J Gynecol Oncol. 2020 Nov;31(6):e81
https://doi.org/10.3802/jgo.2020.31.e81
pISSN 2005-0380·eISSN 2005-0399

JOURNAL OF GYNECOLOGIC ONCOLOGY

Original Article

Uterine clear cell carcinoma risk in White versus non-White US subpopulations: does race matter?

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Received: Jun 5, 2020
Revised: Jun 18, 2020
Accepted: Jun 21, 2020

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Presentation
This study was presented in the Society of Gynecologic Oncology 2020 Annual Meeting Poster Presentation, March 2020.

ABSTRACT

Objective: To determine incidence rates of uterine clear cell carcinoma among non-White US subpopulations.
Methods: Data from the United States Cancer Statistics and National Cancer Database from 2004 to 2016 were analyzed using descriptive statistics.
Results: A total of 488,811 women were diagnosed with uterine cancer from 2004–2016. Of these, 73.3% were endometrioid, 6.6% were serous, 5.3% were carcinosarcoma, 1.4% were clear cell, and 13.4% were other. Blacks had the highest incidence rate of uterine clear cell compared with Whites, Asian/Pacific Islanders, and American Indian/Alaska Natives (0.59 vs. 0.31, 0.29, and 0.24, respectively). Overall mean age at diagnosis was 68.6 years, with the youngest age in Asian/Pacific Islanders compared to Whites, Blacks, and American Indian/Alaska Natives (65.9 vs. 68.7, 68.6, and 66.3 years, respectively). Analysis of the Asian subpopulation revealed significantly younger age at diagnosis in Vietnamese women (55.8 years) compared with 72.4 years in Japanese, 68.6 years in Pacific Islander, 66.6 years in Indian/Pakistani, 65.9 years in Filipino, 65.8 years in Chinese, 65.2 years in Korean, and 63.7 years in other Asians.
Conclusions: Black women are two times more likely to be diagnosed with uterine clear cell carcinoma compared with other races. Asians present at younger ages, with Vietnamese women most likely to be diagnosed at the youngest age.

Keywords: Adenocarcinoma, Clear Cell; Uterine Neoplasms; African Americans; Asian Americans; Incidence; Ethnic Groups

INTRODUCTION

Uterine cancer is the most common gynecologic malignancy in the United States. An estimated 61,880 new cases were diagnosed in 2019, with 12,160 women succumbing to the disease [1].

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Author Contributions
Conceptualization: C.S.; Data curation: L.C.I.; Formal analysis: L.C.I.; Supervision: C.S.; Writing - original draft: W.D.; Writing - review & editing: C.S., M.A., T.C., D.K.M., C.J.K.

White women have the highest incidence of uterine cancer, followed by Black, Asian/Pacific Islander, and American Indian/Alaskan Native [1]. However, while white women have the highest incidence, black women have an 80% higher mortality from the disease compared with Whites [2]. This health disparity has been attributed to multiple factors, including socioeconomic status, comorbidities, treatment response, and genetic mutations [3-6].

Uterine clear cell carcinoma (UCCC) is an aggressive, non-estrogen driven histologic subtype, representing 1%–3% of all uterine cancers [7,8]. Though it is rare, overall 5-year survival for UCCC is approximately 58% [9]. Black women have the highest incidence rates of UCCC, with studies showing rates for Blacks at 1.8–2.1 times greater than for Whites [10,11]. Furthermore, black women with UCCC have been shown to have a worse prognosis compared with white women. Progression free survival in black women with UCCC has been reported to be nearly 50% shorter than in white women [12].

The risk of UCCC in other racial minorities has not been as thoroughly studied as that in Blacks. Given the low rate of UCCC and small sample sizes of minority populations, prior studies on UCCC in Asians have pooled UCCC with other aggressive uterine histologic subtypes, such as serous carcinoma [13,14]. Asians have been shown to be diagnosed at younger ages and have higher proportions of aggressive histologic subtypes (including UCCC) compared with white women [13,15]. However, differences in survival have not been found between Whites and Asians with UCCC [15].

This population-based study is the largest of its kind to focus solely on UCCC and race. We examined the incidence rates of uterine clear cell carcinoma in the non-White US population, particularly in Blacks and Asians, to better understand the racial disparities present in the US.

MATERIALS AND METHODS

Demographic and histologic information from women with uterine cancer between 2004 to 2016 were extracted from the United States Cancer Statistics (USCS) and National Cancer Database (NCDB) [16]. Given that the data obtained is from a public, de-identified database, this study was exempt from Institutional Review Board approval. All women diagnosed with uterine cancer were included. Age at diagnosis, race, ethnicity, and region were obtained. Regions of the United States were defined based on the US Department of Commerce Economics and Statistics Administration US Census Bureau consensus [17].

All incidences reported are per 100,000 women and age-adjusted to the 2000 US Standard Population. Case numbers were provided for each histologic subtype based on International Classification of Disease for Oncology 3rd edition (ICD-O-3) data from the USCS database and describe the absolute number of patients with the disease. Analyses were performed using SPSS v25.0 and Surveillance, Epidemiology, and End Results (SEER)*Stat Software, Version 8.3.4, released March 23, 2017 [18].

RESULTS

From the NCDB, a total of 488,811 women were diagnosed with invasive uterine cancer from 2004–2016. The majority, 358,520 (73.3%), were of endometrioid histology. Clear cell

Table 1. Patient demographic features

NCDB (2004–2016)	Patient number (%)
Uterine cancer histology	
Total	488,811 (100.0)
Endometrioid carcinoma	358,520 (73.3)
Clear cell carcinoma	6,963 (1.4)
Serous carcinoma	32,134 (6.6)
Carcinosarcoma	25,914 (5.4)
Other	65,280 (13.4)
Race (all histology)	
White	411,904 (84.3)
Black	51,093 (10.5)
Asian/Pacific Islander	14,145 (2.9)
American Indian/Alaska Native	1,560 (0.3)
Other/Unknown	10,109 (2.1)
Race (clear cell histology only)	
White	5,368 (77.1)
Black	1,224 (17.6)
Asian/Pacific Islander	214 (3.1)
Chinese	41 (19.2)
Japanese	13 (6.1)
Korean	10 (4.7)
Filipino	48 (22.4)
Vietnamese	5 (2.3)
Indian/Pakistani	27 (12.6)
Pacific Islander	24 (11.2)
Other Asian	46 (21.5)
Total Asian/Pacific Islander	214 (100.0)
American Indian	16 (0.2)
Other/Unknown	141 (2.0)

NCDB, National Cancer Database.

histology was diagnosed in 6,963 (1.4%) of the cases. Of the remainder, 32,134 (6.6%) were serous, 25,914 (5.3%) were carcinosarcoma, and 65,280 (13.4%) were other or not specified. Demographics for the study population are summarized in **Table 1**. The overall age-adjusted incidence of UCCC was 0.34 (per 100,000 women).

The overall mean age at diagnosis of UCCC was 68.6. Asian/Pacific Islanders had the youngest mean age at diagnosis (65.9 years) compared with Whites (68.7 years), Blacks (68.6 years), and American Indian/Alaska Natives (66.3 years). Analysis of the Asian subpopulation revealed significantly younger age at diagnosis in Vietnamese women (55.8 years) compared with 72.4 years in Japanese, 68.6 years in Pacific Islander, 66.6 years in Indian/Pakistani, 65.9 years in Filipino, 65.8 years in Chinese, 65.2 years in Korean, and 63.7 years in other Asians (**Fig. 1**).

Patients with UCCC were more likely to be Black, with age-adjusted incidence rates of 0.59, compared with 0.31 in Whites, 0.29 in Asian/Pacific Islanders, and 0.24 in American Indian/Alaska Natives (**Fig. 2**). Within the Asian population, the proportion of uterine cancers with clear cell histology was highest in Chinese at 2.2%, followed by 2.0% Korean, 1.8% Filipino, 1.6% Pacific Islander, 1.4% Indian/Pakistani, 1.3% Japanese, 0.8% Vietnamese, and 1.4% other Asian (**Table 2**).

Geographically, UCCC was more likely diagnosed in black women living in the South. Among the Asian subpopulations, UCCC was more likely diagnosed in Chinese, Japanese, Filipino, Vietnamese, and Pacific Islander women living in the Western region of the US. Indian/Pakistani women were more likely diagnosed in the South, and Korean women in the Northeast.

https://doi.org/10.3802/jgo.2020.31.e81

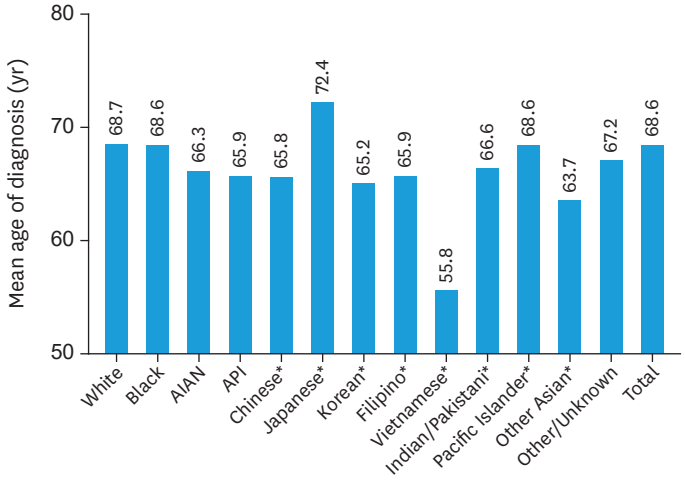

Fig. 1. Mean age of UCCC diagnosis by race/ethnicity.
AIAN, American Indian/Alaskan Native; API, Asian/Pacific Islander; UCCC, uterine clear cell carcinoma.
*A subpopulation of API.

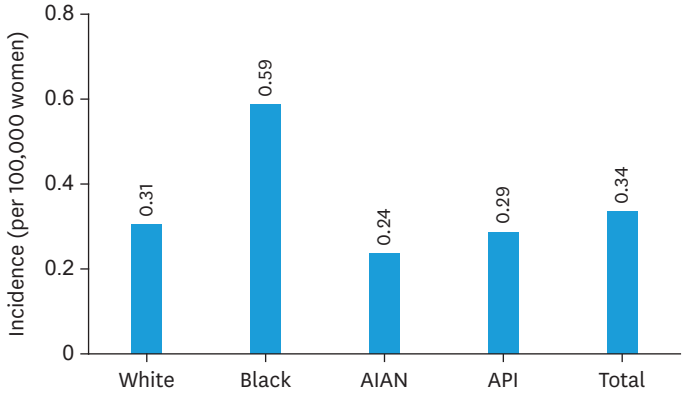

Fig. 2. Incidence of UCCC by race.
AIAN, American Indian/Alaskan Native; API, Asian/Pacific Islander; UCCC, uterine clear cell carcinoma.

Table 2. Proportion of UCCC in Asian subpopulations

Ethnicity	No. of all uterine cancers (%)	No. of UCCC (%)	Proportion of UCCC (%)
Chinese	1,856 (13.9)	41 (19.2)	2.2
Japanese	997 (7.5)	13 (6.1)	1.3
Korean	510 (3.8)	10 (4.7)	2.0
Filipino	2,596 (19.4)	48 (22.4)	1.8
Vietnamese	655 (4.9)	5 (2.3)	0.8
Indian/Pakistani	1,878 (14.0)	27 (12.6)	1.4
Pacific Islander	1,518 (11.4)	24 (11.2)	1.6
Other Asian	3,363 (25.1)	46 (21.5)	1.4
Total Asian population	13,373 (100.0)	214 (100.0)	1.6

UCCC, uterine clear cell carcinoma.

DISCUSSION

Uterine clear cell carcinoma is a rare aggressive cancer associated with a poor prognosis. Our population-based study is the largest of its kind to focus solely on UCCC and race, and we examined the incidence rates of uterine clear cell carcinoma in White versus non-White US

https://doi.org/10.3802/jgo.2020.31.e81

subpopulations to determine if racial disparities exist. Overall, black women are approximately 2 times more likely to be diagnosed with this histologic subtype compared with Whites, and Asians are of notably younger age upon diagnosis compared with other races.

In this report, the age-adjusted incidence rate of UCCC was the highest in black women, almost twice that of the next highest rates in Whites and Asians. This finding is consistent with a prior study by Cote et al. [4] who showed that black women were 1.9 times more likely to be diagnosed with clear cell histology compared with Whites. Doll and colleagues also showed a 1.9-fold increased incidence rate of high-risk endometrial cancer in black women compared with Whites, however their study lumped clear cell histology with endometrioid grade 3, serous, and carcinosarcoma [19]. In addition, both studies used the SEER database, which is estimated to represent only 34.6% of the US population [18]. Sabatino and colleagues [10] analyzed the NPCR and SEER databases from 2001–2003 and reported the age-adjusted incidence of UCCC to be highest in Blacks but 32% lower in Asians compared with Whites. This differs from our finding that Asians have a minimally decreased incidence rate compared with Whites (0.29 vs. 0.31, respectively), which is likely due to the smaller sample size used by Sabatino and colleagues [10].

Older age at diagnosis for UCCC has been shown to be an independent poor prognostic factor [9]. Tarney et al. [11] analyzed the SEER database between 1991–2010 and found that the median age of diagnosis did not appear to vary significantly for Blacks vs. Whites. Our finding that Blacks are diagnosed with UCCC at approximately the same age as Whites was consistent with this previous study. For Asians, prior studies have shown that UCCC is diagnosed at significantly younger ages compared with Whites. Zhang and colleagues [15] found the mean age of diagnosis was 60.4 years for Asians compared with 69.1 years for Whites. However, very few studies have examined UCCC in Asian subpopulations. We found a wide range of ages among the subpopulations, from age 55 in Vietnamese to 72 in Japanese, which suggests potential discrepancies in risk factors for each of the Asian subpopulations. Factors such as immigration status have been shown to be associated with uterine cancer age of diagnosis and histologic subtype, and each Asian subpopulation experiences different rates of immigration [14,20]. Foreign-born Asians have been found to be younger at diagnosis compared with those born in the US [13]. Notably, data extracted from the 2015 US Census Bureau shows that 64% of the Vietnamese in the US are foreign-born compared with only 27% of the Japanese, which may help explain discrepancies between age of diagnosis for these subpopulations [21]. Furthermore, Simons et al. [14] reported that Asian immigrants have higher proportions of type II uterine cancer, which includes UCCC, endometrioid grade 3 carcinoma, and serous carcinoma, compared with US-born Asians. Type II uterine cancer was found to be highest in immigrants who were Japanese, followed by Chinese and Filipino. Their study, however, did not specifically look at uterine clear cell histology.

Incident rates of aggressive uterine cancers have been rising for all women across the US [4,22]. A recent study by Clarke et al. [22] reported that the highest age-adjusted incidence rates for non-endometrioid uterine cancer were in the Northeast and Midwest. However, we found that black women were more likely diagnosed with UCCC in the South. Our findings do not align with Clarke's and may be a reflection of the rarity of clear cell histology, in addition to underlying socioeconomic and biologic differences for Blacks with UCCC compared with women with other non-endometrioid uterine cancers. The geographic differences observed in UCCC incidence rates for the Asian subpopulations may be inconclusive given the small sample sizes for each Asian subpopulation. Larger studies need to be conducted for accurate results.

The racial disparity seen in UCCC has also been attributed to genetics, and certain mutations have been implicated in the clear cell subtype. The most comprehensive molecular study of uterine cancers to date has been The Cancer Genome Atlas (TCGA), which established 4 categories that correlated with progression free survival and response to post-surgical adjuvant treatment [23]. Subsequent analysis of TCGA showed each race had differing rates of recurrently mutated genes [5], which may partially explain the racial disparities seen—i.e., a higher incidence of UCCC in black women, younger age at diagnosis in Vietnamese women. However, TCGA looked only at endometrioid and serous histologic subtypes. Genomic and molecular studies of UCCC have been smaller, but have identified uterine clear cell histology to be correlated with being HNF1ß-positive, napsin A-positive, ER-negative, and mutations in TP53, PIK3CA, PPP2R1A, FBXW7, and ARID1A, among others [24-27]. UCCCs were less likely to have PTEN, CTNNB1, or POLE mutations, compared with endometrioid or serous cancers [24]. Mutations distinguishing UCCC from other histologic subtypes may help identify drivers of this cancer to better understand the differences in incidence rates for each race and ethnicity. Continued progress in the molecular and genetic makeup of uterine clear cell histology provides hope that molecularly targeted therapies will benefit patients with UCCC.

UCCC is difficult to study on a large scale given the rarity of disease. To our knowledge, this study is the largest of its kind to focus solely on clear cell uterine cancer and race, and it is the first study analyzing the incidence of UCCC in Asian subpopulations in the United States. There are several limitations to this study, including those pertaining to its retrospective nature. There was a lack of central pathology review, potential information bias, and missing data. However, our data is highly generalizable, as the USCS database represents 97.0% of the entire US population [16]. Despite being the largest study focusing on UCCC, our sample size remains small for the Asian subpopulations. Therefore, our observed differences may not truly represent the disease statistics for that ethnicity. Our study also did not include immigration status, which may confound differences in disease rates among immigrant and US-born Asians.

Our study of UCCC in the US reveals black women are approximately two times more likely to be diagnosed with clear cell histology compared with other races and are more likely diagnosed in the South. Asians present at younger ages, with Vietnamese women most likely to be diagnosed at the youngest age. Chinese, Korean, and Filipino women comprise the Asian subpopulations with the highest risk of the clear cell subtype. Our study highlights certain races and ethnicities in the US at risk for UCCC; however, more studies are required to better understand and manage the racial disparities that exist.

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