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The racial disparity in outcomes in endometrial cancer: Could this be explained on a molecular level?

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Abstract

Objective. The racial disparities among patients with endometrial carcinoma have been previously reported. The objective of this study is to analyze and compare the molecular profiles in endometrial cancer in Caucasian and African American patients using a number of known molecular markers.

Materials and methods. 147 patients diagnosed with endometrial cancer between 1995 and 2001 were included in the study. Patients' demographics, clinical and pathological data were reviewed. Immunohistochemical staining for p53, VEGF, Ki-67 and HIF-1α was performed on tissue micro array sections. Tumors' expression of p53, VEGF, Ki-67, and HIF-1α was compared based on ethnicity and tumor type (Type I = endometrioid carcinomas and Type II = non-endometrioid carcinomas). Spearman's correlation and Fisher's Exact Tests were used for statistical analysis and Kaplan–Meier, log-rank and Cox regression were used for survival analysis.

Results. 97 patients were Caucasian and 50 patients were African American. The mean age was 62 (33–91) years for Caucasian patients and 63.5 (24–89) years for the African American patients. African American patients had more Type II carcinoma than Caucasian patients ($P = 0.055$). High p53 expression was statistically significant among the African American patients (49% vs. 30%, $P = 0.035$) versus Caucasian patients. There was no significant difference demonstrated when comparing the VEGF, Ki-67, and HIF-1α expression between the racial groups. Survival analysis showed a trend toward a shorter survival in the African American patients compared to the Caucasian patients; median survival 62 versus 77 months ($P = 0.061$). On the other hand, we did not find a significant difference in survival by ethnicity when we adjusted for tumor histology.

Conclusion. While African American patients with endometrial cancer seem to show a trend toward a shorter survival, this seems to be mainly due to the fact that they have a higher proportion of Type II tumors. The molecular profiles for p53, Ki-67, VEGF and HIF-1α expression of histologically matched tumors were similar between the two ethnic groups.

Keywords: Endometrial carcinoma; Ethnicity; Molecular profile; p53; Ki-67; VEGF; HIF-1α

Introduction

African American (AA) women, while less likely to be diagnosed with endometrial cancer, suffer from disease-specific mortality rates that are nearly double that of Caucasian (C) women. According to the American Cancer Society, the overall survival of AA women diagnosed with endometrial cancer from 1995 to 2000 has remained at approximately 63% versus 86% in Caucasian women [1].

Many studies have tried to address the causes underlying the racial disparity in endometrial cancer outcomes [2–5]. Some have attributed the differences to socioeconomic factors leading to a delay in access to care and different treatments rendered to the AA patients [6–11]. Others have concluded that the discrepant outcomes are due to differences in tumor biology [6,12].

The significant advances in molecular biotechnology have allowed the medical community to characterize and differentiate tumors not only based on their histologic appearances, i.e.,

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Type I or endometrioid carcinomas and Type II or non-endometrioid carcinomas, but also by their molecular signatures. The molecular characteristics of various tumors have been shown to impact its biologic behavior and patients' prognosis.

Several molecular markers have been evaluated in endometrial cancer. P53, VEGF, HIF-1α and Ki-67 are proteins involved in various steps of the process of cancer progression including apoptosis, proliferation and angiogenesis. Changes in these proteins have been described in case series of endometrial cancer and shown to impact tumor biology [13–17].

The objective of the current study was to analyze and compare by ethnicity the molecular characteristics of endometrial cancer cases treated in a single institution using immunohistochemistry (IHC) to evaluate the expression of p53, Ki-67, VEGF and HIF-1α.

Materials and methods

Using the institutional computerized Clinical Information System (CIS) the department of pathology and the Statistics, Epidemiology and End Results (SEER) databases, we identified patients who were diagnosed with endometrial cancer and underwent primary surgery at our institution between 1995 and 2001. Only patients of African American and Caucasian race were included. After obtaining approval from the Institutional Review Board, a retrospective chart review of patients' demographics, clinical and pathological data was performed. Surgical staging was determined using the criteria recommended by the International Federation of Gynecology and Obstetrics (FIGO). The histological type and grade were determined using the World Health Organization (WHO) criteria. The tumors were classified into Type I (endometrioid) and Type II (non-endometrioid) as described by Kurman et al. [18].

Tissue micro-array (Manual Tissue Microarrayer, number 1, Beecher Instruments) was performed on selected paraffin-embedded blocks of tumor for each case. For each paraffin block, 3 cores of 1.5 mm diameter were done. The procedure was repeated a second time and a duplicate paraffin block of tissue micro array was prepared for each case. Using standard IHC techniques each micro-tissue block was stained with antibodies for p53, VEGF, Ki-67 and HIF-1α. For all four markers, both intensity and percentage of positive cells were evaluated. Both the H&E slides and the IHC stains were evaluated separately by two pathologists (RAF and VP).

Methods for IHC staining

In brief, 4- to 5-μ-thick sections were antigen retrieved by steam treatment in a citrate buffer, quenched for 10 min with 3% hydrogen peroxide, pre-incubated with blocking serum at 1:20 in 2% bovine serum albumin/phosphate-buffered saline solution (PBS) for 15 min at room temperature. After rinses with PBS for 30 s, slides were incubated with streptavidin/peroxidase at 1:500 in PBS for 30 min at room temperature, then rinsed with PBS and incubated for 15 min in 0.06% diaminobenzidine and counter-stained with Harris modified hematoxylin (Fisher Healthcare, Hanover Park, IL) (Fig. 1A). The following antibodies were used for IHC staining: p53 (clone: DO7, dilution of 1:100, incubation for 2 h; Nova-Castra, Vector Laboratories, Burlingame, CA) [19], VEGF (clone: C1, 1:20 dilution, incubation for 2 h; Santa Cruz Biotechnology, Inc.) [20], Ki-67 (clone: MM1, 1:100 dilution, incubation for 2 h; Vector Laboratories, Burlingame, CA) [20], and HIF-1α (clone: H1-α67, 1:3000 dilution incubation for 32 min; Novus-Biologica, Littleton, CO) [21]. For Ki-67 and HIF-1α, antigen retrieval was done using an EDTA buffer solution and subsequent steps were done according to the manufacturer's instructions.

Methods for IHC scoring

For VEGF assessment, the staining intensity and the percentage of tumor cells that were stained were analyzed. Staining intensity was scored as 0

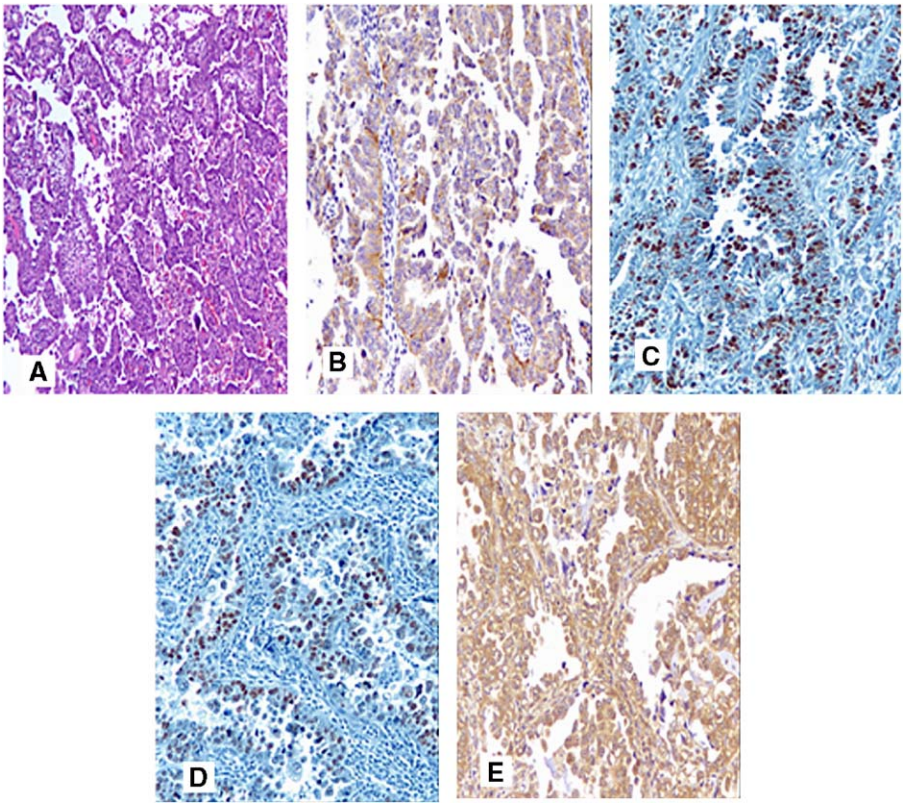

Fig. 1. Examples of Type II (serous) endometrial carcinoma stains. A: H and E; B: IHC staining of VEGF (High expression); C: IHC staining of Ki-67 (High expression); D: IHC staining of p53 (High expression); E: IHC staining of HIF-1α (High expression).