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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).

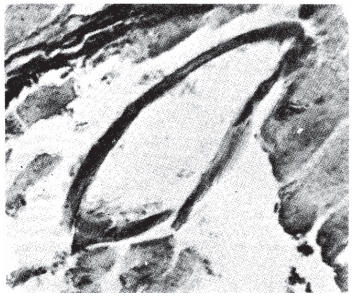
Table 11.2. Bladder Cancer: Adult and Youth Smoking Prevalence, Cigarettes Smoked, and Quit Rate in Cyprus, Israel (Jews and Arabs), Egypt, Jordan, and the United States − 1998-2000

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]*.

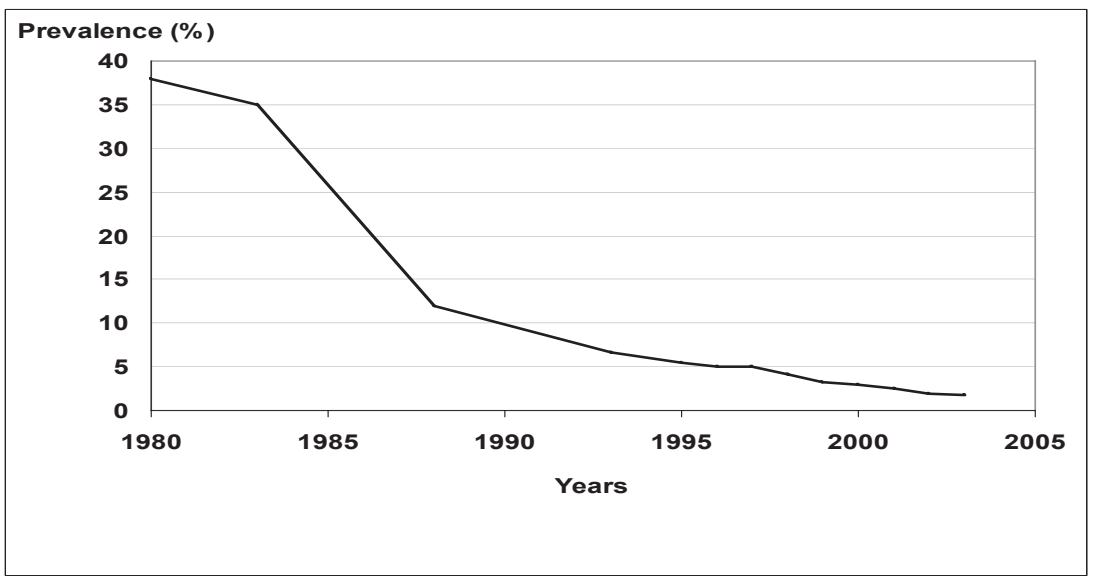
A diet high in saturated fat and consumption of Aristolochia fangchi (an herb used in some weight-loss formulas) have been incriminated as risk factors for bladder cancer. There is also a strong racial/ethnic disparity, with disease much more common in Caucasians than in those of African, Latino, or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

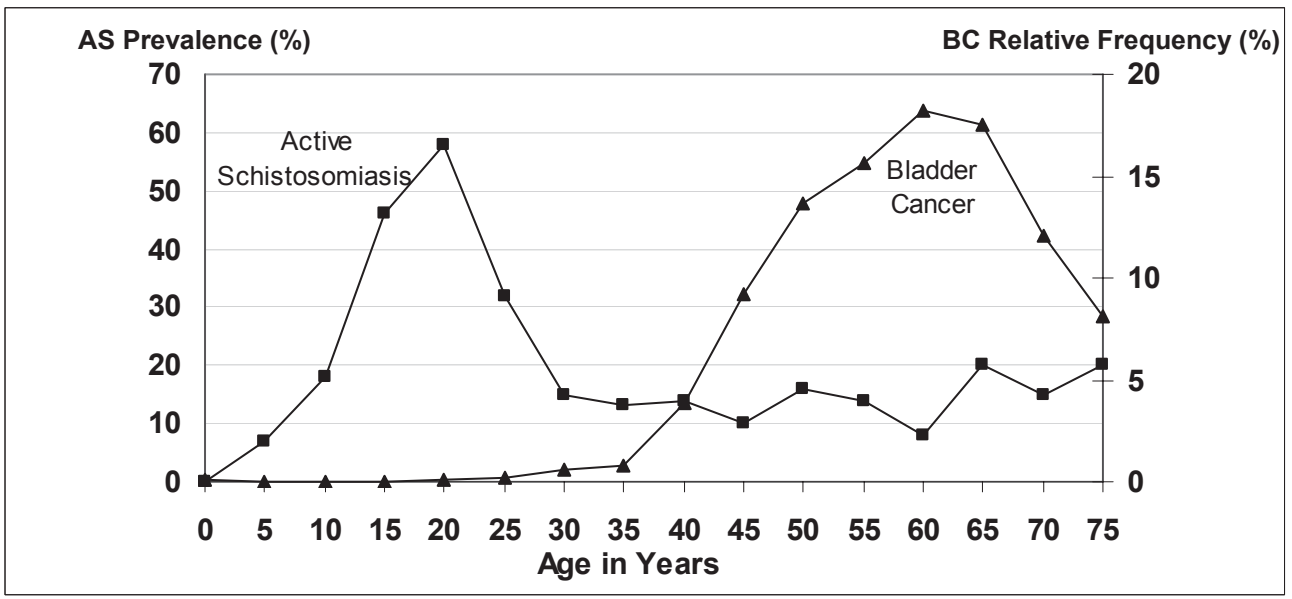
The relatively high frequency of bladder cancer in Egypt supports the etiological relationship to urinary schistosomiasis. Despite the marked decrease in prevalence of endemic schistosomiasis over the last 2 decades, Egypt is still paying the toll of the previously high prevalence of the disease. Comparison 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.

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