



Racial differences in the overexpression of epidermal growth factor type II receptor (HER2/neu): A major prognostic indicator in uterine serous papillary cancer

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KEY WORDS

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Objective: A difference in survival rates between black and white patients with cancer of the corpus uteri is well established. This study was conducted to determine whether the overexpression of HER2/neu oncogene is associated with poor outcome in uterine serous papillary endometrial cancer, which is a highly aggressive variant of endometrial cancer, and whether a racial difference in the frequency of HER2/neu overexpression may contribute to the disparity in endometrial cancer survival.

Study design: Immunohistochemical evaluation was used to examine HER2/neu expression in paraffin blocks from 27 women with stage IA to IV uterine serous papillary endometrial cancer. Univariable analysis was performed and followed by multivariable analysis with Cox's proportional hazard model to evaluate whether HER2/neu expression was associated with poor outcome in uterine serous papillary endometrial cancer.

Results: Black patients tended to be younger ($P = .02$) and have higher HER2/neu expression than white patients (trend $P = .02$). Seven of 10 black patients (70%) showed heavy (3+) expression, compared with 4 of 17 white patients (24%; $P = .04$). The association of heavy HER2/neu expression with race persisted after age was controlled through stratification ($P = .05$). Earlier deaths from uterine serous papillary endometrial cancer were seen among heavy HER2/neu expressers ($P = .002$), black patients ($P = .04$), and patients ≤ 65 years old ($P = .04$). However, multivariate Cox regression showed that short survival was associated significantly with heavy HER2/neu expression ($P = .02$) but not with age ($P = .07$) or race ($P = .35$), which indicates that HER2/neu expression accounted for much of the race disparity in survival in this patient population.

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Conclusion: Overexpression of HER2/neu in uterine serous papillary endometrial cancer is an independent variable that is associated with poor outcome, occurs more frequently in black women, and may contribute to racial disparity in survival. HER2/neu expression may guide clinical treatment of patients with uterine serous papillary endometrial cancer and may have implications for the implementation of novel treatment strategies.

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Cancer of the uterine corpus represents the most prevalent gynecologic tumor in women, with an estimated 40,100 cases and 6800 deaths in the United States in 2003.¹ Two subtypes of endometrial carcinoma, namely type I and type II tumors, have been described, on the basis of both clinical and histopathologic variables.² Type I endometrial cancers, which account for most of cases (ie, approximately 80%), are usually well differentiated and endometrioid in histologic condition. These neoplasms are diagnosed frequently in younger women and are associated with a history of hyperestrogenism as the main risk factor and typically have a favorable prognosis with appropriate therapy. In contrast, type II endometrial cancers are poorly differentiated tumors, often with serous papillary or clear cell histologic condition. Although type II tumors account for only a minority of endometrial cancers, approximately 50% of all relapses occur in this group of patients.

In the last few years, several reports, including population-based data from the National Cancer Institute (NCI), have consistently demonstrated that, although the incidence of endometrial cancer in black women is lower than in white women, a striking racial disparity exists in endometrial cancer survival rates in the United States, with black women having up to 30% worse survival rate than white women.³⁻⁸ Although a black/white disparity in survival has been reported for other malignancies, the disparity that is described for endometrial cancer is greater than the disparity that is seen in any other human cancer. In an attempt to explain racial disparity in cancer survival rates, several correlates have been identified by the NCI black-white endometrial cancer study.⁸ At the time of diagnosis, a higher number of black patients had stage III or stage IV disease compared with white patients. In addition, black women were diagnosed with a 2- to 3-fold higher incidence of aggressive type II tumors, such as uterine serous papillary carcinoma (USPC) and clear cell tumors.³⁻⁸ However, when survival analyses were adjusted to black and white women by stage and by type II endometrial tumors, differences in survival rates still occurred.^{3,5} These findings are similar to the results of the NCI black-white breast cancer study, in which the 2-fold higher risk of death in black patients could not be accounted for by sociodemographic factors.⁹ More importantly, these studies suggest that it is likely

that a different distribution of more aggressive biologic factors in the tumors that develop in black women may underlie the racial disparity in survival rates.

USPC represents the most aggressive histologic subtype of endometrial cancer, constituting up to 10% of all endometrial tumors.¹⁰⁻¹² Unlike the histologically similar high-grade ovarian cancer, USPC is a chemoresistant disease from onset, with responses to combined cisplatin-based chemotherapy in the order of 20% and of short duration.¹¹ USPC has a propensity for early intra-abdominal and lymphatic spread, even at presentation, and is characterized by a highly aggressive biologic behavior.¹⁰⁻¹² Recently, our group has discovered a striking overexpression of the transmembrane epidermal growth factor type II receptor HER2/neu, (score 2+ and 3+) in 80% (8/10 occurrences) of the USPCs that were tested.¹³ Because HER2/neu overexpression has been suggested previously to represent a major prognostic factor in endometrial cancer^{14,15} and in breast and ovarian tumors,^{16,17} we examined whether HER2/neu overexpression is correlated with poor survival outcome in patients with USPC. In addition, we analyzed whether differences in HER2/neu expression may exist between black and white women harboring USPC. Our results show for the first time that HER2/neu overexpression is correlated with a poor survival outcome in patients with USPC and that a striking higher frequency of HER2/neu overexpression is seen in black patients when compared with white patients.

Material and methods

Patient population

Paraffin blocks of endometrial adenocarcinomas were retrieved for 27 women (17 white and 10 black) who underwent treatment for International Federation of Gynecology and Obstetrics stage IA to IV serous papillary endometrial adenocarcinoma at the University of Arkansas for Medical Sciences between 1997 and 2004. Study records were reviewed according to institutional review board guidelines. The patient characteristics are described in Table I. A total abdominal hysterectomy with bilateral salpingo-oophorectomy, pelvic washings, and a pelvic lymphadenectomy was performed in all

Table I Patient characteristics

Patient characteristic	Black patients (n/10)	White patients (n/17)	P value
> 65 Years old	2 (20%)	12 (71%)	.0183*
USPC pure-form	9 (90%)	13 (76%)	.6210*
Stage			
I	2 (20%)	2 (12%)	
II	0	1 (6%)	
III	5 (50%)	7 (42%)	
IV	3 (30%)	7 (42%)	
Mean stage score	2.90	3.12	.5847 [†]
Whole-pelvis radiation	9 (90%)	14 (82%)	1.0000*
Chemotherapy	8 (80%)	9 (53%)	.2305*

* The Fisher exact test.

[†] Cochran-Armitage trend test.

patients. No patient received chemotherapy or radiation before the operation. Among the 27 USPC cases, 22 cases were pure forms, and 5 cases were admixed with endometrioid or clear cell histologic condition (mixed USPC). Complete clinicopathologic information and survival data were abstracted from the hospital records.

HER2/neu immunostaining of formalin-fixed tumor tissue

Study blocks were selected after histopathologic review by a surgical pathologist who was blinded to the patients' race, outcome, and other nonhistologic covariates. In several patients, both primary and metastatic sites were evaluated for HER2/neu expression. Briefly, immunohistochemical stains were performed on 4 μ m-thick sections of formalin-fixed, paraffin-embedded tissue. After pretreatment with 10 mmol/L citrate buffer at pH 6.0 with a steamer, the sections were incubated with anti-HER2/neu monoclonal antibody (Dako Corp, Carpinteria, Calif), both at 1:2000 dilution. Antigen-bound primary antibodies were detected with standard avidin-biotin immunoperoxidase complex (Dako Corp). HER2/neu intensity of immunohistochemical staining was scored as 0 (negative = no staining is observed, or membrane staining is <10% of the tumor cells), 1+ (light staining = a faint partial membrane staining is detected in >10% of the tumor cells), 2+ (moderate staining = a weak to moderate membrane staining is observed in >10% of the tumor cells), or 3+ (heavy staining = a strong complete membrane staining is observed in >10% of the tumor cells).

Statistics

The trends with race and immunohistochemical staining were summarized as mean scores and assessed with the Cochran-Armitage test for trend. Immunohistochemical staining for HER2/neu expression was dichotomized as none-to-moderate (0/1+/2+) versus heavy (3+). Age

Table II HER2/neu relationship with race

HER2/neu expression	Black patients (n/10)	White patients (n/17)	P value
Staining intensity			
0 (None)	1 (10%)	4 (24%)	
1+ (Light)	0	5 (29%)	
2+ (Moderate)	2 (20%)	4 (24%)	
3+ (Heavy)	7 (70%)	4 (24%)	
Mean score	2.50+	1.47+	.0241*
Dichotomized			
Low-moderate (0/1/2+)	3 (30%)	13 (76%)	
Heavy (3+)	7 (70%)	4 (24%)	.0402 [†]

* Cochran-Armitage trend test.

[†] The Fisher exact test.

was dichotomized as old if >65 years or young if \leq 65 years; this dichotomization coincided with the overall study median age of 66 years. The Fisher exact test was used to assess patient characteristics for race imbalance and also to examine the race disparity in dichotomized HER2/neu expression. Cochran-Mantel-Haenszel (CMH) analysis was used to examine the race disparity in dichotomized expression; age was controlled through stratification. In CMH analysis, the common odds ratio across strata was the Mantel-Haenszel estimate. The CMH test was used to assess the statistical significance of the common odds ratio; the Breslow-Day test was used to assess the strata for evidence of odds ratio in homogeneity. Disease-related survival was defined as the time from diagnosis to death that was related to cancer progression, with right-censoring at last follow-up or at death not related to USPC. The log-rank test was used to assess nonparametrically the impact of HER2/neu, race, and age on disease-related survival. The relationship among these 3 variables was explored further through univariate and multivariate Cox regression, with particular attention paid to the effect of race on survival when in a multivariate model with HER2/neu. All tests were 2-sided. Probability values were deemed statistically significant if <.05.

Results

Patient characteristics

Twenty-seven patients satisfied study inclusion criteria; 10 women (37%) were black, and 17 women (63%) were white. The median age of the patients in the study was 66 years (interquartile range, 62-75 years). The breakdown by surgical stage was I (4 patients), II (1 patient), III (12 patients), and IV (10 patients). Twelve deaths (8 within 2 years of diagnosis) have occurred among these patients. Two patients died of causes other than USPC (ie, cardiovascular accidents), and 10 deaths were USPC

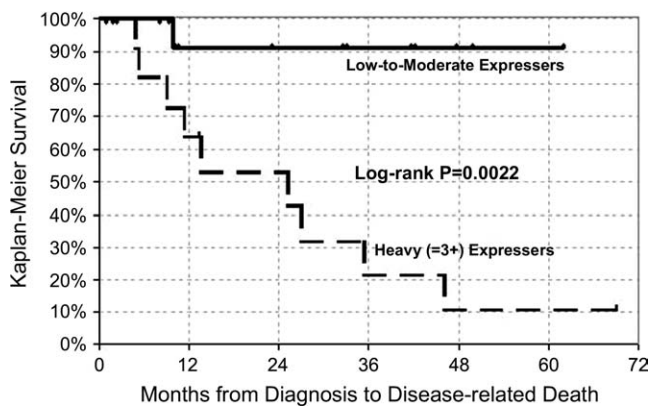


Figure 1 Relationship between HER2/neu overexpression and survival in patients with USPC.

related. Among living patients, the length of the follow-up period had a median of 33 months (interquartile range, 10-48 months). Table I shows the distribution of patient characteristics by race. Twelve of 17 white patients (71%), but only 2 of 10 black patients (20%), were at or above the study's median age of 66 years ($P = .02$). The races did not differ appreciably in percentage of pure versus mixed USPC (90% black vs 76% white; $P = .62$) or in mean stage scores (2.90 black vs 3.12 white; trend $P = .58$). The high mean scores for stage are consistent with the discovery that 80% of black patients and 82% of white patients had advanced-stage (III/IV) disease at the time of the staging laparotomy. For this reason, most patients received adjuvant therapy in the form of whole-pelvis radiation (90% black vs 82% white; $P = 1.00$) and adjuvant chemotherapy (80% black vs 53% white; $P = .23$).

Race association with HER2/neu expression in USPC

Moderate-to-heavy expression of HER2/neu protein was noted in 17 of 27 USPC samples (63%) that were evaluated, with 6 samples (22%) showing moderate staining (2+) and 11 samples (41%) showing heavy staining (3+) for HER2/neu. In all cases in which HER2/neu expression was evaluated in both the primary tumor and a metastatic site (ie, omentum and/or pelvic lymph nodes, 9 cases), the intensity of staining was the same when the 2 sites were compared (data not shown). Next, we compared the overexpression of HER2/neu protein between black and white patients whose condition harbored USPC; Table II shows the results. We found a statistically significant difference in staining intensity in samples from black patients that manifested itself as a > 1-unit race disparity in mean intensity scores (2.50+ black vs 1.47+ white; trend $P = .02$). Indeed, we found that 90% of black women (9/10) had moderate to heavy staining for HER2/neu expression versus 48% of the white women (8/ 17; $P < .02$). When we

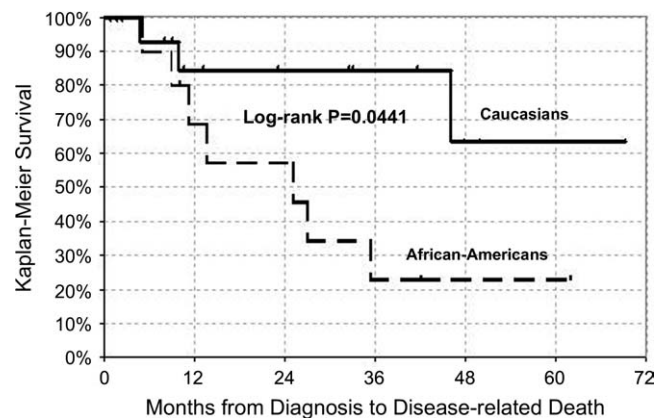


Figure 2 Relationship between race and survival in patients with USPC.

dichotomized HER2/neu staining intensity as heavy (3+) versus none-to-moderate (0/1+/2+), 7 black samples (70%) showed heavy staining compared with 4 white samples (24%; $P = .04$). The prevalence by age of heavy staining was 7 of 13 in the younger (< 65 years) patients (54%) compared with 4 of 14 in the older (> 65 years) patients (29%; $P = .25$). CMH analysis was then used to study the race association with heavy staining; age was controlled through stratification. In the younger patients, 6 of 8 black patients (75%) versus 1 of 5 white patients (20%) had heavy HER2/neu expression; in the older patients, 1 of 2 black patients (50%) versus 3 of 12 white patients (25%) had heavy HER2/neu expression. The common odds ratio for race versus expression across age groups was 6.76, which favored heavy expression in black patients ($P = .05$).

Survival and HER2/neu expression in USPC

Next, we evaluated the disease-related survival rate of patients with USPC in relation to HER2/neu expression. We found 9 disease-related deaths among the 11 patients with heavy expression, but only 1 disease-related death among the 16 patients with none-to-moderate expression. The Kaplan-Meier curves of Figure 1 show that heavy HER2/neu expressers have dramatically shorter survival time from diagnosis to disease-related death than do patients with none-to-moderate expression ($P = .002$). Among the latter patients, disease-related survival held steady at 91% from month 10 to year 4 but fell to 11% by the fourth year among heavy HER2/neu expressers. Figure 2 displays the corresponding Kaplan-Meier curves for black patients versus white patients. A clear disparity is shown ($P = .04$), with disease-related survival dropping by year 4 to 23% for black patients and 63% for white patients. Kaplan-Meier analysis for age (not shown) disclosed a higher disease-related mortality rate for younger patients than for patients > 65 years old ($P = .04$). Four-year survival dropped to 29% for younger patients and 59% for older patients. To assess the

strength and independence of HER2/neu as a prognostic determinant to explain racial disparity in USPC outcomes, multivariate Cox regression analysis was used to study the simultaneous effect of HER2/neu expression, age, and race on survival. Table III shows multivariate Cox-regression models and univariate Cox-regression results for comparison. Under univariate analysis, heavy HER2/neu expression was significantly prognostic for short survival (hazard ratio, 12.43; $P = .02$), and black and younger age were marginally prognostic for short survival (hazard ratios, 3.73 and 4.50, respectively; $P = .06$ for both). When these 3 factors were combined in a trivariate Cox-regression model, heavy expression retained its prognostic significance (hazard ratio, 28.00; $P = .02$), although younger age and race became prognostically insignificant (Table III). In our statistical analysis we also derived bivariate Cox-regression models from the trivariate model by dropping either black or younger age. In bivariate model 1 (HER2/neu and race), heavy expression was prognostically significant for short survival (hazard ratio, 10.30; $P = .03$), but black was not (hazard ratio, 2.67; $P = .21$). In bivariate model 2 (HER2/neu and age), heavy expression was significantly prognostic (hazard ratio, 14.29; $P = .02$), and younger age was marginally prognostic (hazard ratio, 5.50; $P = .06$) for short survival. Therefore, the bivariate models are consistent with the trivariate model with respect to their results; together, these results indicate that heavy HER2/neu expression accounted for much of the shorter survival seen among black patients with USPC in this study.

Comment

Proto-oncogenes are a group of normal genes that play important roles in the regulation of cell proliferation. Abnormalities in the expression, structure, or activity of proto-oncogene products contribute to the development and maintenance of the malignant phenotype. The human HER2/neu (c-erbB2) gene product, like the epidermal growth factor receptor, is a transmembrane receptor protein that plays an important role in coordinating the complex ErbB signaling network that is responsible for regulating cell growth and differentiation.^{18,19} In breast, endometrial, and ovarian cancer, several studies have reported that overexpression of this gene is associated with resistance to treatment and poor survival, which suggests that tumors that overexpress HER2/neu may manifest a more aggressive biologic behavior.¹⁴⁻¹⁷

In this report, we have analyzed whether overexpression of the HER2/neu oncogene is associated with poor outcome in uterine serous papillary endometrial carcinoma, a relatively rare but highly aggressive variant of endometrial cancer. In addition, we evaluated whether a racial difference in the frequency of HER2/neu overexpression may contribute to the consistently observed

Table III Effect of HER2/neu, race, and age on survival

Characteristic	Hazard ratio	<i>P</i> value
Univariate Cox-regression results		
HER2/neu = 3 +	12.43	.0169
Black race	3.73	.0596
Age ≤65 years	4.50	.0575
Multivariate Cox-regression results		
Trivariate model: HER2/neu, race, and age		
HER2/neu = 3 +	28.00	.0219
Black race	0.26	.3504
Age ≤65 years	17.65	.0691
Bivariate model 1: HER2/neu and race		
HER2/neu = 3 +	10.30	.0287
Black race	2.67	.2077
Bivariate model 2: HER2/neu and age		
HER2/neu = 3 +	14.29	.0155
Age ≤65 years	5.50	.0577

racial disparity in endometrial cancer survival rates between black and white women. The absence of a racial disparity in diagnosis and treatment, coupled with the worse survival of black patients (even when compared with white patients with the same initial stage of disease) indeed suggests that underlying biologic differences may contribute to the poor survival of black patients.^{3,5,20}

In our patients with USPC, all of whom were surgically staged by a gynecologic oncologist, most conditions were found to harbor advanced-stage disease. Consequently, adjuvant therapy in the form of radiation therapy and chemotherapy was administered to most black and white patients with USPC, without significant differences between the 2 groups. Our results show, for the first time, that HER2/neu overexpression is correlated with a poor survival outcome in patients with USPC, regardless of their race. Strikingly however, a significantly higher number of black women were found to harbor USPC with strong HER2/neu expression when compared with white women. In this regard, in our series, the percentage of tumors that show strong HER2/neu expression in the black population was almost 3-fold higher compared with that identified in the white population. Of interest, USPC developed in black women at a significantly younger age compared with white women.

At this time it remains poorly understood why the black population more frequently experiences USPC with the dominant molecular pathways characterized by the aberrant HER2/neu overexpression. In light of our results, however, it is very likely that the significantly higher frequency of these biologically more aggressive tumors in black women may at least partially explain the consistently demonstrated racial disparity in endometrial cancer survival rate. Consistent with this view, previous reports in patients with endometrial cancer found p53

gene overexpression to be associated with poor survival rates in both black and white patients, but with p53 overexpression found to occur more than twice as frequently in black patients.^{21,22} However, these studies also showed that, among cancers with p53 overexpression, survival of black patients was still worse than that of white patients, which suggests that p53 status was not the sole or most important determinant of the racial disparity in survival.^{21,22} Importantly, when in our study multivariate Cox regression analysis was used to evaluate the simultaneous effect of HER2/neu expression, age, and race on USPC patient survival, HER2/neu overexpression remained the only independent variable that was correlated with survival. These results strongly support the hypothesis that the higher frequency of HER2/neu overexpression found in black patients with USPC may contribute greatly to the racial disparity in survival.

In conclusion, we found a significantly higher frequency of HER2/neu overexpression in black women who were diagnosed with USPC, and we have shown that HER2/neu may represent a crucial molecular-genetic prognostic factor that contributes to the racial disparity in survival. Nevertheless, high overexpression of HER2/neu provides support for the proposal that trastuzumab (Herceptin; Genentech, Inc, San Francisco, Calif), a humanized anti-HER2/neu antibody that is showing great promise for the treatment of patients with metastatic breast cancer whose condition overexpresses HER2/neu protein may be a novel, potentially highly effective therapy against USPC.²³ Consistent with this view, high sensitivity of USPC cells to natural killer cell-mediated antibody-dependent cytotoxicity triggered by anti-HER2/neu-specific antibody *in vitro*¹³ and clinical responses *in vivo*²⁴ have recently been reported with the use of Herceptin in patients with USPC. The future design and implementation of clinical trials will ultimately determine the validity of this approach.

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