History of allergies and autoimmune diseases and risk of brain tumors in adults. Int J Cancer 2002;99:252-9.
[29] Wiemels JL, Wiencke JK, Sison JD, Miike R, McMillan A, Wrensch M. History of allergies among adults with glioma and controls. Int J Cancer 2002;98:609-15.
[30] Wiemels JL, Wiencke JK, Patoka J, Moghadassi M, Chew T, McMillan A, et al. Reduced immunoglobulin E and allergy among adults with glioma compared with controls. Cancer Res 2004;64:8468-73.
[31] Sivak-Sears NR, Schwartzbaum JA, Miike R, Moghadassi M, Wrensch M. Case-control study of use of nonsteroidal antiinflammatory drugs and glioblastoma multiforme. Am J Epidemiol 2004;159:1131-9.
[32] Pardridge WM. Introduction to the blood-brain barrier. Methodology, biology and pathology. Cambridge (MA): Cambridge University Press; 1998.

[33] Druckrey H. Specific carcinogenic and teratogenic effects of 'indirect' alkylating methyl and ethyl compounds, and their dependency on stages of ontogenic developments. Xenobiotica 1973;3:271-303.

[34] Kleihues P, Lantos PL, Magee PN. Chemical carcinogenesis in the nervous system. Int Rev Exp Pathol 1976;15:153-232.

[35] Magee PN, Montesano R, Preussmann R. N-nitroso compounds and related carcinogens. In: Searle CE, editor. Chemical carcinogens, ACS monograph 173. Washington (DC): American Chemical Society; 1976. p. 491-625.

[36] Kleihues P, Aguzzi A, Wiestler OD. Cellular and molecular aspects of neurocarcinogenesis. Toxicol Pathol 1990;18:193-203.

[37] Preston-Martin S, Henderson BE. N-nitroso compounds and human intracranial tumours. IARC Sci Publ 1984;887-94.

[38] Preston-Martin S. Epidemiological studies of perinatal carcinogenesis. In: Napalkov NP, Rice JM, Tomatis L, Yamasaki H, editors. Perinatal and multigenerational carcinogenesis. Lyon (France): International Agency for Research on Cancer; 1989. p. 289-314.

[39] Sadetzki S, Modan B, Chetrit A, Freedman L. An iatrogenic epidemic of benign meningioma. Am J Epidemiol 2000;151:266-72.

[40] Finfacts Ireland. Finfacts Reports/Services: global income per capita - published 2005. 2005. Available at: http://www.finfacts.com/biz10/globalworldincomepercapita.htm. [Last Accessed: 1/06].

[41] Kleihues P, Cavenee WK. Pathology and genetics of the nervous system. Lyon (France): International Agency for Research on Cancer; 1997.

Cécile Ronckers, Elaine Ron

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]*.

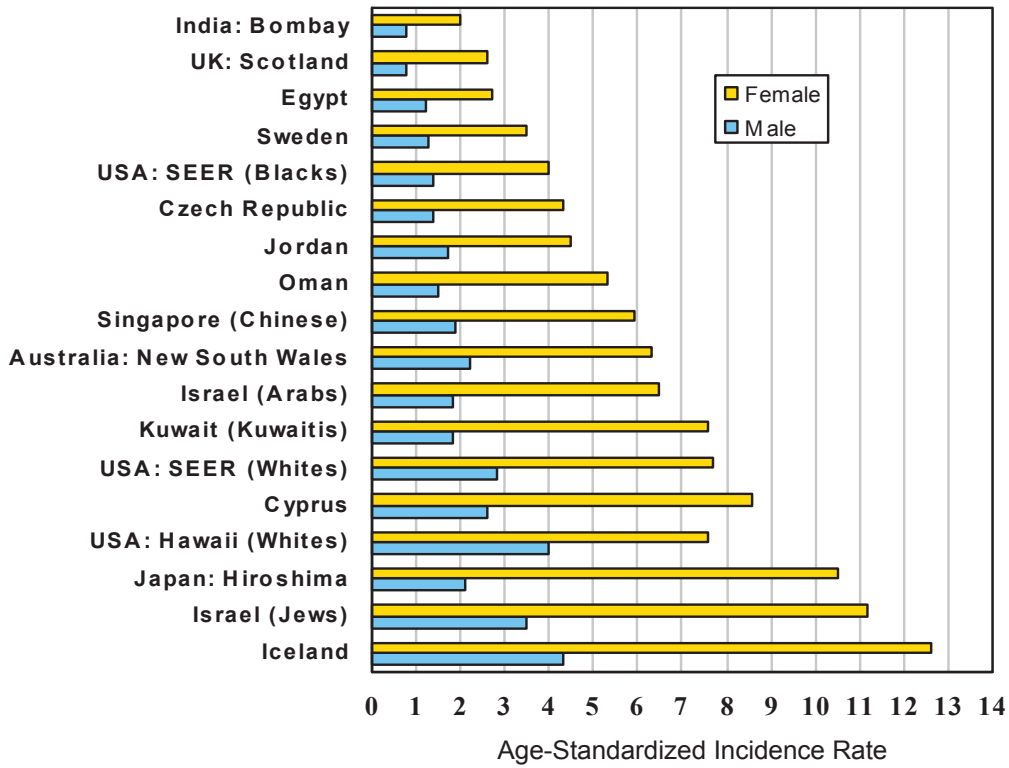
The especially high thyroid cancer ASRs observed among Israeli Jews is of interest because high rates also were observed in some *[23-25]*, though not all, epidemiologic studies *[26]* of Jewish communities in the United States. These findings may indicate a role for genetic factors, as has been seen 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*

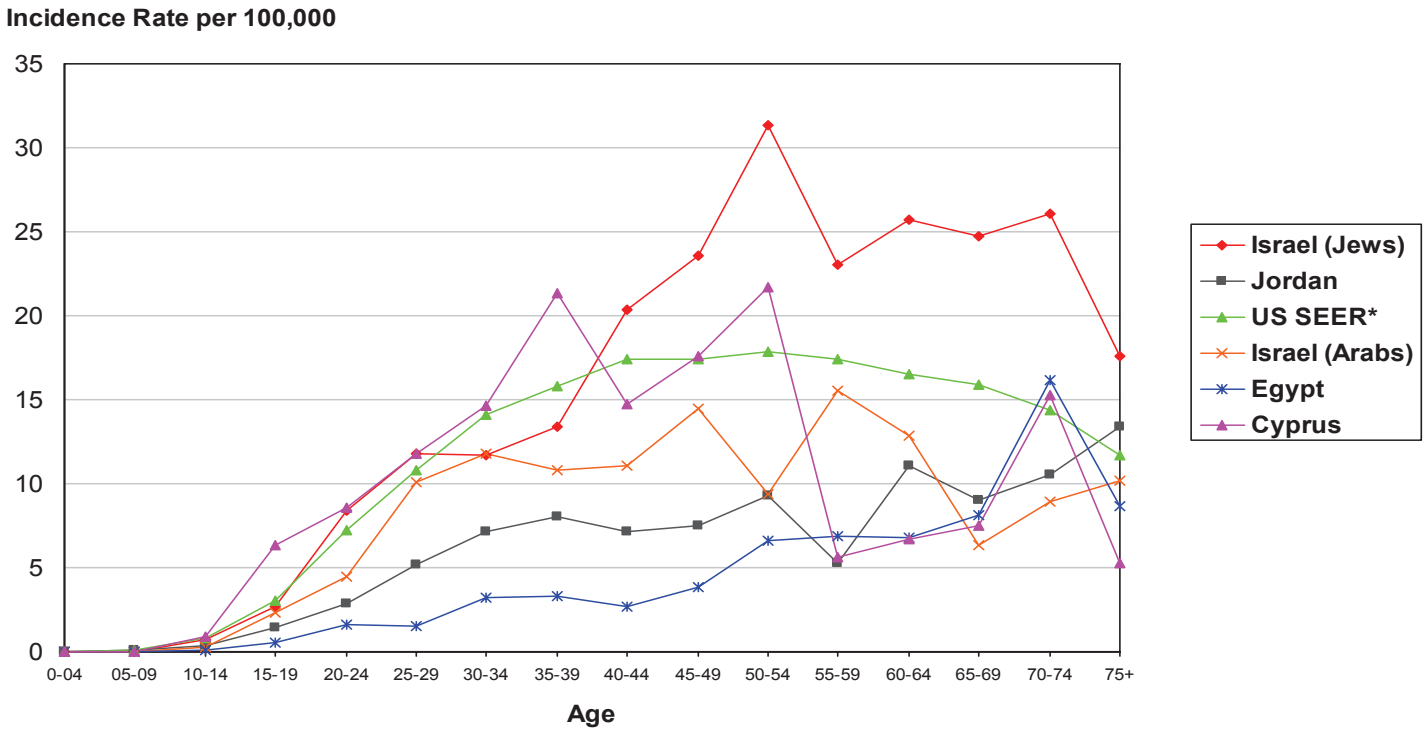
	Cyprus 1998-2001			Israel (Jews) 1996-2001			Israel (Arabs) 1996-2001			Egypt 1999-2001			Jordan 1996-2001			US SEER† 1999-2001		
	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female
Total cases	179	40	139	2,404	546	1,858	227	45	182	154	45	109	617	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.

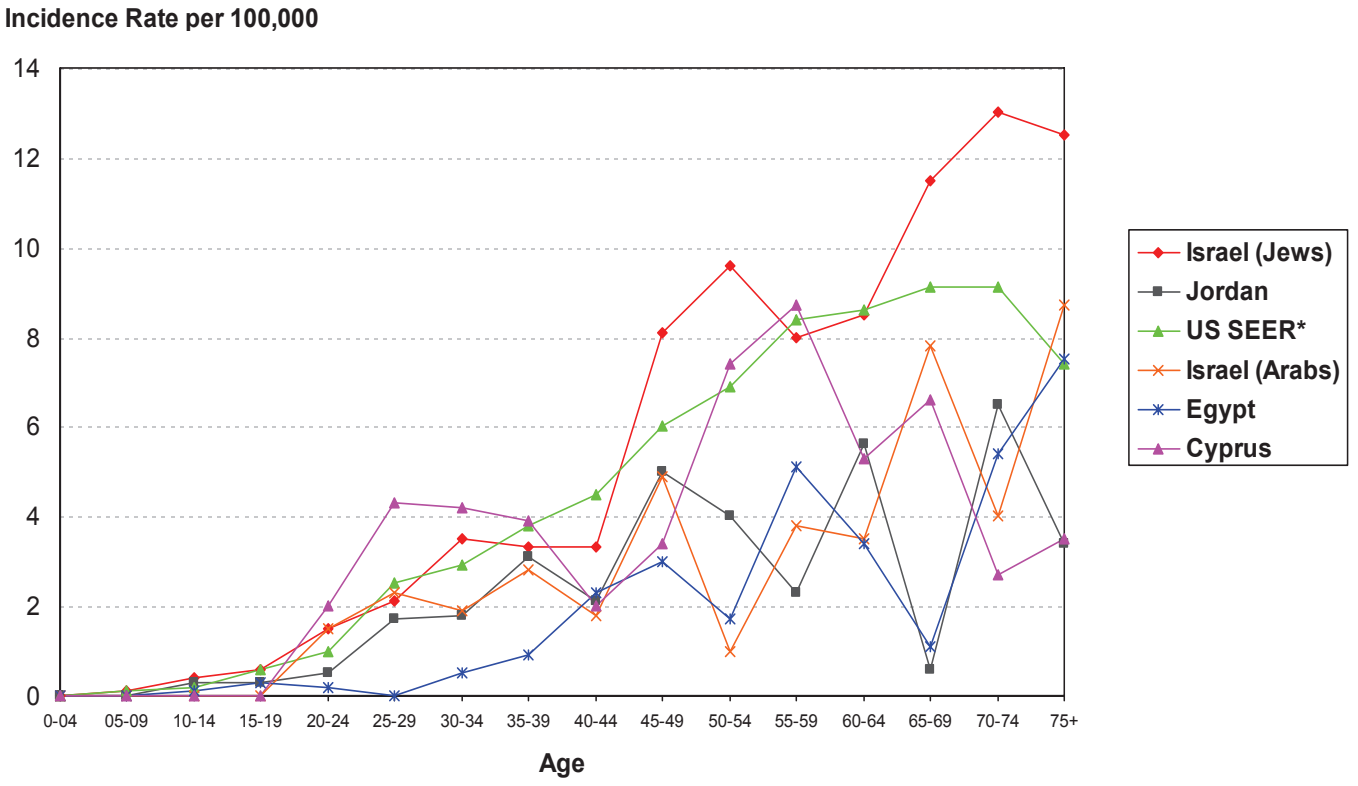
‡Rates are per 100,000 and are age-standardized to the World Standard Million.

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.

REFERENCES

[1] American Cancer Society. Cancer facts and figures 2005. Atlanta, GA: American Cancer Society; 2005.

[2] Memon A, Darif M, Al Saleh K, Suresh A. Epidemiology of reproductive and hormonal factors in thyroid cancer: evidence from a case-control study in the Middle East. Int J Cancer 2002;97:82-9.

[3] Parkin DM, Whelan SL, Ferlay J, Teppo L, eds. Cancer incidence in five continents, volume VIII. IARC Scientific Publication No. 155. Lyon (France): International Agency for Research on Cancer; 2002.

[4] Ries LAG, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg L, et al. SEER cancer statistics review. 2003. Available at: http://seer.cancer.gov/csr/1975_2000/. [Last Accessed: 12/05].

[5] Ron E, Lubin JH, Shore RE, Mabuchi K, Modan B, Pottern LM, et al. Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. Radiat Res 1995;141:259-77.

[6] Thompson DE, Mabuchi K, Ron E, Soda M, Tokunaga M, Ochikubo S, et al. Cancer incidence in atomic bomb survivors. Part II: Solid tumors, 1958-1987. Radiat Res 1994;137:S17-S67.

[7] Kerber RA, Till JE, Simon SL, Lyon JL, Thomas DC, Preston-Martin S, et al. A cohort study of thyroid disease in relation to fallout from nuclear weapons testing. JAMA 1993;270:2076-82.

[8] Hamilton TE, van Belle G, LoGerfo JP. Thyroid neoplasia in Marshall Islanders exposed to nuclear fallout. JAMA 1987;258:629-35.

[9] Cardis E, Kesminiene A, Ivanov V, Malakhova I, Shibata Y, Khrouch V, et al. Risk of thyroid cancer after exposure to 131I in childhood. J Natl Cancer Inst 2005;97:724-32.

[10] Franceschi S, Preston-Martin S, Dal Maso L, Negri E, La Vecchia C, Mack WJ, et al. A pooled analysis of case-control studies of thyroid cancer. IV. Benign thyroid diseases. Cancer Causes Control 1999;10:583-95.

[11] Negri E, Dal Maso L, Ron E, La Vecchia C, Mark SD, Preston-Martin S, et al. A pooled analysis of case-control studies of thyroid cancer. II. Menstrual and reproductive factors. Cancer Causes Control 1999;10:143-55.

[12] La Vecchia C, Ron E, Franceschi S, Dal Maso L, Mark SD, Chatenoud L, et al. A pooled analysis of case-control studies of thyroid cancer. III.

Oral contraceptives, menopausal replacement therapy and other female hormones. Cancer Causes Control 1999;10:157-66.

[13] Bosetti C, Negri E, Kolonel L, Ron E, Franceschi S, Preston-Martin S, et al. A pooled analysis of case-control studies of thyroid cancer. VII. Cruciferous and other vegetables (International). Cancer Causes Control 2002;13:765-75.

[14] Memon A, Varghese A, Suresh A. Benign thyroid disease and dietary factors in thyroid cancer: a case-control study in Kuwait. Br J Cancer 2002;86:1745-50.

[15] Bosetti C, Kolonel L, Negri E, Ron E, Franceschi S, Dal Maso L, et al. A pooled analysis of case-control studies of thyroid cancer. VI. Fish and shellfish consumption. Cancer Causes Control 2001;12:375-82.

[16] Mack WJ, Preston-Martin S, Dal Maso L, Galanti R, Xiang M, Franceschi S, et al. A pooled analysis of case-control studies of thyroid cancer: cigarette smoking and consumption of alcohol, coffee, and tea. Cancer Causes Control 2003;14:773-85.

[17] Malchoff CD, Malchoff DM. The genetics of hereditary nonmedullary thyroid carcinoma. J Clin Endocrinol Metab 2002;87:2455-9.

[18] Liaw D, Marsh DJ, Li J, Dahia PL, Wang SI, Zheng Z, et al. Germline mutations of the PTEN gene in Cowden disease, an inherited breast and thyroid cancer syndrome. Nat Genet 1997;16:64-7.

[19] Leboulleux S, Baudin E, Travagli JP, Schlumberger M. Medullary thyroid carcinoma. Clin Endocrinol (Oxf) 2004;61:299-310.

[20] Negri E, Ron E, Franceschi S, La Vecchia C, Preston-Martin S, Kolonel L, et al. Risk factors for medullary thyroid carcinoma: a pooled analysis. Cancer Causes Control 2002;13:365-72.

[21] Wiseman SM, Loree TR, Rigual NR, Hicks WL, Jr., Douglas WG, Anderson GR, et al. Anaplastic transformation of thyroid cancer: review of clinical, pathologic, and molecular evidence provides new insights into disease biology and future therapy. Head Neck 2003;25:662-70.

[22] Zidan J, Kassem S, Karen D, Kuten A, Robinson E. Differentiated thyroid cancer in Arabs in northern Israel [Hebrew]. Harefuah 1997;132:6-9, 72.

[23] Mack TM, Berkel J, Bernstein L, Mack W. Religion and cancer in Los Angeles County. Natl Cancer Inst Monogr 1985;69:235-45.

[24] Bross ID, Shimaoka K, Tidings J. Some epidemiological clues in thyroid cancer. Tonsillectomy, acne, allergy, ethnicity. Arch Intern Med 1971;128:755-60.

[25] Shore RE, Hildreth N, Dvoretsky P, Andresen E, Moseson M, Pasternack B. Thyroid cancer among persons given X-ray treatment in infancy for an enlarged thymus gland. Am J Epidemiol 1993;137:1068-80.

[26] Ron E, Kleinerman RA, Boice JD, Jr., LiVolsi VA, Flannery JT, Fraumeni JF, Jr. A population-based case-control study of thyroid cancer. J Natl Cancer Inst 1987;79:1-12.

[27] Struewing JP, Hartge P, Wacholder S, Baker SM, Berlin M, McAdams M, et al. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. N Engl J Med 1997;336:1401-8.

[28] McCredie M, Coates M, Grulich A. Cancer incidence in migrants to New South Wales (Australia) from the Middle East, 1972-91. Cancer Causes Control 1994;5:414-21.

[29] Abdulmughni YA, Al Hureibi MA, Al Hureibi KA, Ghafoor MA, Al Wadan AH, Al Hureibi YA. Thyroid cancer in Yemen. Saudi Med J 2004;25:55-9.

[30] Ron E, Modan B, Preston D, Alfandary E, Stovall M, Boice JD, Jr. Thyroid neoplasia following low-dose radiation in childhood. Radiat Res 1989;120:516-31.

[31] Sadetzki S, Modan B, Chetrit A, Freedman L. An iatrogenic epidemic of benign meningioma. Am J Epidemiol 2000;151:266-72.

[32] El Ghamrawi KA, Khalifa MS. Thyroid cancer in Kuwait: review of 117 cases. Br J Surg 1979;66:139-42.

[33] Hedinger C, Williams ED, Sobin LH, World Health Organization. Histological typing of thyroid tumors. Berlin: Springer-Verlag; 1988.

[34] Kahan E, Ibrahim AS, El Najjar K, Ron E, Al Agha H, Polliack A, et al. Cancer patterns in the Middle East – special report from the Middle East Cancer Society. Acta Oncol 1997;36:631-6.

[35] Richards MA, Coleman RE, Hamsa R, Khaled H, el Mawla MG, Kadry I, et al. Advanced breast cancer in Egyptian women: clinical features and response to endocrine therapy. The Anglo-Egyptian Health Agreement Collaborative Study. Eur J Surg Oncol 1992;18:219-23.

[36] el-A Helal T, Khalifa A, Kamel AS. Immunohistochemical expression of p53 and c-erbB2 proteins in breast cancer in Egypt. Anticancer Res 2000;20:2145-50.

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BACKGROUND

In recent years, a new classification of lymphoid and hematopoietic malignancies has been adopted, based upon the Revised European-American Lymphoma classification system *[1]* and the World Health Organization (WHO) classification *[2]*. The new classification includes lymphomas, leukemias, and multiple myeloma as one group of malignant diseases.

Lymphomas encompass a diverse group of neoplasms with the common characteristic of originating from the cells of the lymphopoietic system. Traditionally, 2 main groups of lymphoma have been distinguished: Hodgkin Lymphoma (HL), characterized by large polynuclear (Reed-Sternberg) cells; and a diverse group of other lymphomas, defined as non-Hodgkin lymphomas (NHL). The new classification further divides NHL into T-cell NHL and B-cell NHL. Lymphocytic leukemias fall within the B-cell NHL group. However, in this chapter we will use the traditional classification, and lymphocytic leukemia will be counted as leukemia.

The classification of leukemias is complex and has seen several changes over the years *[3]*. The traditional classification, which we will use here, includes acute myeloid leukemia, chronic myeloid leukemia, acute lymphocytic leukemia, and chronic lymphocytic leukemia (CLL). Other types include acute monocytic leukemia, other myeloid/monocytic leukemias, other lymphocytic and acute leukemias, and aleukemic leukemia.

Using the traditional classification, NHLs are estimated at 287,000 new cases in the world annually, HLs at 62,000, and leukemias at 257,000. Together, these account for approximately 7% of all incident cancers worldwide *[4]*.

In general, the etiology of lymphomas and leukemias is not well understood. Many studies show groups of risk factors associated with both malignancies.

Etiology of Lymphoma

The risk factors for lymphoma can be classified into 3 groups: immunological function, infections, and lifestyle and occupational exposures.

Immunological function. Strong evidence suggests that altered immunological function, either immunostimulation or immunosuppression, entails an increased risk of lymphoma. For example, renal transplant patients have a 30 times greater risk for developing lymphoma than the general population. Lymphomas that develop in immunosuppressed patients share common characteristics: They are generally high-grade B-cell lymphomas, and they are more likely to be extranodal and of worse prognosis *[5]*. Lymphomas have been reported for a variety of conditions that are either autoimmune in nature or that require immunosuppressive treatment. These include rheumatoid arthritis and Sjogrens syndrome *[6,7]*. An association with celiac disease and NHL of the intestinal tract has also been noted *[8]*.

Infections. The biological agents associated with NHL are human immunodeficiency virus (HIV), human T-cell lymphotropic virus 1 (HTLV-1), and Epstein Barr virus (EBV) *[9-11]*. Hepatitis C virus (HCV) *[12,13]* and human herpes virus 8 (HHV8) have also been linked to the development of NHL *[10,14,15]*. EBV has been shown to be particularly prominent in lymphomas developing in immunosuppressed patients *[16]*. EBV has also been implicated as a causal factor in the etiology of HL *[17]*. In addition, infection with *Helicobacter pylori* is a risk factor for gastric lymphoma *[18]*.

NHL is 80 times more frequent among HIV-infected persons worldwide than in the general population *[19]*. The type of HIV virus that is generally involved with the development of NHL is HIV-1 *[5]*. About 4% of persons with symptoms from their HIV infection develop an NHL each year *[19]*, but this nevertheless represents a relatively modest contribution to the overall incidence of NHL in countries with a low prevalence of AIDS, such as those in the Middle East Cancer Consortium (MECC). The AIDS-related lymphomas tend to be high-grade B-cell lymphomas, and more than 40% occur in uncommon sites such as the brain and heart *[20]*.

Recently it has been shown that EBV can infect normal T lymphocytes *[21]*. The clinical manifestation of primary delayed EBV infection is infectious mononucleosis. EBV is associated with Burkitt's lymphoma in endemic areas, nasopharyngeal carcinoma, and HL, and with NHL among immunosuppressed persons.

Lifestyle and occupational exposures. The third group of putative risk factors includes farming, exposure to pesticides and organic solvents, tobacco use, alcohol consumption, and sun exposure. However, despite extensive research, no conclusions can be drawn regarding the role of these factors in lymphomagenesis.

Etiology of Leukemia

The etiology of leukemia remains rather unclear. Ionizing radiation is a known cause of leukemia in humans. Other suspected risk factors include pesticides; medical conditions such as infectious mononucleosis, autoimmune diseases, and immunodeficiency; and tonsillectomy.

Except for HTLV-1 and a rare type of leukemia, no viruses or infections have been implicated in the etiology of leukemia. Adult leukemia has been associated with working in the chemical industry, and with exposure to benzene, synthetic fiber dust, radioactive materials, and toluene *[22]*.

RESULTS

Overall Incidence

Age-standardized incidence rates (ASRs) of NHL in the United States have been reported to be among the highest in the world *[23]*. Rates have been reported to be low in East Asia, intermediate in Africa and the Middle East, and high in Western Europe, Australia, and Canada. International variations reflect differences in exposure to risk factors or variable reporting *[23]*.

As shown in Table 14.1, in MECC registries, multiyear averages showed very high ASRs for lymphoma among Israeli Jews (18.6) and Egyptians (16.3). These rates exceeded the US SEER incidence rate (15.3) – considered one of the highest in the world – as well as the rates of the other MECC populations. Rates of nodal NHL were also higher among Israeli Jews (11.6) and Egyptians (10.0) than in the other MECC populations and the US SEER rate (8.3), also considered one of the highest worldwide. Extranodal NHL rates among Israeli Jews and Egyptians were lower than US SEER, but higher than in other MECC populations.

Among MECC registries, the ASR of HL was highest among Israeli Jews (3.4), followed by Cypriots (3.0). Egyptians had the lowest rate (2.1). The HL ASRs in US SEER, Jordan, and Israeli Arab registries were intermediate (Table 14.1).

For leukemia, the ASR was again the highest among Israeli Jews (8.6), a rate slightly lower than the US SEER rate (8.8). Rates in other MECC countries were approximately 75% of the rate reported among Israeli Jews (Table 14.1). Among the different types of leukemia, the most frequent was CLL, which showed the

Table 14.1. Lymphoma and Leukemia: Age-Standardized Incidence Rates 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
Lymphoma	10.6	18.6	12.9	16.3	8.9	15.3
Non-Hodgkin lymphoma	7.6	15.2	10.2	14.2	6.4	12.9
Nodal	5.2	11.6	7.8	10.0	4.7	8.3
Extranodal	2.4	3.6	2.5	4.1	1.7	4.6
Hodgkin lymphoma	3.0	3.4	2.7	2.1	2.5	2.4
Leukemia	6.9	8.6	6.4	6.0	6.3	8.8
Chronic lymphocytic leukemia	1.8	3.0	1.3	1.3	1.1	2.2

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

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

Table 14.2a. Lymphoma: Number of Cases and Age Distribution, by Sex, of Lymphoma, Hodgkin Lymphoma, and Non-Hodgkin Lymphoma, 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 -- All lymphoma	357	194	163	6,638	3,371	3,267	615	346	269	1,316	820	496	1,733	1,042	691	23,698	12,913	10,785
Total cases -- Hodgkin lymphoma	83	37	46	1,030	521	509	166	99	67	218	151	67	639	383	256	3,099	1,706	1,393
Total cases -- Non-Hodgkin lymphoma	274	274	117	5,608	2,850	2,758	449	247	202	1,098	669	429	1,094	659	435	20,599	11,207	9,392
Age Groups (Distribution) for Lymphoma																		
<50 y	37.8%	37.6%	38.0%	29.9%	32.2%	27.5%	57.1%	60.7%	52.4%	55.2%	58.2%	50.4%	61.1%	63.1%	58.0%	28.0%	30.8%	24.6%
50-69 y	37.0%	38.7%	35.0%	34.2%	34.3%	34.2%	28.6%	26.0%	32.0%	37.2%	34.1%	42.1%	29.3%	28.9%	29.8%	32.7%	34.4%	30.8%
70+ y	25.2%	23.7%	27.0%	35.9%	33.5%	38.4%	14.3%	13.3%	15.6%	7.6%	7.7%	7.5%	9.6%	8.0%	12.2%	39.3%	34.8%	44.6%
Age Groups (Distribution) for Hodgkin Lymphoma																		
<50 y	84.3%	86.5%	82.6%	74.4%	74.1%	74.7%	83.7%	87.9%	77.6%	84.4%	82.8%	88.1%	83.9%	84.6%	82.8%	71.2%	70.9%	71.6%
50-69 y	*15.7%*	*13.5%*	*17.4%*	15.5%	17.3%	13.8%	12.7%	*11.1%*	*14.9%*	14.2%	15.2%	*11.9%*	12.5%	12.8%	12.1%	17.0%	18.5%	15.1%
70+ y	*0.0%*	*0.0%*	*0.0%*	10.1%	8.6%	11.6%	*3.6%*	-	*7.5%*	*1.4%*	*2.0%*	*0.0%*	3.6%	*2.6%*	*5.1%*	11.8%	10.6%	13.3%
Age Groups (Distribution) for Non-Hodgkin Lymphoma																		
<50 y	23.7%	26.1%	20.5%	21.7%	24.6%	18.7%	47.2%	49.8%	44.1%	49.5%	52.6%	44.5%	47.8%	50.7%	43.4%	21.5%	24.7%	17.6%
50-69 y	43.4%	44.6%	41.9%	37.7%	37.4%	37.9%	34.5%	32.0%	37.6%	41.7%	38.4%	46.9%	39.0%	38.2%	40.2%	35.1%	36.8%	33.1%
70+ y	32.8%	29.3%	37.6%	40.6%	38.0%	43.3%	18.3%	18.2%	18.3%	8.8%	9.0%	8.6%	13.2%	11.1%	16.3%	43.4%	38.5%	49.3%

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.

highest rates in Israeli Jews (3.0), compared with a range from 1.1 (Jordanians) to 2.2 (US SEER) (Table 14.1).

It is interesting to note the high rates of NHL in Egyptians and Israeli Jews. Rates of NHL have increased dramatically in Western Europe and North America over the past 20 years, due in part to AIDS. However, NHL as a complication of AIDS does not occur in a sufficient proportion of AIDS cases to explain the full extent of the increase in NHL in Western countries. Furthermore, AIDS rates in Egyptians and Israeli Jews are not especially high (although they are thought to be rising, especially in Israel). Other possible explanations for the higher NHL rate in Egypt may be the high prevalence of HCV infections *[9]*, HHV8 infections, other types of infections, or adverse environmental exposures and pollution in that country. It should be noted that lymphoid and hematopoietic cancers were recognized as being relatively common in Egypt *[24]*, even before the high prevalence of HCV. Several studies have reported the possible role of infectious agents in the etiology of NHL. Cowgill et al. (2004) *[25]* reported in an Egyptian case-control study a statistically significant association of HCV RNA with NHL (OR = 2.9; 95% CI, 1.9-4.5), after adjustment for age, sex, rural versus urban birthplace, and rural versus urban residence. Iscovich and Parkin (1997) *[26]* reported large differences in NHL incidence rates among subpopulations in Israel, with relatively high rates in migrants from Asia and Africa. Those high rates persisted into the second generation, suggesting that inherited susceptibility may underlie some of the variation.

Age and Sex

Tables 14.2a, 14.2b, and 14.3 show the age and sex distribution and specific rates for each registry for lymphoma and leukemia over broad age groups.

As seen in these tables and Table 14.1, Egyptians and Israeli Jews showed the highest rates of lymphoma and NHL. Also, Israeli Jews showed the highest ASR for HL. Table 14.4 shows that the 5-year age patterns of NHL and HL rates differed between these 2 registries. Egyptians had higher rates for NHL and HL in age groups 0-14 years than did Israeli Jews.

Contrary to the observations of higher lymphoma rates in Egyptian children than in Israeli Jewish children**,** the age-specific rate among Egyptians over age 75 (41.9) was less than half the rate in their Israeli Jewish counterparts (104.4) (Table 14.4). The low reported rates of lymphoma in older patients in Egypt could be due to cultural factors such as reluctance of older persons to seek medical care. It also could be due to lack of diagnostic facilities for older populations in peripheral regions in Egypt.

The higher rates of lymphoma and NHL reported in Egyptians and Israeli Jews did not differ by sex. As shown in Table 14.5, lymphoma ASRs were higher for Egyptian and Israeli Jewish males, 20.0 and 20.6, respectively, than for males in other registries. Also, lymphoma ASRs for females were higher in Egyptians (12.6) and Israeli Jews (16.9) than in other populations. NHL sex-specific rates were higher for Egyptian (11.3) and Israeli Jewish (13.6) females than for females in other registries. These data represent male-to-female ratios of 1.6:1 for NHL in Egyptians and 1.2:1 for NHL in Israeli Jews.

HL, which showed the highest rate in Israeli Jews (3.4), did not show a significant sex difference (3.5 in males; 3.3 in females) (Table 14.5).

The sex-specific rates of leukemia followed the same pattern as the overall rates (Table 14.1), with higher rates in US SEER and Israeli Jews than in the other registry populations (Table 14.5).

Subsites

As shown in Table 14.6, extranodal NHL represented about one-fourth to one-third of all NHL in the MECC registries, with the lowest proportion in Israeli Jews (23.2%) and the highest in Cypriots

(32.5%). Proportions of extranodal NHL were highest in US SEER (35.9%) (Table 14.6). Further analysis of the anatomical sites of extranodal NHL in our data showed there were no differences in the distribution of stomach extranodal NHL. Nevertheless, skin extranodal sites were higher in Israeli Jews (10.4%) and Israeli Arabs (10.5%) than in other MECC registries, where rates ranged between 1.6% and 2.2% of all extranodal lesions. The US SEER rate for skin NHL was 6.6%. The registry results did not support the previous impression of high prevalence of extranodal lymphoma in the small intestine previously reported in the Middle East in hospital-based studies *[27,28]*.

HL did not vary greatly between MECC registries in relation to nodal and extranodal distribution (Table 14.6). Contrary to the large proportion of extranodal NHL (about one-third of all NHL tumors), extranodal HL represented no more than 5.3% of all HL. Hodgkin extranodal tumors represented 2.3% of Hodgkin tumors in the United States. Further analysis showed there was no major sex difference.

Table 14.2b. Lymphoma: Age-Standardized Incidence Rates,* by Age and Sex, for Lymphoma, Hodgkin Lymphoma, and Non-Hodgkin Lymphoma, 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
Age Groups (Rates)* for Lymphoma																		
Total rate -- All lymphoma	10.6	12.1	9.3	18.6	20.6	16.9	12.9	14.4	11.4	16.3	20.0	12.6	8.9	10.3	7.4	15.3	18.3	12.6
<50 y	6.0	6.6	5.5	8.5	9.3	7.6	6.3	7.4	5.1	8.6	11.0	6.2	4.8	5.9	3.6	6.3	7.5	5.2
50-69 y	25.6	30.5	21.2	48.8	53.5	44.6	32.8	34.1	31.3	46.8	54.1	39.4	23.0	25.9	19.8	40.0	48.0	32.8
70+ y	42.4	49.4	36.9	100.4	113.7	90.8	65.4	76.3	56.7	48.5	64.9	34.1	35.3	37.0	33.8	95.3	117.1	80.5
Age Groups (Rates)* for Hodgkin Lymphoma																		
Total rate -- Hodgkin lymphoma	3.0	2.7	3.3	3.4	3.5	3.3	2.7	3.0	2.3	2.1	2.9	1.4	2.5	3.0	2.0	2.4	2.7	2.2
<50 y	3.2	3.0	3.5	3.3	3.4	3.3	2.3	2.9	1.7	2.0	2.7	1.4	2.2	2.7	1.7	2.3	2.4	2.1
50-69 y	*2.5*	*1.9*	*3.0*	3.5	4.1	2.9	3.8	*3.9*	*3.7*	2.9	4.3	*1.6*	3.5	4.1	2.9	2.7	3.3	2.0
70+ y	*0.0*	*0.0*	*0.0*	4.8	*4.9*	*4.7*	*4.8*	-	*7.0*	*1.4*	*3.1*	*0.0*	4.8	*4.5*	*5.0*	4.0	*5.0*	*3.3*
Age Groups (Rates)* for Non-Hodgkin Lymphoma																		
Total rate -- Non-Hodgkin lymphoma	7.6	9.4	6.0	15.2	17.1	13.6	10.2	11.4	9.1	14.2	17.1	11.3	6.4	7.3	5.4	12.9	15.7	10.5
<50 y	2.8	3.6	2.0	5.1	6.0	4.3	3.9	4.5	3.4	6.6	8.3	4.8	2.6	3.2	1.9	4.1	5.0	3.1
50-69 y	23.1	28.5	18.2	45.3	49.4	41.8	29.0	30.3	27.6	43.8	49.9	37.9	19.4	21.7	16.9	37.4	44.7	30.7
70+ y	42.4	49.4	36.9	95.6	108.8	86.1	60.7	74.3	49.7	47.1	61.8	34.1	30.5	32.5	28.8	91.3	112.1	77.2

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

†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.

CLL, which in the new classification is counted as a type of lymphoma, showed high rates (3.0) in Israeli Jews, with higher rates in males (3.8, compared with 2.3 in females), and a male-to-female ratio of 1.7:1. Rates of CLL ranged in other MECC registries and US SEER from 1.1 to 2.2, with male-to-female ratios ranging between 1.25:1 and 2.2:1 (Table 14.5).

Basis of Diagnosis

Histopathological diagnostic rates were over 90% for most types of lymphomas and leukemias (see Table 1.2). However, it should be noted that available diagnostic facilities might not be available at peripheral remote medical centers, and patients may die before reaching cancer centers for correct diagnosis and management. This may be the case for myeloma in Egypt, where a pathologic diagnosis was observed for 100% of cases. The low incidence of myeloma and NHL in the older population in Egypt, and possibly other MECC registries, might be due to misdiagnosis or short life expectancy. It is difficult to know how much the age structure of the population and local factors in each country might influence access to medical care and interfere with the diagnostic facilities for diagnosis and management of hematopoietic malignancies.

Table 14.3. Leukemia: 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	223	134	89	3,220	1,790	1,430	325	192	133	515	283	232	1,354	782	572	13,178	7,528	5,650
Age Groups (Distribution)																		
<40 y	27.4%	25.4%	30.3%	17.1%	18.1%	15.9%	51.4%	51.6%	51.1%	50.9%	51.6%	50.0%	59.5%	60.0%	58.9%	18.9%	18.7%	19.3%
40-59 y	25.1%	26.9%	22.5%	18.1%	19.7%	16.2%	23.4%	24.5%	21.8%	29.3%	25.1%	34.5%	20.6%	18.7%	23.3%	19.7%	20.5%	18.6%
60-69 y	19.7%	23.1%	*14.6%*	19.8%	19.9%	19.6%	9.5%	9.4%	*9.8%*	14.0%	16.3%	11.2%	12.3%	13.2%	11.2%	16.0%	17.6%	13.9%
70+ y	27.8%	24.6%	32.6%	45.0%	42.3%	48.3%	15.7%	14.6%	17.3%	5.8%	7.1%	*4.3%*	7.5%	8.2%	6.6%	45.3%	43.2%	48.1%
Age Groups (Rates)‡																		
Total rate	6.9	8.5	5.5	8.6	10.5	6.9	6.4	7.8	5.1	6.0	6.7	5.3	6.3	7.1	5.5	8.8	11.0	6.9
<40 y	3.9	4.2	3.7	3.1	3.5	2.6	2.9	3.4	2.4	3.3	3.6	3.0	3.4	3.7	3.0	3.8	4.2	3.5
40-59 y	8.0	10.4	5.7	9.5	11.9	7.3	8.6	10.6	6.5	9.2	8.6	9.8	8.3	8.4	8.2	8.7	10.6	6.9
60-69 y	20.3	30.2	*11.6*	30.7	38.1	24.6	15.2	19.2	*11.9*	17.2	22.4	12.2	20.1	23.2	16.5	27.7	37.1	19.4
70+ y	28.4	32.7	25.2	59.3	74.3	48.6	38.4	47.9	31.1	14.4	20.9	*8.7*	21.4	28.3	15.1	59.5	83.6	43.4

**[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.

SUMMARY AND CONCLUSIONS

Analysis of the MECC registries yields the following interesting observations: (1) Lymphoma and NHL incidence rates in Egyptians and Israeli Jews were high; (2) NHL incidence rates in older Egyptians were relatively low, which could be due to lack of access to medical care in peripheral regions or short life expectancy; and (3) the high rate of CLL in Israeli Jews could be a component of the high lymphoma rate in that population.

Geographic variations in incidence and age distribution of NHL might be a reflection of local environmental factors implicated in the etiology of the disease. Based on the different ethnicities, lifestyles, socioeconomic levels, and adverse environmental exposures among the countries of the Middle East, comparison of populations can provide the background for more sophisticated approaches for disentangling the risk factors for lymphoid and hematopoietic malignancies. Further exploration of potential etiologic risk factors should be the focus of future epidemiologic research.

Table 14.4. Lymphoma: Age-Specific Incidence Rates* of Non-Hodgkin Lymphoma and Hodgkin Lymphoma, by Age and Sex, in Israel (Jews) and Egypt – 1996-2001†

	Non-Hodgkin Lymphoma						Hodgkin Lymphoma					
	Israel (Jews) 1996-2001			Egypt 1999-2001			Israel (Jews) 1996-2001			Egypt 1999-2001		
Age Group	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female
0-4 y	1.0	*1.1*	*0.8*	2.6	3.6	*1.5*	*0.2*	*0.4*	-	*0.6*	*0.7*	-
5-9 y	1.6	2.3	*0.8*	2.3	3.2	*1.3*	0.8	1.4	*0.2*	2.3	4.0	*0.5*
10-14 y	1.0	1.4	*0.6*	1.9	3.1	*0.6*	1.6	1.6	1.5	1.7	2.4	*1.0*
15-19 y	2.1	2.2	2.0	1.6	*2.0*	*1.1*	6.0	5.5	6.5	1.9	2.7	*1.1*
20-24 y	3.4	3.2	3.7	4.1	3.8	4.5	6.1	5.7	6.6	2.7	*2.5*	*2.9*
25-29 y	4.1	4.7	3.6	4.6	7.2	*2.3*	6.9	5.8	8.0	*1.8*	*2.8*	*1.0*
30-34 y	7.5	8.4	6.6	7.8	10.7	4.9	4.5	4.2	4.8	*1.2*	*1.6*	*0.8*
35-39 y	8.7	11.0	6.6	10.8	13.7	8.0	3.9	4.1	3.6	*1.5*	*2.0*	*1.1*
40-44 y	13.9	16.2	11.7	16.4	22.0	10.6	3.3	4.3	2.3	3.2	5.3	*1.0*
45-49 y	18.8	22.2	15.7	26.9	29.4	24.0	2.4	3.0	1.8	4.6	*3.8*	*5.5*
50-54 y	30.0	30.9	29.2	37.7	36.7	38.6	3.5	4.1	3.0	*3.3*	*6.1*	-
55-59 y	39.8	46.6	33.6	39.7	48.4	30.5	2.7	3.4	*2.2*	*3.0*	*4.3*	-
60-64 y	51.9	54.7	49.5	50.6	59.6	42.5	4.1	4.3	4.0	*2.0*	-	*2.3*
65-69 y	69.4	77.0	63.4	50.6	60.8	40.4	3.4	5.1	*2.0*	*3.5*	*4.6*	-
70-74 y	86.9	98.2	78.4	52.3	70.8	35.7	6.3	6.2	6.4	-	-	*0.0*
75+ y	104.4	119.5	93.8	41.9	52.8	*32.5*	3.3	3.6	3.1	-	-	*0.0*

*Rates are per 100,000..

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

Table 14.5. Lymphoma and Leukemia: Age-Standardized Incidence Rates, 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
Lymphoma						
Total rate	10.6	18.6	12.9	16.3	8.9	15.3
Male	12.1	20.6	14.4	20.0	10.3	18.3
Female	9.3	16.9	11.4	12.6	7.4	12.6
Non-Hodgkin Lymphoma						
Total rate	7.6	15.2	10.2	14.2	6.4	12.9
Male	9.4	17.1	11.4	17.1	7.3	15.7
Female	6.0	13.6	9.1	11.3	5.4	10.5
Hodgkin Lymphoma						
Total rate	3.0	3.4	2.7	2.1	2.5	2.4
Male	2.7	3.5	3.0	2.9	3.0	2.7
Female	3.3	3.3	2.3	1.4	2.0	2.2
Leukemia						
Total rate	6.9	8.6	6.4	6.0	6.3	8.8
Male	8.5	10.5	7.8	6.7	7.1	11.0
Female	5.5	6.9	5.1	5.3	5.5	6.9
Chronic Lymphocytic Leukemia						
Total rate	1.8	3.0	1.3	1.3	1.1	2.2
Male	2.4	3.8	1.5	1.7	1.3	3.1
Female	1.2	2.3	1.2	0.9	0.8	1.4

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

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

Table 14.6. Lymphoma: Distribution of Non-Hodgkin Lymphoma and Hodgkin Lymphoma, by Nodal and Extranodal Status, 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
Non-Hodgkin lymphoma – Nodal	67.5%	76.8%	75.3%	70.5%	74.1%	64.1%
Non-Hodgkin lymphoma – Extranodal	32.5%	23.2%	24.7%	29.5%	25.9%	35.9%
Hodgkin lymphoma – Nodal	95.2%	98.4%	97.6%	96.3%	94.7%	97.7%
Hodgkin lymphoma – Extranodal	*4.8%*	1.6%	*2.4%*	*3.7%*	5.3%	2.3%

**[Numeral]* (italic) = 0 or 3-15 cases.

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

REFERENCES

[1] Harris NL, Jaffe ES, Stein H, Banks PM, Chan JK, Cleary ML, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood 1994;84:1361-92.

[2] Jaffe ES, Harris NL, Stein H, Vardiman JW, editors. World Health Organization classification of tumors. Pathology and genetics of tumors of hematopoietic and lymphoid tissues. Lyon (France): International Agency for Research on Cancer; 2001.

[3] Bain BJ. Routine and specialised techniques in the diagnosis of haematological neoplasms. J Clin Pathol 1995;48:501-8.

[4] Stewart BW, Kleihues P, editors. World cancer report. Lyon (France): International Agency for Research on Cancer; 2003.

[5] International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans, vol. 67. Human immunodeficiency viruses and human T-cell lymphotropic viruses. Lyon (France): International Agency for Research on Cancer; 1996.

[6] Baecklund E, Sundstrom C, Ekbom A, Catrina AI, Biberfeld P, Feltelius N, et al. Lymphoma subtypes in patients with rheumatoid arthritis: increased proportion of diffuse large B cell lymphoma. Arthritis Rheum 2003;48:1543-50.

[7] Palacios E, Larusso G, Rojas R, Ramirez G. Lymphoma of the parotid gland in Sjogren's syndrome. Ear Nose Throat J 2004;83:156.

[8] Smedby KE, Akerman M, Hildebrand H, Glimelius B, Ekbom A, Askling J. Malignant lymphomas in coeliac disease: evidence of increased risks for lymphoma types other than enteropathy-type T cell lymphoma. Gut 2005;54:54-9.

[9] Mueller NE, Mohar A, Evans A. Viruses other than HIV and non-Hodgkin's lymphoma. Cancer Res 1992;52:5479s-81s.

[10] Nagore E, Ledesma E, Collado C, Oliver V, Perez-Perez A, Aliaga A. Detection of Epstein-Barr virus and human herpesvirus 7 and 8 genomes in primary cutaneous T- and B-cell lymphomas. Br J Dermatol 2000;143:320-3.

[11] Killebrew D, Shiramizu B. Pathogenesis of HIV-associated non-Hodgkin lymphoma. Curr HIV Res 2004;2:215-21.

[12] Turner NC, Dusheiko G, Jones A. Hepatitis C and B-cell lymphoma. Ann Oncol 2003;14:1341-5.
[13] Matsuo K, Kusano A, Sugumar A, Nakamura S, Tajima K, Mueller NE. Effect of hepatitis C virus infection on the risk of non-Hodgkin's lymphoma: a meta-analysis of epidemiological studies. Cancer Sci 2004;95:745-52.
[14] Luppi M, Barozzi P, Maiorana A, Artusi T, Trovato R, Marasca R, et al. Human herpesvirus-8 DNA sequences in human immunodeficiency virus-negative angioimmunoblastic lymphadenopathy and benign lymphadenopathy with giant germinal center hyperplasia and increased vascularity. Blood 1996;87:3903-9.
[15] Blattner WA. Human retroviruses: their role in cancer. Proc Assoc Am Physicians 1999;111:563-72.
[16] Knowles DM. Immunodeficiency-associated lymphoproliferative disorders. Mod Pathol 1999;12:200-17.
[17] Bechtel D, Kurth J, Unkel C, Kuppers R. Transformation of BCR-deficient germinal-center B cells by EBV supports a major role of the virus in the pathogenesis of Hodgkin and posttransplantation lymphomas. Blood 2005;106:4345-50.
[18] Crowe SE. Helicobacter infection, chronic inflammation, and the development of malignancy. Curr Opin Gastroenterol 2005;21:32-8.
[19] AIDS.ORG. Lymphoma. 8-12-2004. Available at: http://www.aids.org/factSheets/512-Lymphoma.html. [Last Accessed: 1/06].
[20] Levine AM. AIDS-related malignancies: the emerging epidemic. J Natl Cancer Inst 1993;85:1382-97.
[21] Pallesen G, Hamilton-Dutoit SJ, Zhou X. The association of Epstein-Barr virus (EBV) with T cell lymphoproliferations and Hodgkin's disease: two new developments in the EBV field. Adv Cancer Res 1993;62:179-239.
[22] Adegoke OJ, Blair A, Shu XO, Sanderson M, Jin F, Dosemeci M, et al. Occupational history and exposure and the risk of adult leukemia in Shanghai. Ann Epidemiol 2003;13:485-94.
[23] Parkin DM, Ferlay M, Hamdi-Cherif M, Sitas F, Thomas J, Wabinga H, et al. Cancer in Africa: epidemiology and prevention. IARC scientific publication no. 153. Lyon (France): International Agency for Research on Cancer; 2003.
[24] Mokhtar A, editor. Cancer Pathology Registry (1985-1989). Cairo (Egypt): Cairo National Cancer Institute; 2001.
[25] Cowgill KD, Loffredo CA, Eissa SA, Mokhtar N, Abdel-Hamid M, Fahmy A, et al. Case-control study of non-Hodgkin's lymphoma and hepatitis C virus infection in Egypt. Int J Epidemiol 2004;33:1034-9.
[26] Iscovich J, Parkin DM. Risk of cancer in migrants and their descendants in Israel: I. Leukaemias and lymphomas. Int J Cancer 1997;70:649-53.
[27] Isaacson PG. Middle Eastern intestinal lymphoma. Semin Diagn Pathol 1985;2:210-23.
[28] Salem P, el Hashimi L, Anaissie E, Geha S, Habboubi N, Ibrahim N, et al. Primary small intestinal lymphoma in adults. A comparative study of IPSID versus non-IPSID in the Middle East. Cancer 1987;59:1670-6.

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BACKGROUND

There are marked differences between childhood and adult cancer. First, cancer is generally a rare disease among children. Annual incidence of all cancer in children under 5 years of age in developed countries is only 0.5%, according to a new report *[1]*. In European countries, 1% of all malignant neoplasms occur in patients younger than 20 years of age *[2-4]*. Second, childhood cancers are histologically variable, and embryonic tumors are the most common, while the majority of adult cancers are carcinomas *[1,5,6]*. Twelve types of malignant childhood tumors have been classified according to the International Classification of Childhood Cancer (ICCC) *[1,7-10]*; however, pediatric cancers can also be divided into 3 subgroups *[6]*:

1. Embryonal tumors, which show early age peaks. Retinoblastoma, neuroblastoma, and hepatoblastoma have the highest incidence rate in the first year of life.

2. Juvenile neoplasms, which are unique to younger age groups.

3. Adult-type tumors, which are rarely seen in children.

Prenatal factors are considered to affect the incidence of tumors in children under the age of 5 years *[11]*. It is generally accepted that cancer results from genetic changes *[1,12]*. The carcinogenic process in children is much shorter than in adults. Infancy is the age when cancer incidence rates are the highest during childhood; therefore, it is reasonable to assume that many pediatric cancers result from aberrations in early developmental stages and in utero. An increased risk of childhood cancers has been described to be associated with certain genetic conditions or syndromes such as chromosomal abnormalities, DNA repair disorders, congenital anomalies, hereditary immune deficiency states, and other hereditary syndromes *[1,6]*.

Racial differences have been observed in childhood tumors, even within Western countries *[2,12]*. A peak incidence in acute lymphocytic leukemia (ALL) usually occurs between the ages of 2 and 3 years in White American children and 1 to 4 years in European children, but not among African Americans *[1,2]*. Ewing sarcoma is another well-established example of racial differences, with the lowest incidence rate in Black children (African or American) *[1,6]*. Furthermore, there are marked variations between populations in the incidence of specific types of childhood cancers. Nearly one-third of all childhood neoplasms are leukemias, with an age-standardized incidence rate (ASR) of 35-50 per million *[1,7]*. International variation occurs in the rate of ALL, and the higher incidence of ALL in early childhood has usually been associated with higher levels of socioeconomic status. This suggests that environmental factors play a role *[1,9,13]*. Although a considerable number of environmental or exogenous factors have been suggested as risk factors for childhood cancers, only a few have been proven, and they are mostly infectious agents, including Epstein-Barr virus, hepatitis B virus, human immunodeficiency virus, and human herpesvirus 8. These infections are probably responsible for the international variation in the incidence of some childhood cancers, such as lymphoma, nasopharyngeal carcinoma, hepatic cancer, and Kaposi sarcoma *[1,6,13,14]*. In addition, some parasitic infections have been implicated, particularly malaria in tropical Africa, acting as a co-factor for Burkitt's lymphoma, and schistosomiasis in Egypt, causing bladder cancer *[1,11,15]*.

RESULTS

The total number of childhood cancers registered under 15 years of age varies greatly among the Middle East Cancer Consortium (MECC) registries, ranging from 102 in Cyprus to 1,339 in Jordan (Table 15.1). This is due both to different periods of registration in these countries and to variations in the size of their respective populations.

Table 15.2 shows the ASRs of all cancers and the main types of cancer, and Figure 15.1 shows the ASRs of all cancers, by sex, in children under 15 years of age in MECC countries. The most striking finding is that the highest incidence of childhood cancer occurred among female children in Cyprus (179.5). This rate was even higher than that found among females in the SEER data (146.3). Males had a higher incidence rate than females in all other MECC countries (ranging from 130.6 to 150.3). The lowest overall incidence was in Jordan (114.8).

In terms of the type of malignancy, leukemia was the most common neoplasm in males in all MECC countries, with the exception of Egypt, where lymphoma in males exceeded the incidence of leukemia (56.7 vs. 33.6) (Table 15.2; Figures 15.2 and 15.3). The second highest lymphoma rate was in Israeli Arabs, with an ASR of 32.6 in males (Table 15.2 and Figure 15.3). The incidence rate of ALL was 38.2, 21.4, 15.9, 24.3, 27.8, and 39.7 in Cypriots, Israeli Jews, Israeli Arabs, Egyptians, Jordanians, and US SEER, respectively, whereas it was 12.7, 5.5, 6.4, 3.1, 5.7, and 7.3 for acute myeloid leukemia in the same countries. Interestingly, the rate of central nervous system (CNS) tumors was found to be the highest in females (55.6) in Cyprus (Table 15.2 and Figure 15.4). Although lymphomas were more common than CNS tumors in male Israeli Jews, male and female Israeli Arabs, male Egyptians, and male Jordanians, the opposite was true for the rest of the registries. Sympathetic nervous system tumors were also higher in Cyprus than in the other MECC countries and the US SEER population, particularly in males (28.4). Jordan had the lowest incidence of sympathetic nervous system tumors**.** It is of interest that no retinoblastoma was diagnosed in Cyprus, even in the under-5-years age group. As far as renal tumors were concerned, incidence rates were again the highest in Cypriot children, particularly in females (14.6), compared with the other MECC countries (Table 15.2).

Table 15.1. Childhood Cancer: Number of Cases for All International Classification of Childhood Cancer Sites, 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		
Age Group	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female
<5 y	41	19	22	404	220	184	170	98	72	157	86	71	557	336	221	1,699	898	801
5-9 y	27	14	13	291	183	108	93	60	33	156	100	56	404	229	175	1,013	583	430
10-14 y	34	17	17	303	175	128	74	41	33	168	99	69	378	217	161	1,096	553	543
15-19 y	47	18	29	554	287	267	106	54	52	185	104	81	462	244	218	1,644	882	762
<15 y	102	50	52	998	578	420	337	199	138	481	285	196	1,339	782	557	3,808	2,034	1,774
<20 y	149	68	81	1,552	865	687	443	253	190	666	389	277	1,801	1,026	775	5,452	2,916	2,536

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

The total incidence of hepatic tumors ranged from 2.5 in Israeli Arabs to 1.1 in Jordanians (Table 15.2).

The incidence of malignant bone tumors was slightly higher in Cypriot males (10.2) and Israeli Jewish males (9.5) as well as in female Egyptians (9.3), compared with other MECC countries.

Interestingly, these tumors had the lowest ASR in Israeli Arabs, although it was found to be high (8.6) among Egyptian children (Table 15.2).

Soft tissue sarcomas showed a slightly higher ASR among Israeli Arabs, particularly in females (14.7) and in male Israeli Jews (12.8) (Table 15.2).

Table 15.2. Childhood Cancer: Age-Standardized Incidence Rates* for International Classification of Childhood Cancer (ICCC) Sites, by Sex, in Children under Age 15 Years 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		
ICCC Site	**Total**	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**	**Male**	**Female**
All cancers	170.0	161.0	179.5	133.3	150.0	115.8	119.9	137.8	100.9	130.9	150.3	110.7	114.8	130.6	98.1	153.3	159.9	146.3
Leukemia	53.0	52.8	*53.2*	31.8	34.7	28.7	29.4	33.8	24.8	31.9	33.6	30.2	39.2	46.5	31.4	50.4	54.0	46.6
Lymphomas and reticuloendothelial neoplasms	*15.7*	*20.1*	*11.2*	20.0	26.5	13.1	24.2	32.6	15.4	37.7	56.7	17.7	19.0	23.8	13.9	13.5	16.3	10.5
Central nervous system and miscellaneous intracranial and intraspinal neoplasms	40.1	*25.3*	*55.6*	24.2	25.9	22.4	16.5	22.7	*10.1*	16.9	15.7	18.1	18.9	21.5	16.2	32.5	34.6	30.3
Sympathetic nervous system tumors	*22.3*	*28.4*	*15.8*	15.8	16	15.5	12.0	12.4	11.7	9.5	11.8	*7.0*	6.1	7.0	5.2	11.2	10.3	12.1
Retinoblastoma	*0.0*	*0.0*	*0.0*	2.8	*2.3*	*3.3*	*2.1*	*2.0*	*2.2*	*2.4*	-	*3.5*	4.6	4.4	4.9	5.6	6.6	4.6
Renal tumors	*11.3*	-	*14.6*	6.9	8.4	5.3	5.7	*4.1*	*7.3*	5.4	*4.4*	*6.4*	5.1	4.4	5.8	9.2	8.0	10.3
Hepatic tumors	-	-	*0.0*	*1.3*	*2.2*	-	*2.5*	*2.1*	*2.9*	*1.9*	*1.9*	*2.0*	*1.1*	*1.2*	*0.9*	2.9	2.5	3.3
Malignant bone tumors	*7.9*	*10.2*	-	8.1	9.5	6.7	*3.3*	*4.3*	*2.3*	8.6	8.0	9.3	6.0	7.3	4.7	5.2	5.3	5.1
Soft tissue sarcomas	*9.8*	*12.1*	-	11.0	12.8	9.1	13.6	12.5	14.7	7.9	9.0	*6.7*	6.3	7.3	5.2	10.8	11.7	9.9
Germ cell, trophoblastic, and other gonadal neoplasms	-	*0.0*	-	3.1	*1.5*	4.7	*3.6*	*2.8*	*4.4*	*2.2*	*1.8*	*2.6*	3.4	*2.7*	4.3	5.3	5.4	5.2
Carcinomas and other malignant epithelial neoplasms	*3.9*	*0.0*	*8.1*	5.6	6.7	4.4	*4.3*	*5.7*	*2.9*	*2.4*	*2.5*	*2.2*	4.3	3.9	4.6	5.7	4.4	7.0
Other and unspecified malignant neoplasms	*0.0*	*0.0*	*0.0*	*1.9*	*2.1*	*1.6*	*2.2*	*2.1*	*2.2*	*3.9*	*3.3*	*4.5*	*0.7*	*0.7*	*0.8*	*0.5*	*0.3*	*0.6*
Not classified by ICCC	-	*0.0*	-	*1.0*	*1.3*	-	-	-	*0.0*	-	*0.0*	-	-	*0.0*	-	0.7	*0.5*	*0.8*

*Rates are per 1,000,000 and are age-standardized to the World Standard Million.

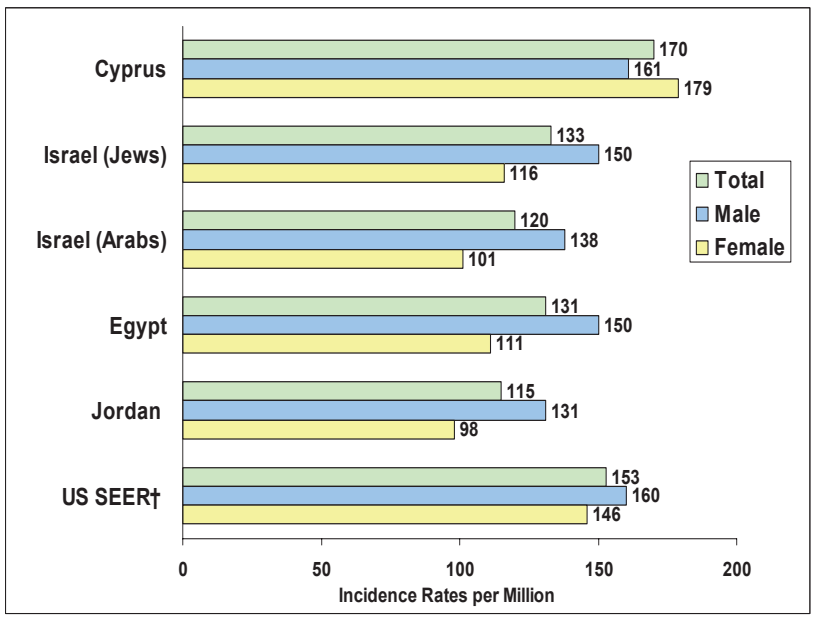
†The symbols "-" = 1-2 cases; and "*[numeral]*" (italic) = 0 or 3-15 cases.

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

The incidence of germ cell tumors was slightly lower in all MECC countries than in US SEER data, with the lowest total ASR of 2.2 noted in Egypt versus 5.3 in US SEER. In Cyprus, there were only 2 cases, so the ASR could not be properly estimated.

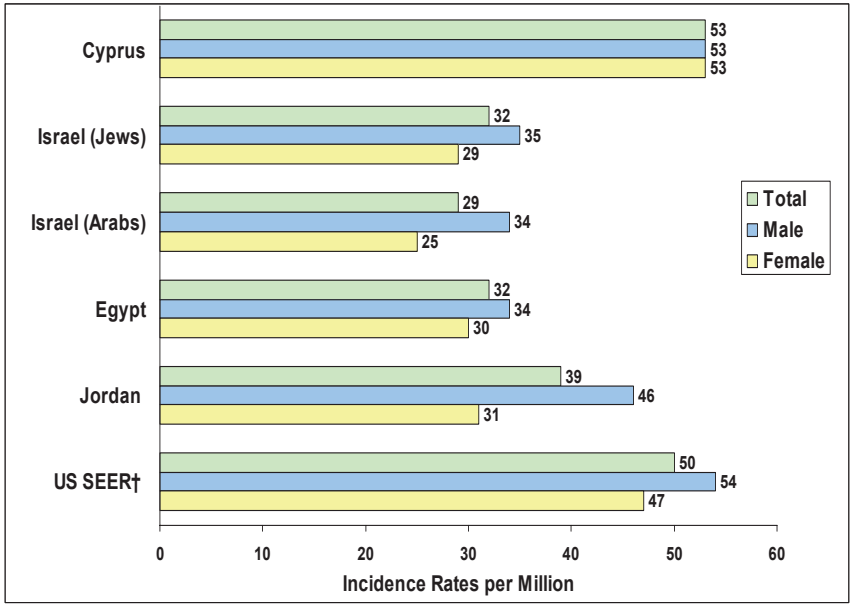
The incidence rate of carcinomas and other malignant epithelial neoplasms was low in all MECC countries. Interestingly, no cases were registered in male Cypriots, whereas female Cypriots (8.1) and male Israeli Jews (6.7) had slightly higher rates (Table 15.2).

Figure 15.1. Childhood Cancer: Age-Standardized Incidence Rates* of All Cancers for Children under Age 15 Years, by Sex, in Cyprus, Israel (Jews and Arabs), Egypt, Jordan, and US SEER – 1996-2001



*Rates are per 1,000,000 and are age-standardized to the World Standard Million.
†SEER 13 Registries, Public Use Data Set, from data submitted November 2004.

Figure 15.2. Childhood Cancer: Age-Standardized Incidence Rates* of Leukemia for Children under Age 15 Years, by Sex, in Cyprus, Israel (Jews and Arabs), Egypt, Jordan and US SEER – 1996-2001



*Rates are per 1,000,000 and are age-standardized to the World Standard Million.

Other and unspecified malignant neoplasms were generally low in MECC countries. No such cases were reported from Cyprus (Table 15.2).

Table 15.3 shows the incidence rates according to the ICCC site for children under 20 years of age. The total ASR of malignant tumors was again highest in Cyprus (178.6), and was also relatively high among Israeli Jews (154.2).

Table 15.4 shows the ASRs of all malignant neoplasms in 5-year age groups for males and females. In Cyprus, the incidence

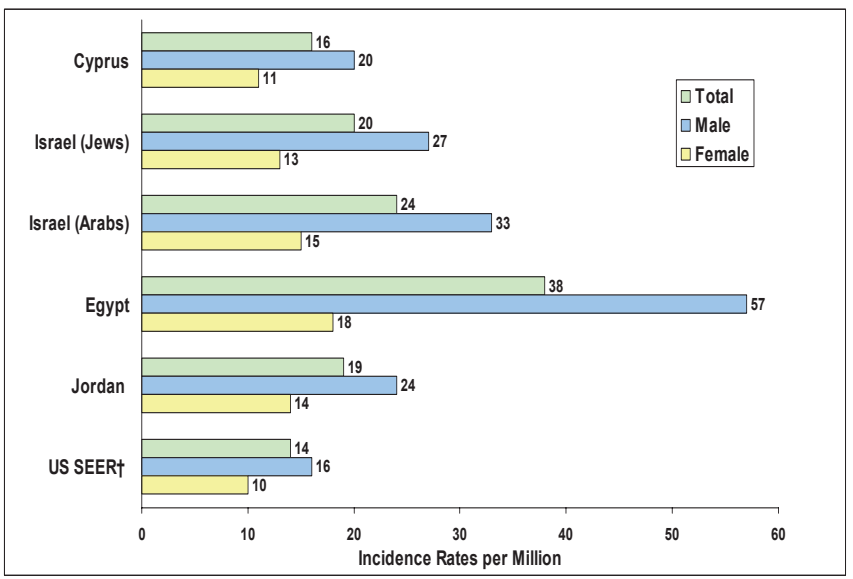
rates of cancers under 5 years (199.2 in males; 241.8 in females) seemed again higher than in the other MECC countries and similar to the US SEER rates (210.4 and 196.9, respectively). The highest incidence rates in adolescents were in female Cypriots (262.0) and male and female Israeli Jews (226.2) (Table 15.4).

Comparing Other Childhood Cancer Registries with MECC

Comparison of the rates reported by cancer registries in some European countries *[2-4]* with those of MECC countries is shown in Table 15.5. Analysis of the total ASRs of childhood cancer in MECC and European countries revealed the highest rates in Cyprus (170.0) and Italy (158.0). These 2 countries had almost the same incidence rate of leukemia (53.0 and 53.9, respectively). With the exception of Cyprus (53.0), MECC registries in general tended to have a lower incidence rate of leukemia (29.4 to 39.2) than in the European countries, where incidence of leukemia varied from 41.0 to 53.9 *[3]*. In a previous study, the frequency of T-cell ALL was found to be high in Egypt *[16]*. Childhood leukemia rates were found to be higher in Jordanians than in Israeli Jews, according to a recent report *[17]*.

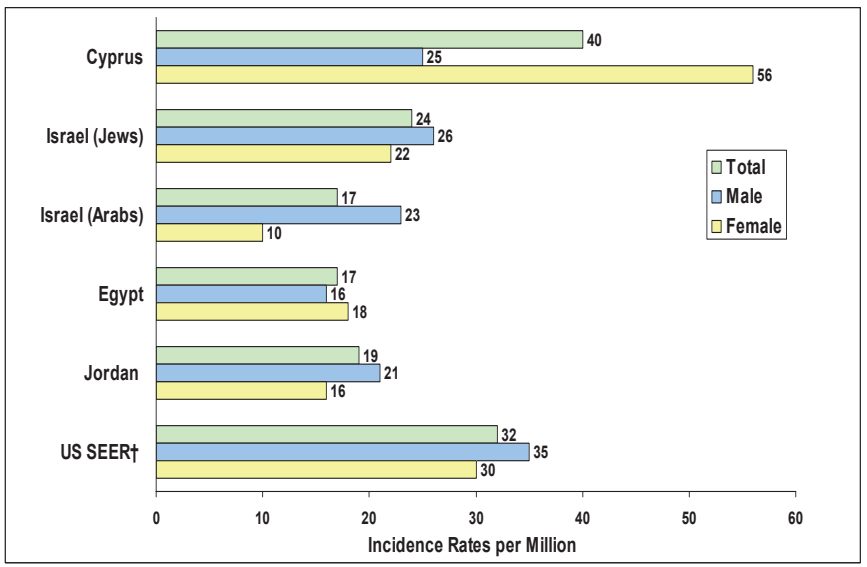
According to Table 15.5, the incidence of lymphoma tended to be higher in the MECC countries than in Europe, but Spain and Italy had a relatively high rate of this malignancy (19.3 and 18.6, respectively). The highest rate of lymphoma within MECC

Figure 15.3. Childhood Cancer: Age-Standardized Incidence Rates* of Lymphoma and Reticuloendothelial Neoplasms for Children under Age 15 Years, by Sex, in Cyprus, Israel (Jews and Arabs), Egypt, Jordan, and US SEER – 1996-2001



*Rates are per 1,000,000 and are age-standardized to the World Standard Million.
†SEER 13 Registries, Public Use Data Set, from data submitted November 2004.

Figure 15.4. Childhood Cancer: Age-Standardized Incidence Rates* of Malignant Central Nervous System and Miscellaneous Intracranial and Intraspinal Neoplasms for Children under Age 15 Years, by Sex, in Cyprus, Israel (Jews and Arabs), Egypt, Jordan, and US SEER – 1996-2001



*Rates are per 1,000,000 and are age-standardized to the World Standard Million.
†SEER 13 Registries, Public Use Data Set, from data submitted November 2004.

Table 15.3. Childhood Cancer: Age-Standardized Incidence Rates* for International Classification of Childhood Cancer (ICCC) Sites, by Sex, in Children under Age 20 Years 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		
ICCC Site	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female
All cancers	178.6	160.0	198.1	154.2	167.6	140.1	126.9	140.7	112.4	134.8	153.1	115.6	119.7	132.4	106.4	164.0	171.0	156.5
Leukemia	49.1	46.8	51.4	30.2	34.1	26.2	27.3	30.6	23.8	32.1	35.2	28.9	36.5	43.1	29.5	45.4	48.5	42.2
Lymphomas and reticuloendothelial neoplasms	26.2	*23.4*	*29.0*	33.7	37.7	29.4	29.7	37.8	21.1	37.3	54.5	19.3	23.1	26.0	20.1	20.3	22.5	18.0
Central nervous system and miscellaneous intracranial and intraspinal neoplasms	34.1	*25.5*	*43.1*	21.5	22.4	20.6	17.0	22.0	11.8	15.2	15.0	15.5	18.7	21.6	15.6	29.3	32.0	26.3
Sympathetic nervous system tumors	*17.2*	*22.0*	*12.3*	12.6	12.6	12.6	9.7	10.2	9.1	7.5	9.2	*5.8*	5.0	5.6	4.3	8.8	8.2	9.5
Retinoblastoma	*0.0*	*0.0*	*0.0*	2.2	*1.8*	*2.6*	*1.6*	*1.6*	*1.7*	*1.9*	-	*2.7*	3.6	3.4	3.8	4.4	5.1	3.6
Renal tumors	*8.7*	-	*11.3*	5.4	6.7	4.1	4.4	*3.2*	*5.6*	4.2	*3.4*	*5.0*	4.1	3.5	4.7	7.4	6.6	8.2
Hepatic tumors	-	-	*0.0*	*1.1*	*1.7*	-	*2.2*	*1.6*	*2.9*	*1.9*	*1.8*	*1.9*	*0.9*	*1.1*	*0.7*	2.5	2.2	2.9
Malignant bone tumors	*14.1*	*19.7*	*8.3*	10.6	13.8	7.3	5.2	*5.9*	*4.4*	10.6	11.1	10.1	8.7	10.0	7.2	6.9	8.1	5.6
Soft tissue sarcomas	*8.6*	*11.3*	-	12.8	13.7	11.9	14.7	13.5	16.0	9.7	9.1	10.4	6.1	6.7	5.5	12.4	13.6	11.0
Germ cell, trophoblastic, and other gonadal neoplasms	*5.0*	-	*8.3*	6.6	7.6	5.6	*3.4*	*2.8*	*4.1*	*2.6*	*1.8*	*3.5*	4.5	3.5	5.5	11.2	13.6	8.6
Carcinomas and other malignant epithelial neoplasms	*13.0*	*0.0*	*26.6*	14.3	12.4	16.3	8.8	*8.1*	*9.5*	6.9	6.5	7.3	7.9	7.4	8.5	14.2	9.7	18.9
Other and unspecified malignant neoplasms	*0.0*	*0.0*	*0.0*	2.2	*2.0*	*2.3*	*2.6*	*2.9*	*2.4*	4.6	*4.3*	*5.0*	*0.6*	*0.5*	*0.7*	0.6	*0.4*	*0.8*
Not classified by ICCC	-	*0.0*	-	*1.0*	*1.2*	*0.9*	-	-	*0.0*	-	*0.0*	-	-	-	-	0.6	*0.5*	*0.7*

*Rates are per 1,000,000 and are age-standardized to the World Standard Million.

†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.

countries was in Egyptians (37.7), followed by Israeli Arabs (24.2). The recently established cancer registry in Turkey has also revealed a high incidence rate of lymphomas (19.6) among Turkish children *[18,19]*.

CNS tumor rates were somewhat low in MECC countries (with the exception of 40.1 in Cyprus) as compared with European countries, where the highest rate of 42.8 was found in Sweden *[19]*.

Table 15.5 shows that within MECC countries, the highest rate of neuroblastoma occurred in Cypriots (22.3); the rate was also high in Israeli Jews (15.8). In Europe, France and Italy showed high rates of this tumor (13.5 and 13.4, respectively). The incidence of retinoblastoma was low in general within MECC countries.

Slightly higher incidence rates, ranging from 3.4 to 4.8, were found in Europe. Renal tumors again had the highest rate in Cyprus (11.3) within MECC countries, an ASR similar to that found in Sweden (10.2). The incidence of hepatic tumors in MECC registries was not grossly different from that in European countries; both showed low rates. The incidence rates of bone tumors were the highest in Egyptians (8.6), followed by Israeli Jews (8.1) and Cypriots (7.9). Among European countries, Spain (7.6) and Italy (7.5) had the highest rates.

Soft tissue sarcoma was most common in Israeli Arabs (13.6), whereas Sweden had the highest rate (10.5) among European countries. Germ cell tumors were lowest in Egypt and Cyprus within the MECC countries (Table 15.5).

Table 15.4. Childhood Cancer: Age-Standardized Incidence Rates* for all International Classification of Childhood Cancer Sites, 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		
Age Group	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female
<5 y	220.0	199.2	241.8	155.9	165.3	145.9	155.3	174.4	135.1	145.9	156.2	135.1	132.2	155.0	108.0	203.8	210.4	196.9
5-9 y	124.4	125.3	123.3	117.5	144.3	89.5	99.1	124.7	72.2	122.6	153.7	90.1	102.9	113.5	91.8	115.1	129.4	100.1
10-14 y	154.1	149.6	158.9	120.8	136.0	104.9	95.7	103.7	87.3	120.2	138.6	100.9	104.8	116.9	92.0	128.3	126.4	130.3
15-19 y	208.3	156.7	262.0	226.2	228.3	224.0	151.1	150.5	151.8	148.1	162.6	132.8	136.8	138.6	134.8	200.8	209.3	191.8
<15 y	170.0	161.0	179.5	133.3	150.0	115.8	119.9	137.8	100.9	130.9	150.3	110.7	114.8	130.6	98.1	153.3	159.9	146.3
<20 y	178.6	160.0	198.1	154.2	167.6	140.1	126.9	140.7	112.4	134.8	153.1	115.6	119.7	132.4	106.4	164.0	171.0	156.5

*Rates are per 1,000,000, and rates for the broad age groups are age-standardized to the World Standard Million.

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

Interestingly, the total ASR of childhood tumors in Turkey (Izmir registry), 115.6, was quite low and similar to the rate (114.8) in Jordan (Table 15.5).

SUMMARY AND CONCLUSIONS

The results of this analysis of MECC registries may be summarized as follows:

1. Among MECC countries, the total incidence of childhood tumors was highest in Cyprus (170.0).

2. Leukemia was the most common childhood malignancy in all MECC countries, with the exception of Egypt. However, the MECC ASR of leukemia was somewhat low compared with the European countries. The incidence of ALL was highest in Cyprus.

3. The total ASR of lymphoma in Egypt (37.7) exceeded leukemia (31.9), with a very high rate among male children (56.7). Male Israeli Arabs also had a high rate of lymphoma. The incidence of lymphoma in MECC countries was generally high, compared with Europe (14.3) and the US SEER population (13.5).

Table 15.5. Childhood Cancer: Comparison of Age-Standardized Incidence Rates* in MECC Countries, Some European Countries, and US SEER†‡

Country/Registry	Total Rate	Leukemia	Lymphoma	CNS§ Tumors	Neuro-blastoma	Retino-blastoma	Renal Tumors	Hepatic Tumors	Bone Tumors	Soft Tissue Sarcomas	Germ Cell Tumors
Europe	130.9	42.4	14.3	28.1	9.8	3.8	8.6	1.4	5.4	8.3	4.0
France	135.6	41.3	15.7	28.2	13.5	4.2	9.3	1.3	6.6	7.4	4.0
Italy	158.0	53.9	18.6	32.7	13.4	3.9	8.6	1.8	7.5	9.2	3.8
United Kingdom	121.0	41.0	11.1	27.6	8.6	4.0	7.7	1.1	4.9	8.0	3.7
Sweden	154.3	41.7	13.8	42.8	4.9	4.8	10.2	2.2	5.6	10.5	3.5
Turkey	115.6	41.4	19.6	16.8	7.6	3.3	6.7	1.1	3.9	7.6	4.1
Cyprus	170.0	53.0	15.7	40.1	22.3	*0.0*	11.3	-	7.9	9.8	-
Israel (Jews)	133.3	31.8	20.0	24.2	15.8	2.8	6.9	1.3	8.1	11.0	3.1
Israel (Arabs)	119.9	29.4	24,2	16.5	12.0	2.1	5.7	2.5	3.3	13.6	3.6
Egypt	130.9	31.9	37.7	16.9	9.5	2.4	5.4	1.9	8.6	7.9	2.2
Jordan	114.8	39.2	19.0	18.9	6.1	4.6	5.1	1.1	6.0	6.3	3.4
Germany	128.7	44.8	14.5	24.3	11.6	3.4	8.9	1.3	5.6	8.5	4.5
Spain	137.9	41.1	19.3	27.6	12.6	3.6	7.6	1.8	7.6	9.0	3.8
US SEER	153.3	50.4	13.5	32.5	11.2	5.6	9.2	2.9	5.2	10.8	5.3

*Rates are per 1,000,000 and are age-standardized to the World Standard Million.

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

‡The period covered is different for each population and ranges from 1968-99. See http://www-dep.iarc.fr/accis.htm for details.

Sources: Data on Cyprus, Egypt, Israel, and Jordan are from the MECC data set, and US SEER data are from the SEER Program, National Cancer Institute. Data from other countries are from the Automated Childhood Cancer Information System (ACCIS), http://www-dep.iarc.fr/accis.htm.

§CNS refers to central nervous system.

4. CNS tumors were the second most common neoplasms after leukemia in Cyprus, particularly in females (55.6), with a total ASR of 40.1.

Within the MECC registries, the pattern of rates in Cyprus showed a similarity to the Western world and somewhat differed from other MECC countries. This may be due to genetic differences between the Cypriots and Arabs and Jews, or to differences in environmental factors in these populations, and needs further investigation. The situation is similar to that in Uruguay, where the incidence and types of childhood tumors were found to be closer to those in North America and Western Europe than in Latin America *[20]*.

5. The rates of other types of childhood tumors in MECC countries were not substantially different from those in the Western world. It is interesting to note the similar ASRs of total childhood tumors in Turkey (115.6) and Jordan (114.8).

The MECC registration system has provided useful information about the incidence of childhood cancers in Middle Eastern countries and should be continued. The higher incidence rate of lymphoma in Egyptians and Israeli Arabs requires further studies from the environmental point of view, including viral (EBV) and nutritional factors. EBV infection has been found to be strongly associated with malignant lymphomas (Hodgkin and Burkitt's lymphoma) serologically and at molecular levels in Turkish children *[14,15]*, so should be investigated further. An important future addition to the registration program would be the collection of survival data for children with malignant disease.

REFERENCES

[1] Stiller CA. Epidemiology and genetics of childhood cancer. Oncogene 2004;23:6429-44.

[2] Steliarova-Foucher E, Stiller C, Kaatsch P, Berrino F, Coebergh JW, Lacour B, et al. Geographical patterns and time trends of cancer incidence and survival among children and adolescents in Europe since the 1970s (the ACCIS project): an epidemiological study. Lancet 2004;364:2097-105.

[3] International Agency for Research on Cancer. ACCIS: automated childhood cancer information system. 2006. Available at: http://www-dep.iarc.fr/accis.htm. [Last Accessed: 1/06].

[4] Gatta G, Corazziari I, Magnani C, Peris-Bonet R, Roazzi P, Stiller C. Childhood cancer survival in Europe. Ann Oncol 2003;14:v119-v127.

[5] Gurney JG, Bondy ML. Epidemiologic research methods and childhood cancer. In: Pizzo P, Poplack DG, editors. Principles and practice of pediatric oncology, fourth edition. Philadelphia (PA): Williams & Wilkins; 2001. p. 13-20.

[6] Pinkerton CR, Cushing P, Sepion B. Epidemiology and aetiology of childhood cancer. In: Childhood cancer management: a practical handbook. London (UK): Arnold; 1994. p. 28-41.

[7] Parkin DM, Kramarova E, Draper GJ, Masuyer E, Michaelis J, Neglia J, et al. International incidence of childhood cancer. IARC publication no. 144. Lyon (France): International Agency for Research on Cancer; 1998.

[8] Kramarova E, Stiller CA, Ferlay J, Parkin DM, Draper GJ, Michaelis J, et al. The international classification of childhood cancer. IARC technical report no. 29. Lyon (France): International Agency for Research on Cancer; 1997.

[9] Parkin DM, Stiller CA, Draper GJ, Bieber CA, Terracini B, Young JL, et al. International incidence of childhood cancer. IARC scientific publications no. 87. Lyon (France): International Agency for Research on Cancer; 1988.

[10] Parkin DM, Stiller CA, Draper GJ, Bieber CA. The international incidence of childhood cancer. Int J Cancer 1988;42:511-20.

[11] Pratt CB. Some aspects of childhood cancer epidemiology. Pediatr Clin North Am 1985;32:541-56.

[12] Stiller CA, Bunch KJ, Lewis IJ. Ethnic group and survival from childhood cancer: report from the UK Children's Cancer Study Group. Br J Cancer 2000;82:1339-43.

[13] Parkin DM, Stiller CA. Childhood cancer in developing countries: environmental factors. Int J Ped Hemat Oncol 1995;2:411-7.

[14] Çavdar AO, Pamir A, Gozdasoglu S. Hodgkin's disease in children: clinico-epidemiologic and viral (Epstein-Barr virus) analyses. Med Pediatr Oncol 1999;32:18-23.

[15] Çavdar AO, Yavuz G, Babacan E, Gozdasoglu S, Unal E, Ertem U, et al. Burkitt's lymphoma in Turkish children: clinical, viral [EBV] and molecular studies. Leuk Lymphoma 1994;14:323-30.

[16] Kamel AM, Ghaleb FM, Assem MM, Hindawy DS, Jaffe ES, Magrath IT. Phenotypic analysis of T-cell acute lymphoblastic leukemia in Egypt. Leuk Res 1990;14:601-9.

[17] Freedman LS, Barchana M, Al Kayed S, Qasem MB, Young JL, Edwards BK, et al. A comparison of population-based cancer incidence rates in Israel and Jordan. Eur J Cancer Prev 2003;12:359-65.

[18] Kutluk T. First national pediatric cancer registry in Turkey: a Turkish pediatric oncology group study (abstract). Ped Blood & Cancer 2004;43:452.

[19] Fidaner C, Eser SY, Parkin DM. Incidence in Izmir in 1993-1994: first results from Izmir Cancer Registry. Eur J Cancer 2001;37:83-92.

[20] Castillo L, Fluchel M, Dabezies A, Pieri D, Brockhorst N, Barr R. Childhood cancer in Uruguay: 1992-1994. Incidence and mortality. Med Pediatr Oncol 2001;37:400-4.