Shen-yi Li En-yu Wang

Endometrial Carcinoma

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With the Collaboration of Michihiro Seta

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Dedicated in Gratitude
to Our Teachers

Preface

During the past 20 years, endometrial carcinoma has continued to increase in frequency and it is quite possible that this carcinoma will become the major gynecologic malignancy in the future. For many years, endometrial carcinoma was considered less malignant than other gynecologic malignancies, simple hysterectomy and bilateral salpingo-oophorectomy or surgery combined with radiation being effective in certain circumstances. It is unfortunate to note that the global 5-year survival rate for patients with advanced or recurrent endometrial carcinoma has improved only slightly. Therefore any complacency regarding this 'benign malignancy' should be reconsidered.

There is a growing awareness of the nature of endometrial carcinoma, with advances in our knowledge ranging from its etiology through its epidemiology to its clinical findings. This volume has been designed to fill a hiatus in the literature in China. To achieve this aim, we have attempted to review the world-wide advances on endometrial carcinoma and summarize systematically and comprehensively this common gynecologic malignancy, including the clinical experiences gathered at the Cancer Institute (Hospital) of the Chinese Academy of Medical Sciences since 1958 as well as a brief description of the psychological problems in patients with gynecologic cancers.

We are very grateful to our photographer, Mr. Liu Xi-Chan for the high quality of the photographs. We would also like to express our sincere thanks to the publishers for their care and efficiency in preparing the text and illustrations, and particularly to Dr. Ute Heilmann, who edited the text with much patience and genuine understanding.

Beijing, March 1990

Shen-yi Li
En-yu Wang

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1 Epidemiology and Etiology

1.1 Epidemiology

Endometrial carcinoma is also called corpus cancer. During the past 20 years there has been a drastic increase in the worldwide incidence of endometrial carcinoma, such that in many areas endometrial carcinoma is now ranked as the second or third most common malignant neoplasm of the female genital tract. The reported incidence varies according to country, area, and race. According to the International Agency for Research on Cancer (1982), incidence rates are especially high in North America and northern Europe and are low in Central America and Asia (Fig. 1.1). The American Cancer Society reported that approximately 37 000 women would develop endometrial carcinoma in 1979. Therefore, this lesion is seen over twice as frequently as carcinoma of the ovary and cervix (Cancer Statistics 1979). Masubuchi et al. (1975) reported 1958 patients with endometrial carcinoma and 38 080 patients with cervical cancer during the 12 years from 1961 to 1972, based on records collected from 33 university hospitals and cancer centers in Japan, giving a ratio of the incidence of endometrial carcinoma to cervical cancer of 1:19.5. In the United States, the ratio of the incidence of endometrial carcinoma to cervical cancer was reported to be 1:2 during the period 1969–1970 (Duun 1974).

Racial differences have been observed such as those between blacks or browns and whites in South Africa, where the ratio of incidence to invasive cervical cancer was 1:8.5 and 2.5:1, respectively. According to the incidence of cancer for the period 1968–1972 in North America, considerable variation exists, the highest being an annual figure of almost 30/100 000 among San Francisco whites. Racial differences such as those between whites and blacks in the San Francisco Bay area, among the inhabitants of New Mexico from European non-Spanish, Spanish and Indian stock, and among inhabitants of the Pacific region – the native Hawaiian, whites, Chinese, Japanese, and Philippines – suggest that the incidence is higher in richer than in poorer communities (Fig 1.2) (Waard and Oettle 1965; Waard 1982). It is interesting that the incidence in groups of similar ethnic origin living in different countries is very variable; for example, the incidence among the Japanese in Hawaii is much higher than those in Japan (Fig. 1.3) (IARC 1982).

In recent years a true epidemic of endometrial carcinoma has occurred in several parts of the United States (Weiss et al. 1976). This is firmly documented for the San Francisco Bay area, where the annual incidence for the 50- to 74-year age group tripled in 15 years (Austin and Roe 1979). Something similar is true for

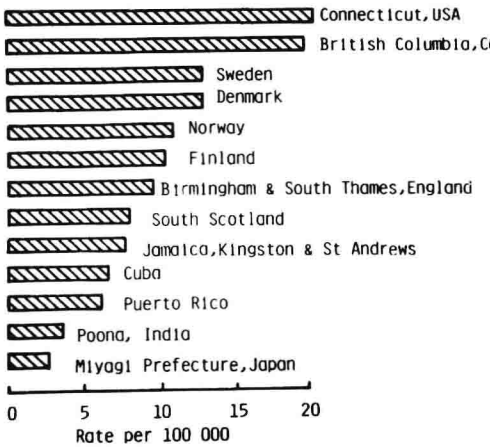

Fig. 1.1. Age-adjusted incidence of endometrial carcinoma in selected countries (IARC 1982)

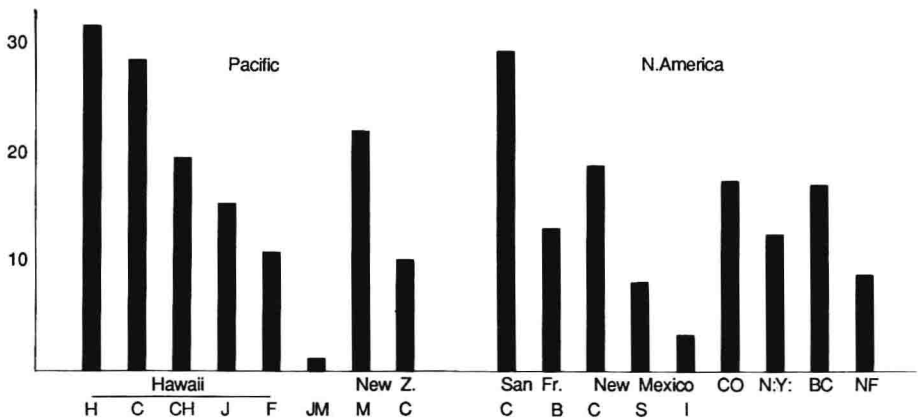

Fig. 1.2. Standardized incidence rates of endometrial carcinoma in some populations of the Pacific region and North America.

Hawaii: *H*, Hawaiian; *C*, Caucasian; *CH*, Chinese; *J*, Japanese; *F*, Filipino origin; *JM*, Japan Miyagi prefecture; **New Zealand**: *M*, Maoris; *C*, non-Maoris (mainly Caucasian); **San Francisco Bay area**: *C*, non-Spanish Caucasians; *S*, Spanish origin; *I*, Indian. *CO*, Conneticut; *NY*, upstate New York; *BC*, British Columbia; *NF*, New Foundland. (Waard 1982)

South Africa. In 1965, Waard and Oettle reported that the number of endometrial carcinoma cases at the large Baragwanath Hospital near Johannesburg seemed to be on the increase. They predicted a further rise due to the improving socioeconomic circumstances of the urban blacks, and further statistics lead to the conclusion that this prediction was probably correct (Table 1.1).

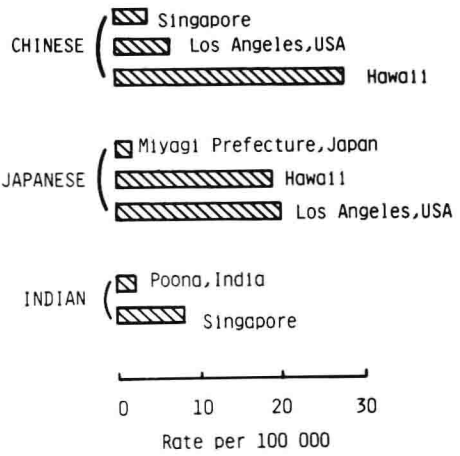

Fig. 1.3. Age-adjusted incidence of endo-metrial carcinoma in Chinese, Japanese, and Indians living in various countries (IARC 1982)

Table 1.1. Endometrial cancer diagnosed in Baragwanath Hospital, which serves the black population of Soweto near Johannesburg. (Adapted from Waard 1982)

Period	Number of cases
1951–1956 (6 years)	0
1957–1962 (6 years)	12
1968–1973 (6 years)	41
1974–1978 (5 years)	76

It has been found that the incidence ratio for endometrial carcinoma to cancer of the cervix is very different in various countries, areas, and races. The incidence of endometrial carcinoma is much higher than that of cancer of the cervix in Alameda, Connecticut, in whites in the Bay area, United States, in Israel, and in Malta. The incidence of endometrial carcinoma is lower and an opposite ratio even appears in Colombia, India, Cuba, and Japan (Table 1.2).

The analysis of cancer registry from Huaxi Medical University and Cancer Institute Hospital, Chinese Academy of Medical Sciences, Beijing, China, also shows that the incidence of endometrial carcinoma has tended to increase (Table 1.3) (Li 1988).

From the above it would appear that either the increased incidence of this disease or increased number of cases in some hospitals could be recognized, and the change in ratio of cases of endometrial carcinoma and cervical cancer could implicate an increase of endometrial carcinoma. Of course, there are several important factors which cannot be excluded in analyzing the increased incidence

Table 1.2. Incidence per 100 000 of endometrial carcinoma and cervical cancer

Geographic area	Cervical cancer	Endometrial carcinoma
United States		
Alameda	12.3	33.3
Bay area	12.1	29.3
Conneticut	9.8	17.8
Israel	4.5	10.8
Malta	7.1	13.1
Brazil, Sao Paulo	27.5	8.5
Colombia, Cali	62.8	5.1
Cuba	19.5	10.9
India	23.2	1.3
Nigeria. Ibadan	21.6	1.6
Japan	13.8	1.3
Osaka	16.2	0.9
Norway	18.1	9.7
Poland, Warsaw	21.5	9.5
United Kingdom, Birmingham	12.6	8.5

Table 1.3. Incidence ratio of endometrial carcinoma to cervical cancer in China

	Period	Ratio
Hua Xi Medical	1955–1966	1:18.1
University	1967–1978	1:6
Cancer Institute	1958–1969	1:44
Hospital	1970–1981	1:18.5

of endometrial carcinoma. Greenblatt and Stoddard (1978) suggested several reasons for the increase in incidence:

1. Greater availability of medical care: more women are provided with medical care; therefore more cancers are detected.
2. More women reach the critical age for the development of endometrial carcinoma.
3. A broadening of criteria for the diagnosis of endometrial carcinoma by the inclusion of severe dysplasia, a typical adenomatous hyperplasia, carcinoma in situ, and the so-called well-differentiated endometrial carcinoma in the cancer registry as adenocarcinoma.

4. A worldwide increase in endometrial carcinoma due possibly to environmental and unknown factors.

However, it is clear that despite these factors there has been a trend toward increased incidence of endometrial carcinoma.

1.2 Etiology

Etiologic investigation into endometrial carcinoma has been vigorously pursued in the past 30 years. Studies on the relationship between steroids and endometrial carcinoma have made great progress, but the cause of disease remains unclear. However, some risk factors associated with endometrial carcinoma have been noted. These include age, obesity, nulliparity, late menopause, hypertension, diabetes mellitus, ovarian estrogen-producing tumors, ovarian dysgenesis, polycystic ovarian syndrome, oral contraceptives, and exogenous estrogen. The majority of these factors may cause excessive estrogen production, and prolonged unopposed estrogen stimulation of the endometrium appears causally related to the development of endometrial carcinoma.

1.2.1 Age

Generally, endometrial carcinoma occurs in the postmenopausal period, primarily in the age group of 55–59 years. The age range is from the 2nd to the 9th decade. Only 20%–25% of the patients with endometrial carcinoma are premenopausal, 2%–5% of whom are under the age of 40 years. The incidence obviously declines over the age of 70 years (Mattingly 1977). A 1958–1981 Cancer Institute Hospital, Beijing, study of 449 women with endometrial carcinoma found that the age range extends from 29 to 76 years, with 45% (202/449 cases) of the patients in the age group of 50–59 years, 34.7% of patients (156/449 cases) premenopausal, and 10.2% of patients (45/449 cases) under the age of 40 years (L 1988).

1.2.2 Obesity

Obesity is associated with an increased risk in some patients with endometrial carcinoma. Damon (1960) demonstrated a 13% increase in the mean body weight of patients with endometrial carcinoma compared with control patients of similar height. Wynder et al. (1966) reported that women overweight by 21–50 lb have a threefold greater risk of developing endometrial carcinoma and women overweight by over 50 lb have a tenfold greater risk of developing endometrial carcinoma. Similar studies in Boston demonstrated 1.8 times the risk for women in the upper third of the weight distribution, increasing to 2.4

Table 1.4. Weight of women with endometrial carcinoma and of control subjects aged 50–59 years. (Modified from Wynder et al. 1966)

Weight	% women with endometrial cancer ($n=90$)	% control women ($n=150$)	Relative risk, cases: controls
Below average weight by			
21 lb or more	7	12	0.9
10–20 lb	9	20	0.7
3–9 lb	10	19	0.9
Average weight ± 2 lb	8	13	1.0
Above average weight by			
3–9 lb	9	9	1.6
10–20 lb	11	9	2.0
21–50 lb	28	15	3.1
51 lb or more	18	3	9.8

times the risk for patients in the top 15% of the weight distribution (MacMahon 1974).

In addition, 32.6% of patients were obese in a group of endometrial carcinoma patients in the Cancer Institute Hospital, Beijing. Wynder et al. (1966) summarized the distribution of body weight in a group of patients with endometrial carcinoma and matched controls (Table 1.4).

1.2.3 Nulliparity

Nulliparity is commonly associated with an increased risk of developing endometrial carcinoma. Some papers have reported that 24%–31% of patients with endometrial carcinoma were nulliparous. Nulliparity was associated with twice the risk of development of endometrial carcinoma compared with primipara and three times the risk of women with five children (Masubichi and Nemoto 1972; MacMahon 1974). Lang et al. (1978) reported that 68.5% (74/108 cases) of patients with endometrial carcinoma in Beijing Union Hospital were women with primary and secondary infertility. Li (1988) also reported 25% of patients with endometrial carcinoma having primary infertility. Some authors comment that pregnancy is a powerful factor in protecting against endometrial carcinoma, which is perhaps related to the shedding of the endometrium which occurs at parturition, protecting the endometrium from estrogen stimulation for one or several years. The more pregnancies a woman has, the greater is her protection from endometrial carcinoma. However, this protection must be absent in women with infertility.

1.2.4 Late Menopause

Late menopause has been recognized as a risk factor in the development of endometrial carcinoma. Menopause after the age of 52 years has a 2.4 times greater risk for the development of endometrial carcinoma compared with menopause before the age of 49 years (Elwood et al. 1977). Screening 5966 women in the Beijing area of China showed that 938 women were postmenopausal, the median age of menopause was 47.8 years and 46.7 years for urban women and rural women respectively, and that menopause occurred at 50 years of age in 25.7% (Wu 1982). Statistical studies of 418 patients with endometrial carcinoma in the Cancer Institute Hospital demonstrated that 296 patients were menopausal, the median age of menopause was 49.3 years, and the menopause in 56% of them occurred at over 50 years of age (Li et al. 1988).

Therefore, it is generally accepted that spontaneous menopause is later in patients with endometrial carcinoma than in normal matched controls, so long-term estrogen stimulation to the endometrium occurred.

1.2.5 Diabetes Mellitus, Hypertension, and Associated Internal Medical Diseases

Diabetes mellitus and hypertension are frequently associated with endometrial carcinoma. Diabetes or a diabetic tendency is present in 11%–45% of patients with endometrial carcinoma and the incidence of hypertension varies from 25% to 60% (Van Nagell et al. 1972). Women with a history of diabetes had a 2.8-fold risk compared with the controls (Elwood et al. 1977). Frick et al. (1973) reported 5.3%–41% of patients with endometrial carcinoma had abnormal carbohydrate intolerance and 25% of the patients will have hypertension or arteriosclerotic heart disease. Fox and Sen (1970), comparing patients with endometrial carcinoma with matched controls, found a statistically significant higher incidence of hypertension in patients with endometrial carcinoma than in the controls, but only at the $P = 0.05$ level. Hypertension is prevalent in the elderly, obese woman and does not appear to be a significant risk factor by itself. A combination of obesity, hypertension, and diabetes mellitus, called a trilogy of endometrial carcinoma, commonly appears in some patients. The pituitary functional disorder may be a common cause of endometrial carcinoma and metabolic abnormality, but is not generally accepted due to lack of sufficient experimental evidence.

In addition, there is a slightly higher frequency of arthritis and hypothyroidism in patients with endometrial carcinoma compared with controls (Elwood et al. 1977). Husslein et al. (1978) reported that one patient with endometrial carcinoma was diagnosed 20 months after successful renal transplantation. Immunosuppressive states and immunodeficiency diseases are highly correlated with the development of malignancy.