Body Mass Index as a Prognostic Factor in Endometrioid Adenocarcinoma of the Endometrium

E. Jason Gates, MD; Lawrence Hirschfield, MD; Roland P. Matthews, MD; and O. W. Stephanie Yap, MD
Atlanta, Georgia

Objective: To determine if body mass index (BMI) influences tumor expression of HER-2/neu, estrogen and progesterone receptors (ER/PR), and survival in women with endometrial adenocarcinoma.

Methods: Patients diagnosed between January 1992 and December 2001 with endometrioid adenocarcinoma of the uterus were identified. Clinical and pathologic data were retrospectively collected. HER-2/neu, estrogen and progesterone receptor expression were determined by immunohistochemistry. Differences in these variables and other prognostic factors were analyzed and correlated with effect on survival.

Results: One-hundred-sixty-five patients were included in this analysis. Lower BMI was associated with high stage (p=0.04) and HER-2/neu expression (p=0.04). Black race, high grade, high stage and lack of ER/PR expression were all associated with decreased survival. Despite having better prognostic factors, women with a BMI >25 had a lower survival than women with a BMI <25 (p=0.36). When five-year survival rates were calculated for BMI category and stratified by prognostic factors, for almost every high risk factor, survival was lower in overweight patients.

Conclusion: In patients with endometrioid adenocarcinoma, low BMI is associated with high stage and tumor expression of HER-2/neu. Despite better prognostic factors, overweight women experience poorer survival.

Key words: endometrial adenocarcinoma ■ prognosis ■ body mass index

 From the Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Morehouse School of Medicine, Atlanta, GA. Send correspondence and reprint requests for *J Natl Med Assoc.* 2006;98:1814–1822 to: Dr. Roland P. Matthews, Department of Obstetrics and Gynecology, Morehouse School of Medicine, 720 Westview Drive SW, Atlanta, GA 30310; phone: (404) 616-9294; fax: (404) 616-4131; e-mail: rmatthews@msm.edu

INTRODUCTION

Carcinoma of the endometrium continues to be the most common gynecologic malignancy in the United States, with 41,200 cases expected to be diagnosed in 2006.[1] Seven-thousand-three-hundred-fifty of these patients will die this year from their disease, making endometrial cancer the eighth leading cause of cancer deaths in women.[1] Excess exposure to estrogen is considered to be one of the risk factors for the development of endometrial cancer.[2-4] Long periods of anovulation, unopposed exogenous estrogen intake, nulliparity and late menopause serve as examples. Obesity is yet another common denominator associated with excess estrogen exposure, even in postmenopausal women. The ovaries in postmenopausal women, together with the adrenal gland, continue to produce androstenedione. The aromatase enzyme found in adipose cells converts this androgen to estrone[5] and, over time, this relatively weak estrogen can stimulate chronic endometrial proliferation and occasionally malignant change.[6,7]

Previously, endometrial cancer has been described as consisting of two groups.[8,9] The first group (type 1) is characterized by well-differentiated indolent tumors that present with localized disease. These patients usually have a favorable outcome; stage-1 disease carries a five-year survival rate of 86%.[10] These patients are generally obese, and it is in this group that excess estrogen exposure is thought to play a carcinogenic role. In contrast, the second group (type 2) is characterized by more-aggressive tumors with associated advanced-stage disease, higher tumor grade and nonendometrioid histology. These patients are generally more slender than their type-1 counterparts, and their tumors are believed to be influenced by nonestrogenic factors and are likely under alternative oncogenic control.[2]

Immunohistochemical analyses have effectively shown expression of estrogen receptors (ER) and progesterone receptors (PR) in low-grade, early-stage endometrial cancers.[11,12] Receptor concentration in these tumors may be an indication of hormone responsiveness.[13] Higher-grade, more-advanced tumors, however, have been shown to lack expression of these receptors.[11,12,14] Genetic alterations as an alternative mechanism have led to the study of oncogenes (HER-2/neu, C-FMS, K-RAS and C-MYC) as well as tumor suppressor genes (p53, PTEN).[15-20] Several groups have demonstrat-

ed an association with HER-2/neu expression and disease characterized by high grade, high stage and poor prognosis.[21-24]

In an effort to define the difference between type-1 and type-2 endometrial cancer, we set out to determine if the measure of a patient's body mass index (BMI) influences tumor expression of HER-2/neu, estrogen and progesterone receptor, prognostic features as well as patient survival.

METHODS

The tumor registry at our institution was queried, and patients diagnosed with endometrial carcinoma between January 1992 and December 2001 were identified. The corresponding office and hospital charts were abstracted for pertinent patient demographics, tumor characteristics, and disease-free and overall survival. Stage was classified as low (1, 2) and high (3, 4). Depth of myometrial invasion was designated as < or >50%. Patients with nonendometrioid histology were excluded from the analysis.

The patient's BMI was calculated by using the patient's weight in kilograms divided by the square of the height in meters. Using the National Institute of Health definition of overweight as having a BMI of >25, patients were classified as having a BMI <25 (normal weight) or >25 (overweight).

The original hematoxylin and eosin slides were reviewed by a single pathologist and confirmed for cell type, grade, depth of myometrial invasion and stage. A representative section was selected, and the corresponding paraffin embedded block was used for the detection of HER-2/neu, ER and PR. These results were interpreted by a single pathologist, who was blinded to all patient and tumor characteristics.

Paraffin-embedded tissue blocks corresponding to a representative section of an individual tumor were obtained from 128 subjects. Immunohistochemistry was performed using a DAKO autostainer. HER-2/neu expression was determined with the use of the DAKO HercepTest (DAKO Corp., Carpenteria, CA). All tissues were fixed in 10% neutral buffered formalin and subjected to heat-induced epitope retrieval. Sections were deparaffinized, rehydrated and retrieved. Tissue samples were placed on the immunoautostainer and peroxidase-blocking agents were applied, followed by the primary antibody, peroxidase-labeled polymer, substrate chromogen polymer (DAB) and, finally, counterstain. Tissue samples were dehydrated, cleared in xylene, mounted and coverslipped. A positive control was used in conjunction with each specimen.

HER-2/neu expression was interpreted on a scale of 0–3+, assessing for the presence and intensity of membrane staining. A score of 0 indicated no staining or <10% of the tumor cells having membrane staining. A score of 1+ indicated a faint or barely perceptible partial membrane staining in >10% of the tumor cells. A score of 2+ indicated a weak-to-moderate complete membrane staining in >10% of the tumor cells. A score of 3+ indicated a strong complete membrane staining in >10% of the tumor cells. For our analysis, tumors were considered to be HER-2/neu negative for a score of 0 and HER-2/neu positive for a score of 1+–3+.

ER and PR expression was interpreted on a scale of

Table 1. Patient characteristics

	Total (n=165)	BMI <25 (n=56)	BMI >25 (n=109)	p Value
Age				
Mean	64.24	65.18	63.75	0.51
Range	27–95	32–95	27–93	
Race				0.03
White	132 (81.0%)	48 (87.3%)	84 (77.8%)	
Black	17 (10.4%)	1 (1.8%)	16 (14.8%)	
Other	14 (8.6%)	6 (10.9%)	8 (7.4%)	
BMI				
Mean	30.64	22.26	39.64	
Range	17.49–60.29	17.49–24.78	25.11–60.29	
Parity				
Mean	1.86	1.17	2.20	0.002
Range	0–13	0–3	0–13	
0	48 (30.0%)			
≥1	112 (70.0%)			
Smoker	20 (12.1)	6 (10.7%)	15 (13.8%)	0.58
Tamoxifen	8 (4.8%)	3 (5.4%)	5 (4.6%)	0.83
HRT	27 (16.4%)	20 (35.7%)	7 (6.4%)	0.00
Ca. Hx	18 (10.9%)	6 (10.4%)	12 (11.0%)	0.95

BMI: body mass index; HRT: hormone replacement therapy; Ca. Hx: cancer history

0–4+, assessing for the presence of nuclear staining. A score of 0 indicated ≤10% of the tumor cells had nuclear staining. A score of 1+ indicated between 11–25% of the tumors cells stained. A score of 2+ indicated that between 26–50% of the tumor cells stained. A score of 3+ indicated that between 51–75% of the tumor cells stained. A score of 4+ indicated that between 76–100% of the tumor cells stained. For our analysis, tumors were considered to be ER or PR negative for a score of 0, and positive for a score of 1+–4+.

Differences in prognostic factors were compared among the groups using Chi-squared analysis for discrete variables or Student's t test for continuous variables. If data were ordinal, such as stage of disease at diagnosis, a Chi-squared analysis for trend was performed. Analysis of variance (ANOVA) was used to examine differences in prognostic factors for >2 groups for continuous variables such as age. Survival curves were plotted using the Kaplan-Meier method and differences were tested by the Breslow statistic. Finally, Cox's proportional hazard model was used to examine survival among groups adjusting covariates. Several multivariate models were examined, including various combinations of prognostic variables. The final model selected was the one with the greatest likelihood ratio. The statistical analysis was performed with the SPSS® (version 10.0), and statistical significance was set at $p \leq 0.05$.

RESULTS

From January 1992 through December 2001 181 patients with carcinoma of the endometrium were identified. Eleven (6%) had clear cell or papillary serous histology, five (2.8%) had carcinosarcoma histology and 165 (91.2%) had endometrioid histology. Only patients with endometrioid histology were included in this analysis.

Patient characteristics are outlined in Table 1. The mean age of our study population was 64.24 years. Eighty-one percent were white, 10.4% were black, and 8.6% were either Hispanic or of another background. The mean parity was 1.86, with 30% of all patients being nulligravida. The mean BMI for all patients was 30.64 with a range from 17.49–60.29.

Table 2. Tumor characteristics

	Total (n=165)	Mean BMI	p Value	BMI <25 (n=56)	BMI >25 (n=109)	p Value
Her-2/neu						
Positive	21 (16.4%)	26.62		12 (24.5%)	9 (11.4%)	
Negative	107 (83.6%)	30.88	0.04	37 (75.5%)	70 (88.6%)	0.05
Estrogen Receptor						
Positive	113 (90.4%)	30.24		45 (93.8%)	68 (88.3%)	
Negative	12 (9.6%)	29.44	0.77	3 (6.2%)	9 (11.7%)	0.32
Progesterone Receptor						
Positive	104 (83.2%)	30.81		37 (77.1%)	67 (87.0%)	
Negative	21 (16.8%)	26.94	0.07	11 (22.9%)	10 (13%)	0.15
Stage						
Low (1, 2)	135 (84.9%)	31.35		41 (78.8%)	94 (87.9%)	
High (3, 4)	24 (15.1%)	27.30	0.04	11 (21.2%)	13 (12.1%)	0.14
Grade						
Low (1)	60 (36.4%)	30.89		20 (35.7%)	39 (36.1%)	
High (2, 3)	105 (63.6%)	30.44	0.76	36 (64.3%)	69 (63.3%)	0.96
Depth of Invasion						
<50%	110 (68.8%)	30.97		36 (67.9%)	74 (69.2%)	
≥50%	50 (31.2%)	30.07	0.55	17 (32.1%)	33 (30.8%)	0.87
Cervical Involvement						
Yes	27 (16.8%)	32.98		4 (7.4%)	23 (21.5%)	
No	134 (83.2%)	30.25	0.15	50 (92.6%)	84 (78.5%)	0.02
Lymph Node Metastases						
Yes	12 (10.3)	27.02		6 (15.0%)	6 (7.9%)	
No	104 (89.7%)	30.56	0.17	34 (85.0%)	70 (92.1%)	0.23
Cytology						
Positive	12 (9.7%)	29.81		4 (9.8%)	8 (9.6%)	
Negative	112 (90.3%)	30.63	0.78	37 (90.2%)	75 (90.4%)	0.64
LVSI						
Positive	17 (10.6%)	27.23		6 (11.3%)	11 (10.3%)	
Negative	143 (89.4%)	31.10	0.91	47 (88.7%)	96 (89.7%)	0.69

BMI: body mass index; LVSI: lymph-vascular space invasion

Of the 165 patients with endometrioid carcinomas, 56 had BMI of <25 and 109 had BMI of >25. There was no significant difference in regard to age, smoking history or tamoxifen use. There was, however, a significant difference in race distribution between the two groups, with a higher proportion of normal-weight patients being white and a higher proportion of overweight patients being black (p=0.03). There was also a significant difference in parity between the two groups, with the overweight patients having a higher parity than the normal-weight patients (2.20 vs. 1.17, p=0.002). The percentage of patients who currently or previously used hormone replacement therapy was also significantly different, with more normal-weight patients having used than overweight patients (p=0.00).

Tumor characteristics are presented in Table 2. There

Table 3. Race and prognostic factors

	White n (%)	Black n (%)	Other n (%)	p
Her-2/neu				0.28
Negative	66 (80.5)	9 (90.0)	9 (100.0)	
Positive	16 (19.5)	1 (10.0)	0.00	
Progesterone Receptor				0.38
Negative	13 (16.3)	3 (33.3)	1 (11.1)	
Positive	67 (83.8)	6 (66.6)	8 (88.9)	
Stage				0.20
Low	85 (86.7)	12 (75.0)	9 (75.0)	
High	13 (13.3)	4 (25.0)	3 (25.0)	
Grade				0.77
Low	36 (35.3)	6 (35.3)	3 (25.0)	
High	66 (64.7)	11 (64.7)	9 (75.0)	
Lymph Node Metastases				0.38
No	64 (88.9)	10 (90.9)	5 (71.4)	
Yes	8 (11.1)	1 (9.1)	2 (28.6)	
Lymph-Vascular Space Invasion				0.11
No	91 (91.9)	12 (75.0)	10 (83.3)	
Yes	8 98.1)	4 (25.0)	2 (16.7)	

Table 4. Mean body mass index for race and prognostic factors

	White			Black			Other			p*
	n	Mean	SD	n	Mean	SD	n	Mean	SD	
Her-2/neu										0.89
Negative	66	31.60	10.17	9	31.70	4.49	9	28.74	8.90	
Positive	16	25.90	7.07	1	34.80		0			
PR										0.26
Negative	13	24.79	4.73	3	32.36	4.50	1	22.76		
Positive	67	31.55	10.25	6	32.74	4.98	8	29.49	9.20	
Stage										0.03
Low	85	31.46	9.71	12	35.91	9.28	9	32.09	7.58	
High	13	27.21	7.30	4	31.74	3.25	3	21.70	0.94	
Grade										0.54
Low	36	31.09	8.87	6	38.34	11.94	3	27.42	8.89	
High	66	30.54	9.94	11	31.71	4.80	9	30.18	8.14	
LN Mets										0.40
No	64	30.69	9.13	10	33.94	8.94	5	31.77	9.27	
Yes	8	27.69	7.95	1	32.73		2	21.16	0.20	
LVSI										0.05
No	91	31.11	9.64	12	36.29	8.90	10	30.98	7.96	
Yes	8	27.50	7.31	4	30.59	4.57	2	22.03	1.04	
Parity										0.13
0	28	29.30	10.98	7	37.24	11.83	3	25.00	3.05	
≥1	72	31.50	9.18	9	33.22	3.89	8	31.69	9.02	

SD: standard deviation; PR: progesterone receptor; LN Mets: lymph node metastases: LVSI: lymph-vascular space invasion

was no significant difference in the mean BMI for all tumor variables except for stage and HER-2/neu expression. Higher stage was associated with a lower mean BMI (27.30 vs. 31.35, p=0.04) as was HER-2/neu expression (26.62 vs. 30.88, p=0.04).

There was no significant difference in the mean BMI in patients with ER/PR-positive tumors vs. ER/PR-negative tumors. Mean BMI was higher in PR-positive patients, but the difference did not reach statistical significance (p=0.07) because of the small sample size.

There was no significant difference in the distribution of stage, tumor grade, degree of myometrial invasion, presence of lymph node metastases, positive cytology or lymph-vascular space invasion (LVSI) when analyzed between patients with BMI of < or >25. HER-2/neu staining was found to be present more often in normal-weight patients than those who are overweight (p=0.05). There was no significant difference in ER or PR staining between the two BMI groups. A higher BMI is thus associated with a lack of HER-2/neu expression, low stage and PR expression, although the latter did not reach statistical significance (p=0.15).

As noted earlier, a significantly higher proportion of black patients had a BMI >25 (Table 1). Table 3 demonstrates that several prognostic factors were in fact worse in blacks but because of small numbers, the differences did not reach statistical significance. After adjusting for race, overweight patients were more likely to have low-stage and negative LVSI (Table 4).

Distribution of tumor characteristics in relation to the tumors' immunohistochemical staining profile is presented in Table 5. Tumors with high stage were more likely to be ER and PR negative (p=0.006 and p=0.00, respectively) as opposed to HER-2/neu staining, which demonstrated no difference. High-grade tumors were more likely to stain positive for HER-2/neu (p=0.003), and negative for ER (p=0.004) and PR (p=0.0). Tumors with deep myometrial invasion were more commonly found to be PR negative (p=0.01) but showed no difference in HER-2/neu or ER staining. Patients with cervical extension of the endometrial cancer were more likely to be ER negative (p=0.01) but demonstrated no difference in HER-2/neu or PR staining. Tumors with lymph node metastases, positive cytology or LVSI showed no difference in HER-2/neu, ER or PR staining. The lack of ER/PR expression is associated with several other poor prognostic pathologic factors, whereas HER-2/neu expression appears to be independent of other prognostic factors.

Table 6 shows the five-year survival rates for selected characteristics. Death from disease was used as the primary endpoint. Black race, high grade, high stage and lack of ER/PR expression were all significantly associated with poorer survival. Despite having better prognostic factors, women with a BMI >25 have lower survival than women with a BMI <25, but it was not statistically significant (p=0.36). Patients with tumors that expressed HER-2/neu also had a worse survival, but that

Table 5. HER-2/neu, ER, PR and prognostic variables

	Her-2/neu (+)	Her-2/neu (-)	p Value	ER (+)	ER (-)	p Value	PR (+)	PR (-)	p Value
Stage									
Low (1, 2)	12 (11.7%)	91 (88.3%)		94 (94%)	6 (6%)		92 (92%)	8 (8%)	
High (3, 4)	6 (28.6%)	15 (71.4%)	0.99	15 (71.4%)	6 (28%)	0.01	11 (52.4%)	10 (47.6%)	0.00
Grade									
Low (1)	5 (11.9%)	37 (88.1%)		37 (94.9%)	2 (5.1%)		38 (97.4)	1 (2.6%)	
High (2, 3)	16 (18.6%)	70 (81.4%)	0.24	76 (88.4%)	10 (11.6%)	0.21	66 (76.7%)	20 (23.3%)	0.00
DOI									
<50%	12 (14.0%)	74 (86.0%)		77 (92.8%)	6 (7.2%)		75 (90.4%)	8 (9.6%)	
>50%	7 (18.0%)	32 (82.0%)	0.80	33 (84.6%)	6 (15.4%)	0.14	28 (71.8%)	11 (28.2%)	0.01
Cx Inv									
Yes	4 (17.4%)	19 (82.6%)		17 (73.9%)	6 (26.1%)		15 (65.2%)	8 (34.8%)	
No	16 (15.5%)	87 (84.5%)	0.72	94 (94.0%)	6 (6.0%)	0.01	88 (88%)	12 (12%)	0.99
LN Mets									
Yes	1 (10.0%)	9 (90.0%)		7 (70.0%)	3 (30.0%)		5 (50.0%)	5 (50.0%)	
No	11 (12.8%)	75 (87.2%)	0.64	77 (92.8%)	6 (7.2%)	0.99	74 (89.2%)	9 (10.8%)	0.99
Cytology									
Positive	5 (45.5%)	6 (54.5%)		7 (63.6%)	4 (36.4%)		6 (54.5%)	5 (45.5%)	
Negative	9 (10.5%)	77 (89.5%)	0.99	78 (92.9%)	6 (7.1%)	0.99	72 (85.7%)	12 (14.3%)	0.99
LVSI									
Positive	4 (30.8%)	9 (69.2%)		9 (69.2%)	4 (30.8%)		8 (61.5%)	5 (38.5%)	
Negative	16 (13.4%)	97 (86.6%)	0.97	101 (92.7%)	8 (7.3%)	0.99	95 (87.2%)	14 (12.8%)	0.99

ER: estrogen receptor; PR: progesterone receptor; DOI: depth of invasion; Cx Inv: cervical involvement; LN Mets: lymph node metastases; LVSI: lymph-vascular space invasion

also was not statistically significant (p=0.14).

A Cox's proportional hazard model was created (Table 7) that included stage, BMI, race, parity, PR expression and HER-2/neu expression. When all factors are adjusted, having a BMI >25 is a potentially potent risk factor (5.4x), but it was not significant (p=0.17). The presence of HER-2/neu was associated with 4x increase in risk of death but also did not achieve statistical significance (p=0.10). Stage, race and lack of PR expression, however, remained significant. Table 8 shows the five-year survival rates for BMI category stratified by parity, HER-2/neu and PR expression, LVSI, stage and grade. In every case, overweight women had a poorer survival when stratified for unfavorable prognostic factors. For example, overweight women with tumors that expressed HER-2/neu had poorer survival than women of normal weight, overweight women who lacked PR expression had poorer survival than women of normal weight, and overweight women with high stage had significantly poorer survival than women of normal weight.

DISCUSSION

BMI was chosen as the primary condition that represents estrogen excess because its presence or absence was readily identifiable. A history of other conditions that may predispose a woman to excess estrogen (infertility, menstrual irregularities) could not be reliably sequestered from hospital or office records. Calculation of the BMI, however, was readily available and served as one reliable indicator of estrogen excess. Anderson et al. also analyzed BMI and its influence on survival.[25] They concluded, as we did, that overweight women had better prognostic factors. Overweight patients in their study had better survival, although it was not statistically significant. This differed from our findings in that overweight patients in our analysis had poorer survival. However, we too were unable to demonstrate statistical significance in this regard.

Unlike other studies,[21,24-26] only tumors of endometrioid histology were included in our analysis. The number of patients that were identified who had tumors of papillary serous, clear cell or mixed mullerian histology was small. Thus, definitive conclusions in regard to obesity status and especially HER-2/neu and hormone receptor expression were unable to be obtained. These tumors may be the result of different oncogenic potential than type-2 endometrioid tumors, may behave more aggressively and skew the survival of the entire population. The omission of these histologic subtypes from analysis gives more strength to any conclusions, as the population of tumors that were analyzed is homogeneous.

The rate of 16.4% HER-2/neu positivity in our analysis conforms to that described by other authors.[23,27,28] In contrast to other studies,[26] we were able to demonstrate a significant difference in HER-2/neu expression between patients who were overweight (negative expression) as opposed to those who were of normal weight (positive expression). This suggests that HER-2/neu may play a role in the development of endometrial cancer in patients who are not overweight and thus not exposed to excess estrogen. Duska et al. reported on BMI in premenopausal endometrial cancer patients and included HER-2/neu expression in their analysis.[26] They did not demonstrate a difference in expression between patients of normal weight and those who are overweight. Their sample size was smaller than

Table 6. Cumulative five-year survival

	n	Survival (%)	p
BMI			0.36
<25	49	87.9	
>25	97	83.1	
Race			0.005
White	117	87.9	
Black	16	55.4	
Other	11	100.0	
Her-2/neu			0.14
Negative	94	85.6	
Positive	17	74.6	
ER			0.001
Negative	11	56.8	
Positive	97	86.2	
PR			0.0001
Negative	17	37.0	
Positive	91	90.0	
Stage			0.003
Low	119	89.0	
High	23	61.9	
Grade			0.001
Low	55	97.4	
High	90	75.9	
Parity			0.69
0	40	80.8	
≥1	103	87.8	

BMI: body mass index; ER: estrogen receptor; PR: progesterone receptor

Table 7. Cox's Proportional Hazard Model— 99 women, 11 deaths

	HR	p	95% CI
Stage (High vs. Low)	4.1	0.06	1.03–15.57
BMI (<25 vs. >25)	5.4	0.17	0.49–59.00
Race			
Black vs. white	4.7	0.05	1.01–22.04
Other vs. white	1.0	0.99	
Parity (0 vs. ≥1)	2.0	0.40	0.62–9.46
PR (Negative vs. Positive)	13.9	0.00	2.96–65.22
HER-2/neu (Positive vs. Negative)	4.0	0.10	0.77–20.80

HR: hazard ratio; CI: confidence interval; BMI: body mass index; PR: progesterone receptor

ours and a BMI cut off of 30 was used. Both of these factors may have influenced the results.

The effect of HER-2/neu on the survival of patients with endometrial cancer has been described by many authors. Most studies support the theory that HER-2/neu expression negatively impacts survival.[21-23] Our data suggest that HER-2/neu expression may negatively affect survival, but we could not show statistical significance. This raises the question of the exact role of HER-2/neu in endometrial carcinogenesis and may lend support to the theory that HER-2/neu may be involved in early endometrial cancer development and that other factors are involved in the overall progression of the disease.[22]

We were unable, however, to show a difference in either ER or PR expression between the two BMI groups. This has been previously demonstrated in premenopausal patients only.[26] The mean BMI was in fact higher in patients with ER- and PR-positive tumors as opposed to negative tumors, but these results did not reach statistical significance. Despite the lack of significance, our data shows that ER- and PR-negative tumors are associated with advanced stage, high grade, deep myometrial invasion (PR only) and cervical involvement (ER only). This is consistent with most other studies, as well.[11,12,19] Few have analyzed their data, as we have, in regard to BMI.[26] Our findings of ER/PR equality between the two groups suggest that there are factors other than estrogen involved in the development of endometrial cancer, even in overweight patients.

One possible explanation for the lack of difference in ER and PR expression between the two BMI groups is that BMI may not be the most important factor in regard to producing conditions of excess estrogen. Distribution of body fat as well as the rate of weight gain over time have been suggested to be important factors in the development of endometrial cancer.[29-33] Data which we were unable to reliably obtain (history of menstrual irregularities and periods of anovulation) may also synergistically add to the overall estrogen status and impact on the ER/PR expression. Furthermore, these factors may eventually cause infertility and, hence, affect the measurement of parity (which was in fact different between normal-weight and overweight patients). These factors may potentially counterbalance the excess estrogen from peripheral conversion that can occur in overweight patients.

Our finding that the grade was not different between the BMI groups may serve as another explanation for the lack of difference in ER/PR expression between the two BMI groups. It had been previously demonstrated that tumor grade correlates with estrogen exposure; well-differentiated tumors tend to arise in conjunction with estrogen excess, whereas high-grade tumors do not.[34,35] Since the grade was similar between both study groups, hormonal exposure between the two groups may also have been similar. Well-differentiated tumors tend to express hormone receptors, whereas higher-grade tumors tend to lack hormone receptors.[11,12,14] Thus, hormone receptors generally are present in the context of excess estrogen. Since grade correlates with hormonal status, and ER/PR expression correlates with grade, one can hypothesize that the similarity of hormonal status between the two groups can account for the lack of difference in ER/PR expression.

Table 8. Body mass index and survival

	BMI <25			BMI >25			p
	n	Five-Year Survival (%)	± SD	n	Five-Year Survival (%)	± SD	
Parity							
0	16	77.9	14.9	24	82.0	9.6	0.83
≥1	30	100.0		72	72.0	9.2	0.03
HER-2/neu							
Negative	34	88.8	77.0	60	83.7	6.3	0.33
Positive	7	100.0		9	51.9	23.1	0.09
PR							
Negative	8	50.0	35.4	7	29.8	22.1	0.16
Positive	33	95.3	43.0	58	87.0	5.6	0.33
LVSI							
Negative	41	92.4	5.3	89	90.3	3.8	0.37
Positive	6	66.7	27.0	11	26.3	15.8	0.65
Stage							
Low (I,II)	37	88.6	6.3	82	89.1	4.2	0.79
High (III,IV)	9	100.0		13	44.1	5.8	0.04
Grade							
Low (1)	18	100.0		36	95.7	2.3	0.63
High (2,3)	35	76.8	3.3	60	60.5	42.7	0.66

SD: standard deviation; BMI: body mass index; PR: progesterone receptor; LVSI: lymph-vascular space invasion

PR negativity was associated with several poor prognostic pathologic factors and was the only variable to maintain significance in the multivariate analysis. Our small sample size clearly limited the statistical significance in PR expression between patients who are of normal weight and those who are overweight. PR could potentially help explain survival between the two groups if the differences we observed remained in larger samples.

Our findings raise an interesting question: why, despite the expected better prognostic factors, did overweight women in our study experience lower survival as opposed to those of normal weight? A BMI cutoff of 25 may have also been a factor. Distinct differences in survival (and possibly grade and ER/PR expression) between BMI groups may have been demonstrated if patients of normal weight and those with either class-2 obesity (BMI 35.0–39.9) or class-3 obesity (BMI ≥40) were compared.[36] In any event, when we analyzed the survival between the BMI groups and stratified the results according to prognostic factors (Table 8), for almost every high risk factor, survival was lower in overweight patients than in patients of normal weight.

Overweight women are diagnosed with more favorable prognostic factors. Possibly, they come to medical care sooner; they may have slower progressing disease; or BMI may be associated with other factors such as race and parity, which may influence stage of disease at diagnosis. Alternatively, there may be length sample bias in that overweight women with more-aggressive disease may be less likely to survive long enough to be included in our hospital tumor registry. In any event, this is a topic to explore. Once diagnosed, heavier patients have survival no better and possibly worse than others, despite the appearance of a more favorable prognosis. Once these other factors are adjusted, heavier women tend to have a poorer experience. BMI may not truly be related to survival but may appear to be so because of confounding and secondary associations, as evidenced by its association with race and several other prognostic factors noted earlier. The apparent better prognosis is most likely an artifact of these secondary associations.

This is one of the largest studies to date analyzing prognostic factors, including HER-2/neu and hormone receptor status in endometrioid cancers among normal-weight and overweight patients. BMI correlates with some, but not all, prognostic factors as they relate to type-1 and type-2 endometrioid cancers. HER-2/neu expression is more common in normal-weight patients and may be related to carcinogenesis but not disease progression. Type-1 and type-2 cancers are not easily distinguished by the patient's body habitus. Other factors are involved in the development and progression of these tumors, and further study is warranted.

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