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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

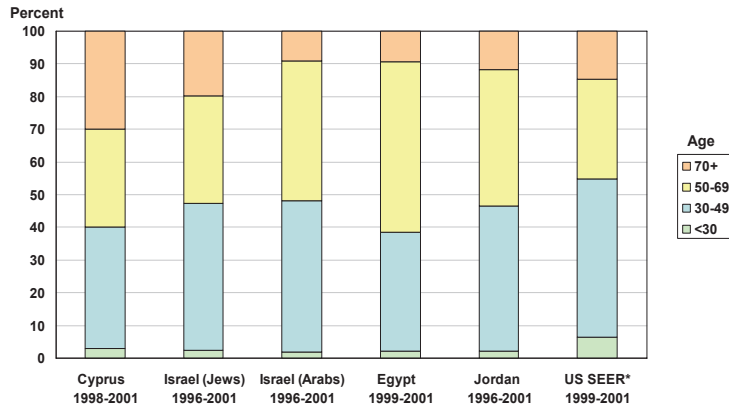
*Rates are per 100,000 females and are age-standardized to the World Standard Million.

†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.

in those aged 70 years and above (30.0%), compared with the other registries (Table 9.1 and Figure 9.1).

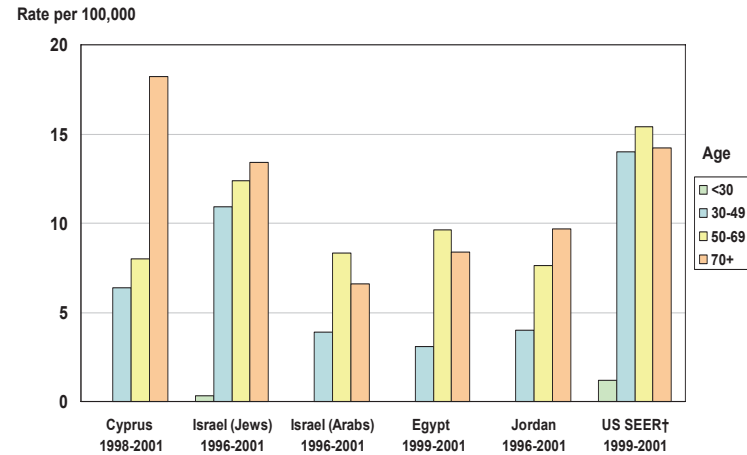
Just as the percentage of cervical cancer cases below the age of 30 years was very low, so were the incidence rates in this age group (Table 9.1). In Cypriots, Israeli Jews, and Jordanians, the ASR was highest for ages 70 and above, while in Egyptians, Israeli Arabs, and the US SEER population, the rate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

Overall Age Distribution

Cervical Cancer

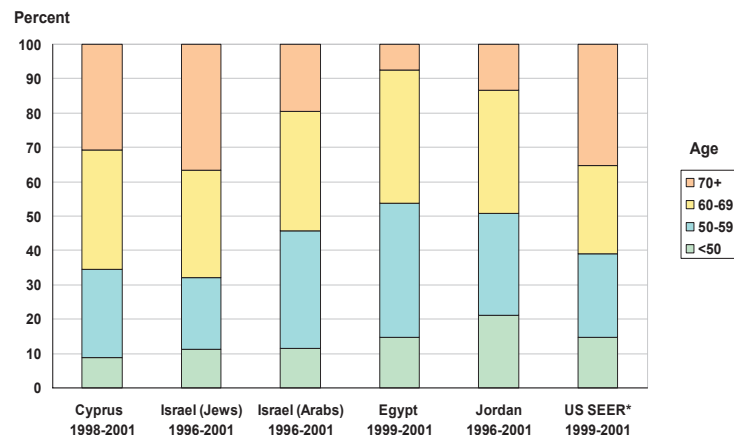
In all MECC countries and US SEER, the proportion of cervical cancer diagnosed under the age of 30 years was low. However, the proportion in the MECC registries (about 2%) did appear to be lower than in US SEER (6.4%). This may be explained by the well-established cervical cancer screening program in 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

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).

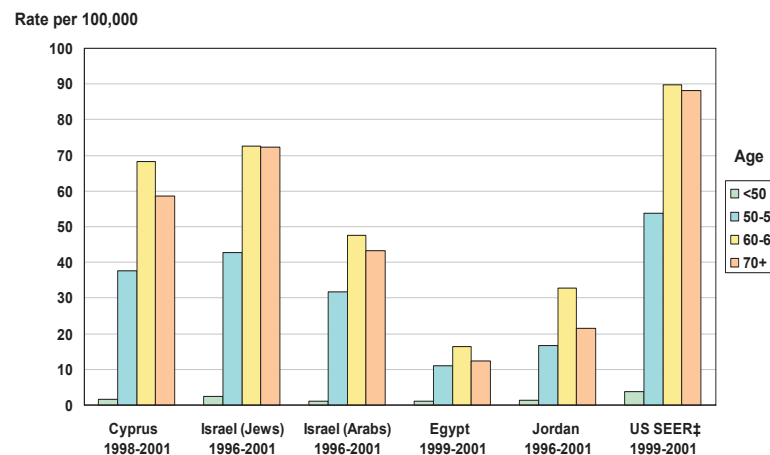
In each age group, incidence rates were highest in US SEER, followed by those in Israeli Jews and in Cypriots (Table 9.1 and Figure 9.4).

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 number of 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.

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