Gynecologic Oncology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Impact of age at diagnosis on racial disparities in endometrial cancer patients

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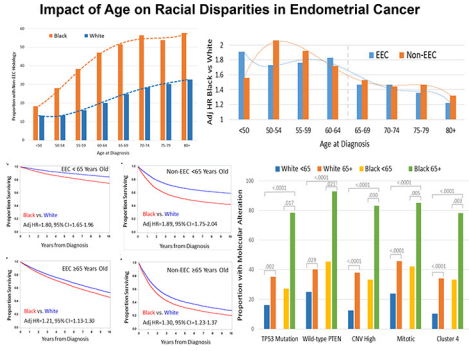
HIGHLIGHTS

- Racial differences in age at diagnosis for uterine serous cancer and carcinosarcoma.
- Increased presentation of type II tumors with age was larger in black vs. white patients.
- Survival differences between white and black patients decreases with increasing age.
- Mutations in *TP53* and *PTEN*, and molecular subtypes vary by age of diagnosis and race.

GRAPHICAL ABSTRACT

Impact of age of diagnosis on the proportion of the high-risk histology (upper left), adjusted risk of death (upper right), survival (lower left), and the proportion with a TP53 mutation, wildtype PTEN, copy number variant (CNV) high subtype, mitotic transcript-based subtype and the cluster 4 subtype in black compared with white endometrial cancer patients.



ARTICLE INFO

Article history:
Received 25 June 2017
Received in revised form 29 July 2017
Accepted 31 July 2017
Available online xxxx

ABSTRACT

Introduction. Although black patients with endometrial cancer (EC) have worse survival compared with white patients, the interaction between age/race has not been examined. The primary objective was to evaluate the impact of age at diagnosis on racial disparities in disease presentation and outcome in EC.

Methods. We evaluated women diagnosed with EC between 1991 and 2010 from the Surveillance, Epidemiology, and End Results. Mutation status for *TP53* or *PTEN*, or with the aggressive integrative, transcript-based, or

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http://dx.doi.org/10.1016/j.ygyno.2017.07.145
0090-8258/

Please cite this article as: C.M. Tarney, et al., Impact of age at diagnosis on racial disparities in endometrial cancer patients, Gynecol Oncol (2017), http://dx.doi.org/10.1016/j.ygyno.2017.07.145

Keywords:
Endometrial cancer
Race
Disparity
SEER
Age
Survival

somatic copy number alteration-based molecular subtype were acquired from the Cancer Genome Atlas. Logistic regression model was used to estimate the interaction between age and race on histology. Cox regression model was used to estimate the interaction between age and race on survival.

Results. 78,184 white and 8518 black patients with EC were analyzed. Median age at diagnosis was 3-years younger for black vs. white patients with serous cancer and carcinosarcoma ($P < 0.0001$). The increased presentation of non-endometrioid histology with age was larger in black vs. white patients ($P < 0.0001$). The racial disparity in survival and cancer-related mortality was more prevalent in black vs. white patients, and in younger vs. older patients ($P < 0.0001$). Mutations in *TP53*, *PTEN* and the three aggressive molecular subtypes each varied by race, age and histology.

Conclusions. Aggressive histology and molecular features were more common in black patients and older age, with greater impact of age on poor tumor characteristics in black vs. white patients. Racial disparities in outcome were larger in younger patients. Intervention at early ages may mitigate racial disparities in EC.

1. Introduction

Endometrial cancer (EC) is the most common cancer of female reproductive organs in the United States [1]. The American Cancer Society estimates that 61,380 new cases of EC will be diagnosed in 2017 and 10,920 women will succumb to their disease [1]. The incidence for EC is similar for black and white women, but black women are 2.5 times more likely to die from EC [2]. Compared with white women, black women are diagnosed with higher stage and grade, higher-risk histology, and have worse survival [3,4]. Unfortunately, this disparity continues to grow at a rate that exceeds that of other racial or ethnic groups [5]. Racial disparities in EC are multifactorial with varying response to treatment, comorbidities, and genetic mutations being often cited reasons [4,6–10]. Racial differences have also been reported in prevalence of prognostic transcripts including PSPHL, SERPINA4, ITGA3, BET1L, FAM228B and HEATR6 [11–13], the aggressive copy number variant (CNV) high, somatic copy number alteration (SCNA) cluster 4 and transcript-based mitotic molecular subtypes [14], mutations in TP53 and PTEN [9,15], oncoproteins such as HER2 [8,16,17] or copy number alterations in 1q23 [18] in EC. Additionally, socioeconomic factors and access to care limitations contribute to racial variations seen in EC [19–21].

Age is an important prognostic factor and may provide insight on the racial disparities seen in EC, both from biologic and patient-care views [22]. Compared with younger women, older women tend to be diagnosed with higher stage and grade, more aggressive histology, greater depth of myometrial invasion, and have worse recurrence-free survival [19,23–25]. Among black women these poor prognostic factors are more pronounced leading to inferior survival [19]. Previous studies examining race and age have discriminated young and old based on a single age threshold but did not evaluate the interaction between them [19,23,26]. Careful examination of the impact of increasing age at time of diagnosis may uncover reasons for racial disparities in EC, supporting the evaluation of alternate treatments and changes in practice guidelines.

Using data from the Surveillance, Epidemiology, and End Results (SEER) program, we investigated the impact of increasing age at diagnosis on racial disparity in EC between black and white women. To further investigate whether a difference in access to care may be a cause for the racial disparity seen in EC, we examined survival for black and white women when comparing women <65 and ≥65 years as Medicare is the primary health insurer for 97% of Americans ≥65 years [27]. Lastly, we sought to determine whether prevalence in mutations and aggressive molecular subtypes varied by age at diagnosis and race in EC patients.

2. Methods

This research investigation utilized public data from SEER and the Cancer Genome Atlas (TCGA). An institutional review board (IRB) waiver was obtained from Western IRB in accordance with use of publicly available de-identified data (14-1679).

2.1. SEER cohort

Data for this study were obtained from the 18 geographic region SEER program representing 26% of the United States population [28]. Patients with common EC histologic subtypes between 1991 and 2010 were selected using the following International Classification of Diseases for Oncology, Third Edition (ICD-O-3) [29] codes [S1 in the Supplement]. Eligible cases were dichotomized as endometrioid endometrial cancer (EEC) or non-EEC (serous, mixed, clear cell, and carcinosarcoma). EEC tumors were further classified based on grade (G) of the tumor (G1, G2, G3). Stage of disease was classified as local (stage IA or IB), regional (stage II-III), distant (stage IV), and unstaged. Patients diagnosed at advanced stage had regional or distant disease. Patients with in situ disease were excluded. Races other than black or white were also excluded. Patients with missing follow up time from diagnosis, vital status, stage or grade (EEC only) were removed from survival analyses. Patients with multiple primary malignancies were not excluded. Overall survival was the primary outcome. Cancer-related mortality and non-cancer mortality were also analyzed.

2.2. TCGA cohort

Clinical, mutation, molecular subtype and RNA sequencing data were obtained from TCGA. Mutation data for *TP53* and *PTEN* for uterine corpus endometrial cancers (UCEC) were downloaded from Broad Institute Firehose data standardization run on Nov. 2015 [30]. TCGA UCEC provisional clinical data, and clinical data with molecular subtype annotation published in *Nature* [31] were extracted from *cgdsr* (version 1.2.5) package in R (version 3.1.2) on Aug.18, 2016. This cohort included 291 eligible white patients (207 non-Hispanic white, 3 Hispanic white and 81 with unknown ethnicity) and 46 eligible black patients (22 non-Hispanic black, 1 Hispanic black and 23 with unknown ethnicity). Mutation status for *TP53* or *PTEN* was available in 219 patients. Molecular classification data were available for CNV high subtype in 204 patients, mitotic subtype in 300 patients, and SCNA cluster 4 subtype in 327 patients.

2.3. Statistical methods

Impact of age at diagnosis and race on histologic subtype was evaluated using a logistic regression model, with odds ratio (OR) favoring non-EEC per 10-year increase in age or for black vs. white patients to indicate the strength of effect. The relationship between age and log(OR) of the risk of non-EEC was evaluated using a graphic method proposed by Hosmer and Lemeshow [32], with the assessment generally supporting a linear relationship. The model was also extended by

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