Comparison of the Clinicopathological Characteristics of Premenopausal and Postmenopausal Endometrial Carcinomas: Analysis of Endocrinologically Evaluated Cases

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A study was performed to clarify the clinicopathological differences between premenopausal endometrial carcinoma, which occurs during the reproductive period, and postmenopausal endometrial carcinoma. We analyzed 76 patients with endometrial carcinoma treated in our department between January 1984 and July 1994. Using classification criteria which included menstrual history and results of endocrinological tests (serum FSH, LH and estradiol), 50 (65.7%) patients were defined as postmenopausal, 16 (21.0%) as premenopausal, and 10 (13.1%) as unclassified. From an epidemiologic viewpoint, the incidence of nulliparity was higher in the premenopausal (37.5%) than in the postmenopausal (10%) patients. However, no significant differences were observed between the two groups with regard to the incidence of obesity, diabetes and hypertension. The results of our clinicopathological study revealed that premenopausal endometrial carcinoma had a significantly higher incidence of well differentiated (63.1%) and relatively less advanced (31.1% of cases at stages III and IV) cancers than postmenopausal carcinoma (38% and 46%, respectively). These features were positively correlated with prognosis, i.e., premenopausal patients in general had a much better prognosis than postmenopausal patients.

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Key words: Endometrial cancer—Premenopause—Postmenopause—FSH—Estradiol

Introduction

Endometrial carcinoma can occur during either the reproductive (premenopausal) or postmenopausal period. Although it is predominantly a disease of postmenopausal women, approximately 20% of patients are premenopausal. As the endometrium exhibits cyclic changes under the influence of ovarian hormones, the characteristics of premenopausal endometrial carcinoma have been considered to differ from those of the postmenopausal cancer. A number of researchers have recently reported the clinicopathological characteristics of premenopausal endometrial carcinoma. However, in most of these studies, premenopausal women were defined as those aged 40 years or less, or less than 45 years, without evaluation of ovarian activity.

Furthermore, the studies were performed mostly on American and European populations. Only a few studies have made a clinicopathological comparison between premenopausal and postmenopausal endometrial carcinomas in Japanese women treated at the same hospital during the same period. Differences in the ethnic origins and life style of study populations cannot be ignored when investigating the various risk factors for the development of endometrial carcinoma.

In the present study we performed a retrospective analysis of Japanese patients in whom preoperative ovarian functions were estimated endocrinologically, and attempted to clarify the clinicopathological differences between premenopausal and postmenopausal endometrial carcinomas.

Subjects and Methods

The study subjects were 76 Japanese women with endometrial carcinoma, who were referred to the Department of Gynecology, Yamanashi Medical University Hospital, between January 1984 and July 1994. In all patients, the clinical diagnosis of en-
Pre-menopausal endometrial carcinoma

endometrial carcinoma was confirmed histologically by endometrial biopsy or dilatation and curettage, and the state of ovarian activity was evaluated using a standard questionnaire about menstrual history, and by measuring the levels of serum E2, FSH, and LH. E2 was measured by radioimmunoassay (RIA), and FSH and LH by RIA (during 1985–1991) or immunoradiometric assay (IRMA, during 1992–1994). The RIA and IRMA kits were purchased from Daiichi Isotope, Tokyo. Supplementary measurement of these hormones was done for patients in whom a discrepancy between menstrual history and serum hormone levels was observed.

In July 1995, a chart review was done for all patients, and they were classified into three groups on the basis of menstrual history and serum levels of E2 and FSH. Patients who had no history of amenorrhea for more than 6 months, and high serum E2 (≥20 pg/ml) and low serum FSH (<30 mIU/ml by RIA or <20 mIU/ml by IRMA) levels were defined as premenopausal. Those who had amenorrhea, and low serum E2 (<20 pg/ml) and high serum FSH (≥30 mIU/ml by RIA or ≥20 mIU/ml by IRMA) levels were defined as postmenopausal. The cut-off values for E2 and FSH were based on the standard values for Japanese women. Patients not meeting any of the above criteria were defined as unclassified.

In addition to menstrual history and serum hormone levels, the following details were recorded: age at diagnosis, height, weight, gravidity, parity, exogenous estrogen administration, medical disorders, blood pressure, macroscopic and microscopic appearance of both ovaries, histological type and stage of disease, treatment and survival. In all patients except those with diabetes mellitus (DM), a 75-g oral glucose tolerance test (OGTT) was performed for assessment of carbohydrate metabolism. Hypertension and DM in untreated patients and obesity were diagnosed according to the standard criteria used in our department. These criteria are: a diastolic blood pressure of at least 90 mmHg or a systolic pressure of at least 140 mmHg on two 6-h periods, a fasting blood glucose level of more than 140 mg/dl or an abnormal result in the OGTT, and a body-mass index (BMI) of more than 26. These disorders were considered risk factors for the development of endometrial carcinoma.

Except for two with distant metastasis who were treated by a combination of systemic chemotherapy and local radiotherapy, the patients underwent surgery which included total abdominal hysterectomy, bilateral salpingo-oophorectomy, peritoneal cytology, pelvic lymphadenectomy, and selective paraaortic lymphadenectomy. After surgery, patients with carcinoma confined to the uterine corpus invading more than one-third of the myometrial thickness, and those with carcinoma involving the cervix were given adjuvant radiotherapy of 50 Gy to the whole pelvis. Patients with invasion of less than one-third of the myometrial thickness received no radiotherapy. Patients with carcinoma detected outside the uterus including gross organ involvement, positive peritoneal cytology, positive pelvic and paraaortic lymph nodes, or disease in the adnexa were given adjuvant systemic chemotherapy. All the patients were staged retrospectively according to the 1988 International Federation of Gynecology and Obstetrics (FIGO) surgical staging of endometrial carcinoma. They were then coded and their data were input to a computer. The data were analyzed by chi-squared test or Fisher’s exact test (two-tailed) as appropriate. Survival curves were estimated using the Kaplan-Meier product limited method and generalized Wilcoxon test. Statistical significance was defined as P<0.05.

Results

Seventy-six patients with endometrial carcinoma were investigated. Their mean age at diagnosis was 57.6 years, and 81.5% of them were 50 years old or more. No cancers with clear cells or serous papillary histology were observed. Table I shows the clinical details, disease stage, histology, and follow-up data for all patients. The minimum follow-up period was 12 months, and 61 (80.3%) and 37 (48.7%) patients were followed up for at least 3 and 5 years, respectively. During the follow-up, 15 patients died of progression or recurrence of endometrial carcinoma, and one patient who had no sign of malignant recurrence died of myocardial infarction. No patients took oral contraceptives or estrogen for more than three months. Neither thecal or granulosa cell tumor nor a polycystic appearance was noticed in ovaries in any of the 76 patients. None of the cases was associated with a significantly elevated LH/FSH ratio.

According to the above criteria, 50 (65.7%) patients were defined as postmenopausal, 16 (21.0%) as premenopausal, and 10 (13.1%) as unclassified. The characteristic features in the 10 unclassified patients were: regular menstruation-like bleeding with high FSH and low E2 levels in five cases, amenorrhea with low FSH and high E2 levels in three, and amenorrhea with high FSH and high E2 in two. The details of these patients are shown in Table II.

The clinical and clinicopathological features of the premenopausal and postmenopausal groups are compared in Tables III and IV. Figure 1 shows the Kaplan-Meier survival curves for the premenopausal and postmenopausal groups.
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**Table I. Clinical Details of All Patients**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>BMI (17.5-39.4)</th>
<th>Parity (0-5)</th>
<th>Hypertension</th>
<th>DM</th>
<th>Stage</th>
<th>Histology</th>
<th>Follow-up (12-137 months)</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>Low (&lt;20)</td>
<td>Para 0</td>
<td></td>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>40-49</td>
<td>Normal (20-26)</td>
<td>Para 1</td>
<td></td>
<td>11</td>
<td></td>
<td></td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>50-59</td>
<td>High (&gt;26)</td>
<td>Para 2</td>
<td></td>
<td>11</td>
<td></td>
<td></td>
<td>11</td>
<td>16</td>
</tr>
<tr>
<td>60-69</td>
<td></td>
<td>Para 3 or more</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11</td>
<td>21</td>
</tr>
<tr>
<td>&gt;70</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>(37-82 years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11</td>
</tr>
</tbody>
</table>

BMI, body-mass index; DM, diabetes mellitus.

**Table II. Details of 10 Patients Defined as “Unclassified”**

<table>
<thead>
<tr>
<th>Age (years)*</th>
<th>Height (cm)*</th>
<th>Weight (kg)*</th>
<th>BMI*</th>
<th>Parity*</th>
<th>Unmarried</th>
<th>Nulliparity</th>
<th>Obesity</th>
<th>Hypertension</th>
<th>DM</th>
<th>Gl in histology</th>
<th>Early stage</th>
<th>Advanced stage</th>
<th>Death due to disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>52.4 ± 6.9</td>
<td>153.7 ± 4.2</td>
<td>61.1 ± 13.7</td>
<td>25.7 ± 5.1</td>
<td>1 (10%)</td>
<td>4 (40%)</td>
<td>1 (10%)</td>
<td>4 (40%)</td>
<td>6 (60%)</td>
<td>4 (40%)</td>
<td>6 (60%)</td>
<td>2 (20%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* mean ± S.D.; 1, Stage Ia + Ib in FIGO classification; 2, Stage III + IV in FIGO classification; BMI, body-mass index; DM, diabetes mellitus.

Our clinicopathological study revealed that premenopausal carcinoma was significantly more well differentiated (63.1%: including adenoacanthoma) and relatively less advanced (31.1% of cases at stages III and IV) than postmenopausal carcinoma (38% and 46%, respectively). Also, the premenopausal patients showed a significantly higher incidence of obesity and diabetes, and a relatively lower incidence of hypertension, these differences were not significant.

Our clinicopathological study revealed that premenopausal carcinoma was significantly more well differentiated (63.1%: including adenoacanthoma) and relatively less advanced (31.1% of cases at stages III and IV) than postmenopausal carcinoma (38% and 46%, respectively). Also, the premenopausal patients showed a significantly higher percentage survival than the postmenopausal patients. In addition, two premenopausal patients with stage III A disease were diagnosed only by positive peritoneal cytology and had no extrauterine invasion. No premenopausal patient died of the disease. The clinicopathological characteristics of the “unclassified” group were similar to those of the postmenopausal group except for the percentage incidence of well differentiated carcinoma.

**Discussion**

A well recognized problem inherent to a study like the present one is how to define "post-
menopause". In general, menopause is defined arbitrarily as the absence of menses for 6 months or longer in climacteric women. However, the majority of perimenopausal patients do not remember their last menstrual period exactly. 

Pre/postmenopausal endometrial carcinoma is hardly distinguishable from normal menstrual flow. According to morphological criteria, postmenopausal ovaries are devoid of follicles, but it is well recognized that occasional ovulation does occur in women who are ostensibly postmenopausal. Therefore, we used endocrinological criteria in addition to details of menstrual history in defining menopause.

Another problem that has been pointed out in clinical studies of endometrial carcinoma is the inaccuracy of clinical staging (FIGO, 1971) for prediction of disease spread. However, for our surgical specimens, it was possible to apply the surgical staging system for endometrial carcinoma (FIGO, 1988). The rationale for using surgical rather than clinical staging was based on the ability of the former to determine the full extent of disease.

Endometrial carcinoma in premenopausal women, defined by these criteria, accounted for 21.0% of cases seen at our department. This is considerably lower than the incidence reported in several series which examined the occurrence of endometrial carcinoma in premenopausal women, but similar to or slightly higher than the figures of Geisler et al. and Quinn et al. The apparent discrepancy between our results and those of other series may be readily explained by the fact that in all the other studies, premenopause was determined only by inquiring about the menstrual history of the patients. The incidence of endometrial carcinoma in our patients who were 40 years of age or younger was 3.9%, similar to the figures in other reports.

The clinical-pathological comparison between the premenopausal and postmenopausal groups demonstrated that the ratio of well differentiated tumors was higher, the incidence of advanced-stage tumors significantly lower, and the prognosis of endometrial carcinoma significantly better in the premenopausal patients. Although our results generally agree with most of the previous reports, they differ in that the incidence of early-stage tumors (stages IA and IB of the surgical staging system) in premenopausal patients was not significantly higher than that in postmenopausal patients. This difference may be attributable to ethnic factors as mentioned below, or to a difference in examining the spread of the disease. We collected specimens which were enough for application of the surgical staging system, whereas the authors of the previous reports did not. On the other hand, our results demonstrated more clearly the favorable prognosis of premenopausal carcinoma. This was due to exclusion of the "unclassified" group, since the clinicopathological characteristics of this group were mostly similar to those of the postmenopausal group, except for the percentage of well differentiated tumors.

Our present study showed that nulliparity may be a characteristic predisposing factor for the development of premenopausal endometrial carcinoma. The incidences of obesity and DM were relatively high in the premenopausal group. These findings also agree with previous reports. Although polycystic ovarian disease is regarded as a characteristic risk factor for premenopausal endometrial carcinoma, no evidence of polycystic histology was evident in the ovaries of our premenopausal patients. This difference may have been due to the small number of our patients who were 40 years of age or younger. Several previous reports defined women in this category as premenopausal.

On the other hand, the incidence of hypertension in our premenopausal patients was considerably lower than that in most of the above reports. Whether or not such ethnic differences do, in fact, exist can only be determined in a larger study. However, several ethnic differences in the epidemiology of endometrial carcinoma are well known. The incidence and aggressiveness of endometrial carcinoma vary widely among countries, tending to be higher in the West, and lower in Asia and Africa. An age-adjusted study in the USA showed that the incidence of endometrial carcinoma...
in white women was more than 50% higher than that in black women; whereas the mortality due to the disease in black women was twice as high as in whites. Such differences in risk factors, therefore, might be attributable to the ethnic background and life style of study populations.

It is interesting to speculate that premenopausal and postmenopausal patients have different spectra of tumor differentiation and invasion, which in turn might be related to different etiological factors. Some investigators\(^\text{24, 25}\) have proposed two variants of carcinoma. One seems to be estrogen-dependent, and is associated with adenomatous hyperplasia, a higher degree of histologic differentiation-grading, shallower myometrial invasion, and better prognosis. The other is hormone-independent and carries a worse prognosis. Our present findings do not allow direct identification, but provide indirect support for such a dichotomous disease process except for "shallower myometrial invasion".

In conclusion, endometrial carcinoma was shown to develop in premenopausal women whose ovari-an functions were considered normal, but in most cases the cancer was well differentiated and limited to the uterus. Although the disease invaded the myometrium deeply in some patients, who then required adjuvant therapy, the prognosis was excellent.

References