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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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