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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
Serous papillary uterine cancer
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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.

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