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Endometrial cancer in women 45 years of age or younger: A clinicopathological analysis

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KEY WORDS
Endometrial cancer
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Objective: The purpose of this study was to evaluate the experience with endometrial carcinoma in women ≤45 years of age at Ochsner Clinic Foundation, New Orleans, La.
Study design: We evaluated the clinical history, treatment, and follow-up of 38 women ≤45 years of age diagnosed with endometrial cancer.
Results: Thirty-eight patients received primary treatment for endometrial cancer: stage I, 32 (84.2%); stage II, 1 (2.6%); stage III, 4 (10.5%); stage IV, 1 (2.6%). Tumors were well differentiated in 20 (52.6%), moderately differentiated in 10 (26.3%), and poorly differentiated in 8 (21.1%). At end of study period 32 women (84.2%) were alive with no evidence of disease, 5 had died of recurrent disease, and 1 died of metastatic breast cancer.
Conclusion: Patients ≤45 years of age had lower incidence of advanced stage disease, higher degree of tumor differentiation, and better prognosis compared to patients older than 45 years.

Endometrial carcinoma is the most common malignancy of the lower female genital tract in the US.[1] Approximately 40,880 new cases develop in the US each year, according to the year 2005 figures from the American Cancer Society. This is about 1.3 times the frequency of ovarian cancer and approximately twice the number of new cases of cervical cancer.[1] Overall, about 1 woman in 50 in the US will develop endometrial carcinoma during her life.

Endometrial adenocarcinoma occurs during the reproductive and menopausal years. The median age for adenocarcinoma of the uterine corpus is 61 years; most patients are between the ages of 50 and 59 years. Approximately 5% of women will have adenocarcinoma before age 40 years, and 20% to 25% will be diagnosed before menopause.[2] Multiple factors increase the risk of developing endometrial carcinoma, including obesity, nulliparity, unopposed estrogen, and late menopause. Most young patients who develop endometrial cancer are obese, in many instances massively overweight, often with anovulatory menstrual cycles. Combination oral contraceptive use decreases the risk for development of endometrial cancer.[2]

Postmenopausal bleeding and abnormal premenopausal bleeding are the primary symptoms of endometrial carcinoma. All postmenopausal women with uterine bleeding should be evaluated for endometrial cancer. As a patient's age increases after menopause, the probability that uterine bleeding is caused by endometrial cancer progressively increases.[2] According to Feldman et al, a woman >70 years has about a 50% chance of having cancer when vaginal bleeding is present.[3] A

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high index of suspicion must be maintained if the diagnosis of endometrial cancer is to be made in the young patient. Prolonged and heavy menstrual periods, and intermenstrual spotting, may indicate cancer, and endometrial sampling is advised. Most young patients who develop endometrial cancer are obese, in many instances massively overweight, often with anovulatory menstrual cycles.

Adenocarcinoma, the most common histologic type of endometrial cancer, is sometimes preceded by a predisposing lesion: atypical endometrial hyperplasia. Patients with atypical endometrial hyperplasia have a 30% to 50% risk of simultaneous invasive endometrial cancer.[4] There are various types of endometrial carcinoma.[1]

Endometrial cancer is staged using the surgicopathologic staging system adopted by the International Federation of Gynecology and Obstetrics (FIGO) in 1988.[5] Tumor stage is a well-recognized prognostic factor for endometrial carcinoma; higher stage of disease indicates a worse prognosis.

Another major determinant of prognosis is the histologic grade of the tumor.[2] As the tumor loses its differentiation, survival decreases. A better prognosis for endometrial carcinoma is associated with endometrioid adenocarcinoma, as well as better differentiation of the tumor with or without squamous elements, and secretory carcinomas. Approximately 80% of all endometrial carcinomas fall into the favorable category.[1] Poor prognostic histologic types are papillary serous carcinomas, clear cell carcinomas, and poorly differentiated carcinoma with or without squamous elements.[1]

The incidence of endometrial adenocarcinoma has increased in recent years,[6] but the disease remains uncommon in premenopausal women. Depending on the age cut-off used for the study, proportions between 2% and 14% have been reported.[7-9] A literature review suggests that endometrial adenocarcinoma in young women is often associated with early stage disease, high differentiation of the tumor, and a good prognosis.[7,9-17] Endometrial cancer is frequently unsuspected clinically or pathologically in women under the age of 45 years because greater than 75% of cases occur in patients over 50.[18] The presence of obesity and abnormal vaginal bleeding should encourage a greater practice of endometrial sampling.

The purpose of this retrospective study was to evaluate the risk factors and outcomes of 38 women $\leq$45 years of age with endometrial cancer.

Material and methods

From 1982 through 2002, 463 women underwent therapy at Ochsner Clinic Foundation and Hospital, New Orleans, LA, for adenocarcinoma of the endometrium. Patients with other types of malignancies (leiomyosarcoma, fibrosarcoma, carcinosarcoma, or choriocarcinoma) were excluded. Thirty-eight patients were $\leq$45 years of age, and 425 patients were >45 years of age.

From the hospital records of the 38 patients, data pertaining to age, parity, body mass index (BMI), prediagnostic hormone treatment, result of the last Papanicolaou smear, preceding symptoms, smoking history, past medical history, family history, and postoperative hormone replacement therapy were tabulated. International Federation of Gynecology and Obstetrics (FIGO) staging and grading were investigated.

Tumors were staged according to the FIGO guidelines of 1988.[5] The BMI was calculated as body weight divided by the square of height (kg/m^2). A BMI of 25 indicated the patient was overweight and above 30 as obese.[19]

Statistical analysis consisted of the use of Pearson chi-square or Fisher exact test where appropriate. Survival curves were estimated using the Life-table analysis method. Statistical significance was defined as $P < .05$. SPSS 6.1 statistical analysis software was used (Chicago, IL).

Results

Of the 38 patients in the study group, the mean age at diagnosis was 39 years (range 28-45). The clinical details of each patient are summarized in Table I. Clinical details for the 425 patients >45 years of age are limited to stage and survival data. Three (7.9%) patients had a previous history of colon cancer, 1 (2.6%) had a history of breast cancer, and 1 (2.6%) had a history of thyroid cancer. Thirteen (34.2%) women had 1 first-degree relative with a history of malignant disease, which involved breast, ovarian, endometrial, or colon cancer. Three (7.9%) women had more than 1 first-degree relative with a history of malignant disease.

The presenting symptom was abnormal uterine bleeding in 35 (92.1%) cases and pelvic pain related to a pelvic mass in 1 (2.6%). One patient was diagnosed by dilatation and curettage (D&C) secondary to the evaluation of a high grade squamous intraepithelial lesion pap, and another patient had an endocervical biopsy that revealed atypical hyperplasia, prompting a D&C that resulted in the diagnosis of endometrial cancer. The diagnosis of endometrial cancer was made by endometrial biopsy in 14 (36.8%) patients and by D&C in 18 (47.4%). Six (15.8%) patients failed to have carcinoma diagnosed before hysterectomy.

All women underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy. In 25 (65.8%) instances, pelvic lymph node dissections were also performed. Tumors were classified as endometrioid adenocarcinoma in 34 (89.5%), adenosquamous carcinoma in 3 (7.9%), and adenoacanthoma in 1 (2.6%). Stage I disease was found in 32 (84.2%), stage II in

Table I Clinical details of all patients

		No. of patients	Percent
Age (28–45 y)	<40	19	
	41–45	19	
Body mass index (18–63)	Low (<20)	2	5.3%
	Normal (20–25)	4	10.5%
	Overweight (25–30)	2	13.2%
	Obese (>30)	27	71.0%
Parity (0–3)	Para 0	23	60.5%
	Para 1	4	10.5%
	Para 2	8	21.1%
	Para 3	3	7.9%
Stage	Stage Ia	12	31.5%
	Stage Ib	20	52.6%
	Stage II	1	2.7%
	Stage III	4	10.5%
	Stage IV	1	2.7%
Histology	G1	20	52.6%
	G2	10	26.3%
	G3	8	21.1%
Follow-up (1–260 months)	<3 years	13	34.2%
	3–5 years	10	26.3%
	>5 years	15	39.5%
Medical history	Diabetes	9	23.7%
	Hypertension	8	21.1%
Cervical cytology	Normal	19	79.2%
	Squamous abnormal	3	12.5%
	Glandular abnormal	2	8.3%
Smoking history	Current	8	22.2%
	Never used	28	77.7%
Oral contraceptive use	Yes	8	21.0%
	No	30	79.0%

1 (2.6%), stage III in 4 (10.5%), and stage IV in 1 (2.6%). Tumors were classified as well differentiated in 20 (52.6%), moderately differentiated in 10 (26.3%), and poorly differentiated in 8 (21.1%). Eleven patients had postoperative radiation therapy.

Patient follow-up after surgery ranged from 1 month to 260 months. The follow-up period was <3 years for 13 patients, between 3 and 5 years for 10, and >5 years for 15. During the follow-up period, 5 patients died of progression or recurrence of endometrial carcinoma, and 1 patient who had no sign of recurrence of endometrial cancer died of widely metastatic breast cancer. The Figure shows the Life-table analysis curves for patients 45 years of age or younger (n = 38) and for those older than 45 years (n = 425). The estimated 5-year survival rate for all patients diagnosed with endometrial cancer during the study period was 71%. The estimated 5-year survival rates of women age 45 years or younger and women over the age of 45 were 82% and 70%, respectively. The 5-year survival for patients 45 years of age or younger and patients greater than 45 years of age are shown in Table II. There were not enough patients with stage II or stage IV disease to calculate a survival curve.

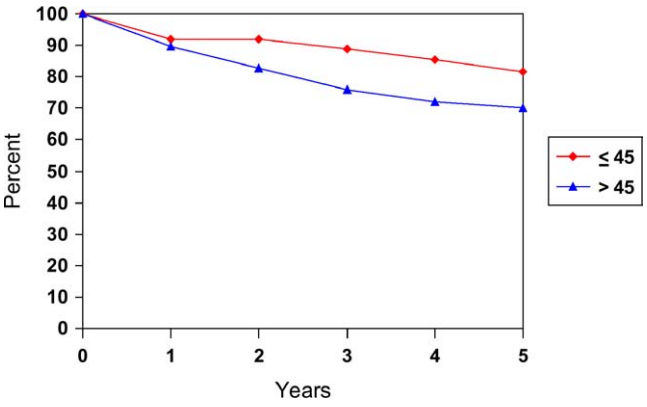

Figure Survival curve (Life-table analysis curves). Age less than or equal to 45 years and combined stage versus age greater than 45 years and combined stage.

Table II Five-year survival by stage for patients less than or equal to 45 years of age versus patients greater than 45 years of age

	Age	
Stage	≤45 years	≥46 years
1	93.1	79.9
2	0.0	68.7
3	66.7	42.3
4	0.0	13.2

Comment

Endometrial cancer in young women can be difficult to diagnose. It is uncommon and usually presents as abnormal uterine bleeding at an age when dysfunctional bleeding is much more common. Obesity seems to be strongly associated with the development of endometrial cancer in young women.[7,12,20-22] This theory is supported in the present review by the finding that 71% of the patients studied were classified as obese with a BMI greater than 30.

In our study, 92.1% of patients presented to their physicians with abnormal vaginal bleeding. The most common physical abnormality was patient obesity. The combination of abnormal vaginal bleeding and obesity should alert the physician to the possibility of underlying endometrial abnormalities, yet the diagnosis of adenocarcinoma was first made after hysterectomy in 15.8% of cases.

No statistically significant correlation was found when age, reproductive history, smoking history, race, past medical history, or family history was compared with histologic grade or surgical stage of the tumor.

The incidence of endometrial carcinoma in our patients who were 45 years of age or younger was 8.1%, similar to the findings in other reports.[7,11,12,20,21,23]

Young patients with endometrial carcinoma tend to have prognostically favorable histologic types, such as well-differentiated adenocarcinoma (G1) and adenoacanthoma.[12] In addition, young patients with endometrial carcinoma were more likely to present with stage I disease. Quinn et al[15] reviewed the literature and their own series of endometrial cancer in premenopausal women and reported that 154 of 231 patients (67%) had a well-differentiated tumor, but on the other hand, 11 of 231 patients (4.8%) exhibited adenosquamous carcinoma, a relatively unfavorable histologic type. Of 106 premenopausal patients investigated by Quinn et al, 96 (91%) of patients were diagnosed with stage I disease. In the series by Crissman et al,[7] all 32 patients had well-differentiated tumors and 12 of the 32 were adenoacanthoma. In the series by Yasumizu et al,[24] 30 of the 76 patients (39.5%) had a well-differentiated tumor with 7 patients (9.2%) having adenosquamous carcinoma. In addition, 40 out of 76 patients (52.6%) had stage I disease.

In our study, the association between cancer cell type and stage of disease was statistically significant. Patients with endometrial adenocarcinoma were more likely to present with stage I disease, whereas patients with adenosquamous carcinoma were more likely to have a higher stage of disease ($P = .040$). There was no statistical significance in relation to cell type versus grade of tumor.

In our study, 84.2% of patients presented with stage I disease. The incidence of early stage disease and well-differentiated tumors in our series is more consistent with the results obtained by Quinn et al,[15] and slightly higher than the results obtained by Yasumizu et al.[24]

In general, endometrial carcinoma in young women has a favorable histology (well-differentiated tumor) and early stage disease (stage I). In our study, 32 of 37 patients were alive and without evidence of tumor recurrence, with 15 patients (39.5%) having a follow-up time greater than 60 months. Of the 6 remaining patients, 5 died of disease and 1 died of widely metastatic breast cancer 4 years after the diagnosis of endometrial cancer.

Statistical analysis revealed a positive association between both recurrence and survival compared with stage of disease and histologic grade of tumor. In terms of recurrence, there was a statistically significant correlation between tumor recurrence and both stage of disease and histologic grade, $P = .001$ and $P = .002$, respectively. Patients with early stage disease or a high degree of tumor differentiation (G1) had a lower rate of recurrence than patients with advanced disease or poorly differentiated tumor (G2 or G3).

Analysis of survival curves demonstrates that patients with endometrial carcinoma who are 45 years of age or younger have a higher 5-year survival rate compared with those older than 45, 82% versus 70%, respectively. Patients 45 years of age or younger with endometrial cancer also had a higher incidence of stage I disease than those older than 45, 84% versus 72%, respectively. The 5-year survival for patients with stage I disease was 92% for those 45 years of age or younger compared with 79% for those older than 45. Stage for stage, patients with endometrial cancer 45 years of age or younger had a better 5-year survival than those older than 45. The reason for improved survival in younger patients compared with older patients cannot be determined from our small sample size. However, likely reasons for improved survival would include a higher ratio of grade I tumor and stage I disease in our patient population. Endometrial carcinoma related to obesity generally has an improved prognosis in younger patients than endometrial carcinoma in older patients with a low BMI.[2] We have found this to be true in our practice as well (Table I). Patients who are younger, obese, and who present with abnormal bleeding should undergo endometrial biopsy. The clinician's index of suspicion of endometrial cancer should be raised in those patients who are at an increased risk.

The clinicopathologic comparison between the patients 45 years or younger and those older than 45 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 those 45 or younger.

In conclusion, patients with endometrial carcinoma 45 years of age or younger were more likely to be obese. Histologically, the tumors of these patients had prognostically favorable histologic findings, such as well-differentiated tumors (G1) and early stage disease (stage I). Thus, the survival rate of patients 45 years of age or younger was significantly better that of patients older than 45 in our series.

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