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The effect of time on racial differences in epithelial ovarian cancer (OVCA) diagnosis stage, overall and by histologic subtypes: a study of the National Cancer Database

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Abstract

PURPOSE—Previous studies assessing racial and ethnic differences in ovarian cancer (OVCA) diagnosis stage fail to present subtype-specific results and provide historic data on cases diagnosed between ten and twenty years ago. The purpose of this analysis is to assess non-Hispanic Black (NHB) and non-Hispanic White (NHW) differences in late stage diagnosis including; 1) factors associated with late-stage diagnosis of invasive epithelial OVCA overall and by histologic subtypes 2) potential changes across time, and, 3) current patterns of trends in a national cancer registry in the US and Puerto Rico between 1998 and 2011.

METHODS—NHB and NHW OVCA cases were derived from the National Cancer Database (NCDB). Diagnosis stage was analyzed as a dichotomous and a four-level category variable, respectively; early (stages I and II; localized) versus late (stages III and IV; regional and distant) and stages I, II, III and IV. Diagnosis period was trichotomized (1998–2002, 2003–2007, 2008–2011). Racial differences in stage were tested using Chi-square statistics. Odds ratios (OR) and 95% confidence intervals (95%CI) were estimated using multivariable binomial and generalized ordered logistic regressions. Interactions between race and diagnosis period were evaluated.

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RESULTS—Between 1998 and 2011, 11,562 (7.8%) NHB and 137,106 (92.2%) NHW were diagnosed with OVCA. In adjusted models, NHB were significantly more likely diagnosed with late-stage OVCA than NHW ($OR_{adj}=1.26$; 95%CI 1.19–1.33). Interaction between race and diagnosis period was marginally significant ($p_{value}=0.09$), with racial differences in stage decreasing over time (1998–2002: $OR_{adj}=1.36$, 95%CI= 1.23–1.49; 2003–2007: $OR_{adj}=1.27$, 95%CI= 1.15–1.39; 2008–2011; $OR_{adj}=1.15$, 95%CI= 1.05–1.27). NHB were also more likely to be diagnosed with stage 4 high grade serous ($OR_{adj}=1.46$; 95%CI 1.22–1.74), clear cell ($OR_{adj}=2.71$; 95%CI 1.94 – 3.79) and mucinous ($OR_{adj}=2.78$; 95%CI 2.24 – 3.46) carcinomas than NHW.

CONCLUSIONS—Racial differences in late-stage OVCA diagnosis exist; however, these differences are decreasing with time. Within NCDB, NHB are significantly more likely diagnosed with late-stage OVCA and more specifically high-grade serous, clear cell and mucinous carcinomas than NHW.

Keywords

ovarian cancer; racial differences; racial disparities; time-trend; diagnosis stage; non-Hispanic Black; non-Hispanic White; high grade serous

PURPOSE

In the United States (US), ovarian cancer (OVCA) is the eighth most commonly diagnosed cancer and the fifth leading cause of female cancer deaths.[1] The American Cancer Society (ACS) estimates that in 2015, 21,290 women will be diagnosed with OVCA and 14,180 will die from the disease.[2] One important reason for such a high mortality is the absence of an effective screening mechanism.[3] Together with the lack of screening, an absence of OVCA-specific symptoms lead to the detection of the disease at an advanced stage (Federation of Gynecology and Obstetrics (FIGO) stage III, IV) in approximately 70% of women.[4] – [5] Late stage tumors have worse outcomes with a five-year relative survival rates for stages I, II, III, and IV of 90%, 70%, 39% and 17% respectively.[1] The high-grade serous carcinoma is the most common and the most lethal subtype of OVCA.[6] Less than 5% of women diagnosed with high-grade serous carcinomas are diagnosed at stage I.[7] – [8]

In the US, OVCA incidence rates are higher in non-Hispanic whites (NHW) than non-Hispanic blacks (NHB).[9] The Centers for Disease Control and Prevention (CDC) estimates the 2012 age-adjusted incidence rates for whites at 11.6/100,000 women, compared to 9.3/100,000 for blacks.[10] However, the five-year survival rate for blacks is 36% compared to 44% for whites (data was not reported for NHB/NHW).[11] Racial differences in diagnosis stage may partly account for the survival disadvantage in NHB.

Previous studies assessing racial and ethnic differences in OVCA diagnosis stage fail to present results for various OVCA subtypes and provide historic data on cases diagnosed between ten and twenty years ago.[11] – [15] Evidence suggests mixed historical study findings between race/ethnicity and OVCA diagnosis stage may be due in part to challenges related to the nature of the data (e.g., small and regional samples, short time-frames).[11] –

[15] Given the National Cancer Data Base (NCDB) includes approximately 70% of OVCA cases and particularly data across 15 years, an up-to-date analysis including patterns of temporal trends for OVCA in general and by histologic subtypes is warranted. Temporal trends may provide a more definitive understanding and explanation for the inconclusive historical results for the relationship between race/ethnicity and OVCA diagnosis stage. The recent National Academy of Medicine report identified a need to perform subtype-specific analyses due to the heterogeneity of ovarian cancers.[6] Subtype-specific analyses may help identify the drivers for the potential disparities. To the best of our knowledge, subtype-specific temporal trends for OVCA have not been assessed in the past. The purpose of this analysis is to assess NHB and NHW differences in late stage diagnosis of invasive epithelial OVCA overall and by histologic subtypes including: 1) current patterns of national trends, 2) potential changes across time, and 3) factors associated with late-stage diagnosis in the US and Puerto Rico between 1998 and 2011.

METHODS

Study population

The NCDB is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the ACS. Cases reported to NCDB represent approximately 70% or more than 194,000 newly diagnosed OVCA cases in the US and Puerto Rico. Cases are collected from over 1,500 hospitals with CoC-accredited cancer programs.[16] Reporting centers consist of community hospitals, academic medical centers and NCI-designated Comprehensive Cancer Centers.[17] This study was reviewed and approved by the Institutional Review Board at University of Illinois at Chicago as exempt given the de-identified nature of the data.

NCDB dataset included 154,253 NHB and NHW women with stage-diagnosed invasive epithelial¹ OVCA between 1998 and 2011. In order to test hypotheses comparing NHB and NHW women, data was restricted to NHB and NHW women, with Hispanics and all others groups omitted. Only cases with complete data on stage were included, representing 11,562 NHB and 137,106 NHW. Cases were sequentially eliminated from analysis if they were younger than 20 years (n=79, <0.1%), because of differences in tumor behavior in young women, and if they reported having an “unknown” or “other governmental health insurance” (n=5,506, 3.6%), as these categories were too small to analyze. In total, 26.6 % of cases; 34.0% NHB and 26.0% NHW had a registry-defined “missing” value for grade; these cases were not eliminated because of the important potential loss of information regarding the analytic sample.

Variables

All variables were based on NCDB categorization, with data collected through CoC’s Facility Oncology Registry Data Standards (FORDS), using standardized data transmission

¹ICD-04 epithelial histology codes included: 8010, 8012, 8013, 8015, 8020, 8021, 8022, 8030, 8031, 8032, 8033, 8040, 8041, 8045, 8046, 8050, 8051, 8052, 8070, 8071, 8072, 8073, 8074, 8120, 8130, 8140, 8141, 8143, 8144, 8145, 8148, 8170, 8190, 8200, 8201, 8214, 8230, 8231, 8240, 8241, 8243, 8244, 8245, 8246, 8249, 8255, 8260, 8310, 8313, 8323, 8380, 8381, 8382, 8440, 8441, 8442, 8450, 8460, 8461, 8462, 8470, 8471, 8472, 8480, 8481, 8482, 8490, 8562, 8570, 8574, 9000, 9014 and 9015

procedures coordinated by the North American Association of Cancer Registries (NAACR). [18] Briefly, diagnosis stage was based on FIGO categorization and defined by the pathologic stage group variable, which if missing, was then based on the clinical stage group. Diagnosis stage was analyzed as a dichotomous and also as a four level-category variable, respectively: early (stages I and II; localized) versus late (stages III and IV; regional and distant) and stages I, II, III and IV. The relationship between race and diagnosis stage was analyzed across three diagnosis periods (1998–2002, 2003–2007, 2008–2011) to assess temporal changes.

Zip code-level measures of income and education were estimated by matching the zip code of the patient recorded at the time of diagnosis against files derived from 2000 US Census data. They were analyzed according to NCDB-defined categories representing quartiles across all registry cancer cases [19] (i.e. OVCA cancer cases were skewed towards higher income; Table 1).

Age was analyzed in quartiles (<50, 50–64, 65–74, 75 years).[20] Tumor grade was analyzed as a three-level variable: (1) cell type well/moderately differentiated, (2) poorly differentiated/undifferentiated/anaplastic, (3) not determined/not stated/not applicable/unknown primaries/high grade dysplasia; and histology as a six-level variable (undifferentiated, unclassified, clear cell, endometrioid, serous and mucinous). Treatment facility case-volume was used as a proxy for surgeon experience.[21] – [23] It was defined using the average annual number of patients diagnosed with OVCA at each facility and analyzed in quartiles of case-volume (quartile distribution of cases per year: 1st = 0–7, 2nd = 8–16, 3rd = 17 – 28 and 4th = 29). Census-derived facility region was used as a proxy for healthcare access.[12]

For the purpose of this study, variables were classified into three groups: (1) tumor characteristics, including grade and histology, (2) socio-demographic, including age, education, income and health insurance, and (3) institutional, including facility type, facility location and facility case-volume.

Statistical analyses

NHB-NHW differences in tumor characteristics, socio-demographic and institutional factors were assessed using Chi-square test statistics. Odds ratios (OR) and 95% Confidence Intervals (95%CI) were estimated using multivariable logistic regression. Four nested models were compared using the log-likelihood ratio test, adjusting for 1) age; 2) age, grade and histology; 3) previous covariates plus health insurance, income and education, 4) previous covariates plus facility type, facility location and facility case-volume. The total sample size was held constant across comparisons.

Effect modification in the final model between race and diagnosis period was assessed by including the pair-wise interaction term and the main effects. Interaction was marginally significant ($P=0.09$); as such, diagnosis period-specific estimates were presented. The P_{trend} was reported from the effect of diagnosis period on diagnosis stage in the final fully adjusted, non-stratified model.

The effect of race on different levels of the outcome variables (late stage vs. early, stage 4 vs. 1, stage 3 vs. 1 and stage 2 vs. 1) was estimated using multivariable generalized logit models, stratified by histology and grade. Effect modification was assessed between race and diagnosis stage.

Statistical significance was set to $P < 0.05$ (two-sided) and all analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC). To rule out biases due to potential NHB-NHW differential case ascertainment over time, several sensitivity analyses were conducted. Sensitivity analyses were performed by estimating the adjusted OR and 95% CI of NHB-NHW differences in late-stage diagnosis for each covariate category, stratified by diagnosis period. First, the temporal pattern (i.e., 1998–2002, 2003–2007, 2008–2011) of NHB-NHW differences in diagnosis stage were assessed across categorizations of each covariate (Table 3). Second, temporal changes in NHB-NHW differences in case volume across the nine US census regions were assessed. Third, temporal changes in NHB-NHW differences in diagnosis stage were compared across hospitals reporting different volumes of cases (0–100, 101–500, 501–1000, 1001–1500). Lastly, patient comorbidity collection began in 2003 and was not available to assess changes over the diagnosis periods, thus a second analysis stratified by the Charlson Comorbidity Index was conducted using the last two periods (i.e., 2003–2007, 2008–2011; Table 3).

RESULTS

Analyses included 148,668 cases; 11,562 (7.8%) NHB and 137,106 (92.2%) NHW. Of these, late-stage disease (III, IV) was diagnosed in 76.3% NHB and 70.1% NHW ($P < 0.001$). In bivariate analyses, NHB were more likely diagnosed with undifferentiated, unclassified or mucinous histologic subtypes when compared to NHW. In addition, NHB and NHW significantly differed in tumor characteristics, socio-demographic, and institutional variables (Table 1).

In the comparison of the nested models (1998 – 2011), overall, NHB women were 1.26 (95% CI 1.19–1.33) times more likely to be diagnosed with late stage OVCA than NHW (Table 2). Across the three diagnosis time periods (1998 – 2002; 2003 – 2007; 2008 – 2011), multivariable logistic regression analyses identified decreasing NHB-NHW stage differences over time (1998–2002: $OR_{adj} = 1.36$, 95% CI = 1.23–1.49; 2003–2007: $OR_{adj} = 1.27$, 95% CI = 1.15–1.39; 2008–2011: $OR_{adj} = 1.15$, 95% CI = 1.05–1.27, $P_{trend} < 0.001$; Table 2). Notably, these NHB-NHW stage differences persisted in the most recent period.

The results from models stratified by histology and grade showed that NHB women diagnosed with various subtypes of OVCA were more likely to be diagnosed with late stage OVCA than NHW, including high-grade serous ($OR_{adj} = 1.13$; 95% CI 1.01–1.27), mucinous ($OR_{adj} = 2.27$; 95% CI 1.93–2.67) and clear cell ($OR_{adj} = 1.77$; 95% CI 1.40–2.24). No differences were detected in women diagnosed with other histologic subtypes. Furthermore, results from the generalized models demonstrated that the disparity in later diagnosis stage was driven by those diagnosed with stage 4 when compared to stage 1 (Figure 1). This pattern was consistent across all histologic subtypes. Effect modification to further explore what OVCA subtype is driving decreasing NHB-NHW stage differences over time

demonstrated no statistically significant interaction between race and diagnosis period across the histologic subtypes. However, varying stage-specific NHB-NHW differences were present over time across the various subtypes (Figure 1).

No evidence of differential NHB-NHW case ascertainment was identified in sensitivity analyses (Table 3; results from all covariates presented), as is evident by comparing temporal patterns of NHB-NHW diagnostic stage differences across categorizations with each covariate. Additional sensitivity analyses indicated that excluding the comorbidity index, which was not collected prior to 2003, was unlikely to bias study results (e.g., OR_{adj} overall time period (1998–2011): without comorbidity index, $OR_{adj}=1.26$ (95%CI 1.19–1.33), with comorbidity index, $OR_{adj}=1.20$ (95%CI 1.12–1.28), and by time periods: without comorbidity index; 2003–2007: $OR_{adj}=1.27$, 95%CI=1.15–1.39, 2008–2011: $OR_{adj}=1.15$, 95%CI=1.05–1.27, with comorbidity index = 2003–2007: $OR_{adj}=1.26$, 95%CI=1.14–1.38, 2008–2011; $OR_{adj}=1.15$, 95%CI=1.04–1.26). In addition, temporal patterns of NHB-NHW diagnosis stage differences persisted across comorbidity index categorizations (Table 3).

DISCUSSION

This study demonstrates that between 1998 and 2011, NHB are more likely diagnosed with late-stage invasive epithelial OVCA than NHW, after adjusting for potential confounders. The relationship between race and diagnosis stage is attenuated with the inclusion of tumor characteristics and demographic variables, but not institutional variables, in a comparison of nested models. Findings also demonstrate that NHB-NHW stage differences decreased significantly across diagnosis periods. However, persisting NHB-NHW differences exist in the most recent period, with NHB significantly more likely diagnosed with late-stage disease. These temporal changes confirm and extend the results from previous studies. After adjusting for appropriate confounders, NHB women were significantly more likely to be diagnosed with late stage OVCA than NHW in analysis of the California Cancer Registry [13] and the Surveillance Epidemiology and End Results (SEER) data [14].

Our results also show that NHB women when compared to NHW are almost three times more likely to be diagnosed with stage 4 vs. stage 1 clear cell and mucinous carcinomas. In addition, they are 50% more likely to be diagnosed with stage 4 vs. stage 1 high-grade serous carcinomas. Our analyses do not show any temporal changes in diagnosis stage over time in any of the histologic subtypes. To our knowledge, no other studies have assessed the effect of time on racial differences in OVCA diagnosis stage overall and by histologic subtypes.

Several potential reasons exist for these NHB-NHW stage difference findings, one of which is differential access to care. Previous literature suggests uninsured or underinsured patients are less likely to participate in cancer-screening programs. [24] – [26] Although no clearly established OVCA screening procedure is available, underinsured women are less likely to have a healthcare provider, which implies symptoms suggestive of OVCA could be missed, or take longer to address. Studies have also demonstrated having a regular source of medical care such as a primary care physician increases the chances of patients being diagnosed with early stage cancer in other sites.[27]–[28] According to the 2013 National Healthcare

Disparity Report [29], blacks have significantly worse healthcare access, are more likely to have communication difficulties with providers, in part to a mixed-race relationship between provider and patient [30], are less likely to have a usual primary care provider, and are more likely to experience medical care delays for financial reasons.[31] Differences in quality of care [30], medical mistrust [32], timing [29], and healthcare access [32] may contribute to late-stage diagnoses. The reasons for the observed differential disparities in late-stage diagnosis across histologic subtype for NHB-NHW are unclear (e.g., absence of differences with low grade serous versus significant differences with clear cell), but likely represent a combination of dissimilarities between both groups in tumor biology, prevalence of subtype-specific risk factors, as well as the access-related issues discussed above.

Documenting patterns in OVCA stage over time is an important surveillance activity, both in quantifying NHB-NHW stage differences and exploring factors that could explain observed differences. The decrease in racial differences in diagnosis stage over time identified may be attributed to factors such as improving healthcare access.[33] We hypothesize additional factors may account for the narrowing NHB-NHW stage differential observed over the study period, including improved delivery of care and doctor-patient relationships, decreased perceived racial discrimination, and increased OVCA awareness.

Results should be interpreted in light of limitations. First, education and income variables were only available at the zip code-level. While area-level socioeconomic status (SES) measures are proxies for individual-level SES, they are useful in assessing area-level health inequalities.[34] – [35] Second, patient comorbidities were omitted from models as they were not collected prior to 2003. Comorbidities are influenced by healthcare access, such that women with comorbidities and healthcare access may have a higher chance of disease diagnosis [36]; however, sensitivity analyses indicate such biases are unlikely. Third, although physician specialty, an important predictor for staging [32], [33] and OVCA cancer outcomes [20], [37]–[39], was not available, we used average facility-case volume as a proxy to minimize this bias, as it has been demonstrated in multiple analyses that a low institutional case volume reflects a lack of gynecologic oncology subspecialty care.[21]–[23] Fourth, although ORs may overestimate the relationship between race and diagnosis stage if the outcomes are highly prevalent, use of ORs is consistent with previous NCDB literature. [12], [39] Lastly, the NCDB does not include cases reported by non-approved hospitals, notably community hospitals serving minorities and women from lower SES groups, so results may be underestimated.

Despite limitations, several strengths exist. First, findings are likely the most accurate representation of racial differences in diagnosis stage across the US, as this investigation approximates a population-based study by using NCDB, which is one of the largest dataset that includes 70% of newly diagnosed OVCA cases in the US and Puerto Rico.[16], [17] NCDB data is collected using nationally standardized definitions specified in FORDS and NAACR.[18] Although SEER has almost complete ascertainment among regions captured, it is limited to regions represented that include more urban areas with foreign-born people in comparison to the US 2010 population [40], and it fails to consider highly segregated cities such as Chicago, Milwaukee and Philadelphia, which could mask racially-patterned OVCA differences. [41], [42] Moreover, SEER only includes 28% of the US population and does

not collect data on health insurance.[40], [43] Second, results of this study are based on data obtained over fifteen years. Notably, the long duration of follow-up allows for detailed comparisons and a temporal assessment of differences in NHB-NHW diagnosis stage, filling an important gap in the literature based on SEER data. [44] Third, the large sample size provides adequate study power to detect changes over time in NHB-NHW stage differences for OVCA in general and by histologic subtypes, with results generalizable to NHB and NHW diagnosed at CoC facilities in the US and Puerto Rico. Additionally, the sample size was sufficient to allow multiple sensitivity analyses across various covariate categories, with results suggesting unlikely differential NHB-NHW case ascertainment.

In summary, results demonstrate that NHB are significantly more likely diagnosed with late-stage invasive epithelial OVCA than NHW, and more specifically, with high grade serous, mucinous and clear cell carcinomas. Results also demonstrate an improvement in NHB-NHW stage differences over time. Documenting such patterns is an important surveillance activity for planning future healthcare needs, helping to quantify NHB-NHW stage differences and identify factors that are contributing to observed differences.

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Fig. 1.

Multivariable logistic regression odds ratios (ORs) for the association between race and diagnosis stage for high grade serous, mucinous and clear cell carcinomas: overall: 1998–2011 and by three periods: 1998–2002, 2003–2007 and 2008–2011. Diagnosis stage was analyzed as a dichotomous (late vs. early) and four level-category variable (stages 2 vs. 1, 3 vs. 1 and 4 vs. 1).

National Cancer Database, 1998–2011) (n=148,668)

Table 1

Sample characteristics by non-Hispanic white (NHW) and non-Hispanic black (NHB), overall and by covariates. (National Cancer Database, 1998–2011) (n=148,668)

	NHB		NHW		Total	Chi-Square <i>p</i> -value
	n	%	n	%	n	
Overall	11,562	7.8	137,106	92.2	148,668	
Diagnosis Stage						<.0001
Early (Stage I and II)	2,738	23.7	41,017	29.9	43,755	
Late (Stage III and IV)	8,824	76.3	96,089	70.1	104,913	
Missing	0	0	0	0	0	
Socio-Demographic Variables						<.0001
<u>Diagnosis Age:</u>						
<50 yrs	2,392	20.7	23,772	17.3	26,164	
50–64 years	4,173	36.1	49,053	35.8	53,226	
60–74 years	2,785	24.1	32,345	23.6	35,130	
75+ years	2,212	19.1	31,936	23.3	34,148	
Missing	0	0	0	0	0	
<u>Diagnosis Period:</u>						<.0001
2008–2012	3,830	33.1	40,179	29.3	44,009	
2003–2007	3,932	34.0	47,216	34.4	51,148	
1998–2002	3,800	32.9	49,711	36.3	53,511	
Missing	0	0	0	0	0	
<u>Income*:</u>						<.0001
\$46,000+	2,162	18.7	56,529	41.2	58,691	
\$35,000–\$45,999	2,497	21.6	36,898	26.9	39,395	
\$30,000–\$34,999	2,331	20.2	22,574	16.5	24,905	
<\$30,000	3,970	34.3	12,725	9.3	16,695	
Missing	633	5.2	8,670	6.1	9,303	

	NHB		NHW		Total	Chi-Square <i>P</i> -value
	n	%	n	%	n	
Education* :						
<14.0 or less without a high-school diploma	1,502	13.0	52,892	38.6	54,394	<.0001
14–19.9% without a high-school diploma	1,568	13.6	32,465	23.7	34,033	
20–28.9% without a high-school diploma	3,462	29.9	27,777	20.3	31,239	
29.0% or more without a high-school diploma	4,427	38.3	15,582	11.4	20,009	
Missing	634	5.3	8,680	6.1	9,14	
Health Insurance:						
Private Insurance	4,569	39.5	68,330	49.8	72,899	<.0001
Medicaid	1,324	11.5	4,930	3.6	6,254	
Medicare	4,828	41.8	59,554	43.4	64,382	
Not Insured	841	7.3	4,292	3.1	5,133	
Missing	524	4.3	4,982	3.5	5,506	
Tumor Characteristics						
Histology:						
Serous	5,366	46.4	69,118	50.4	74,484	<.0001
Endometrioid	972	8.4	16,567	12.1	17,539	
Mucinous	898	7.8	8,747	6.4	9,645	
Clear cell	350	3.0	7365	5.4	7,715	
Undifferentiated	2,672	23.1	22,825	16.7	25,497	
Unclassified	1,304	11.3	12,484	9.1	13,788	
Missing	0	0	0	0	0	
Grade:						
Well/moderately differentiated	2,375	20.5	33,440	24.4	35,815	<.0001
Poorly differentiated/undifferentiated/anaplastic	5,251	45.4	68,054	49.6	73,305	
Not determined, not stated or not applicable, unknown primaries, high grade dysplasia	3,936	34.0	35,612	26.0	39,548	
Missing	0	0	0	0	0	
Institutional Variables						

	NHB		NHW		Total n	Chi-Square <i>p</i> value
	n	%	n	%		
<u>Facility Type:</u>						
Academic/Research programs	5,347	46.3	48,992	35.7	54,339	<.0001
Community Cancer Programs	824	7.1	10,585	7.7	11,409	
Other Specified Types of Cancer Programs	348	3.0	3,405	2.5	3,753	
Comprehensive Community Cancer Programs	5,043	43.6	74,124	54.1	79,167	
Missing	0	0	0	0	0	
<u>Facility Location:</u>						
East North Central	1,805	15.6	23,978	17.5	25,783	<.0001
East South Central	1,118	9.7	9,204	6.7	10,322	
Middle Atlantic	1,955	16.9	21,382	15.6	23,337	
Mountain	103	0.9	7,512	5.5	7,615	
New England	216	1.9	9,086	6.6	9,302	
Pacific	683	5.9	16,934	12.4	17,617	
South Atlantic	4,217	36.5	29,386	21.4	33,603	
West North Central	289	2.5	9,832	7.2	10,121	
West South Central	1,176	10.2	9,792	7.1	10,968	
Missing	0	0	0	0	0	
<u>Treatment Facility Case-Volume** :</u>						
Fourth Quartile	2,429	21.0	34,567	25.2	36,996	<.0001
Third Quartile	3,096	26.8	33,868	24.7	36,964	
Second Quartile	2,874	24.9	34,704	25.3	37,578	
First Quartile	3,163	27.4	33,967	24.8	37,130	
Missing	0	0	0	0	0	

* Measure estimated by matching the zip code of the patient recorded at the time of diagnosis against files derived from year 2000 US Census data. Variables categorized as quartiles representing quartiles across all registry cancer cases.

** Quartile distribution of cases per year: 1st = 0–7, 2nd = 8–16, 3rd = 17 – 28, 4th >29.

Table 2

Multivariable logistic regression odds ratios (ORs) for the association between non-Hispanic Black (NHB) and diagnosis stage: a) overall: 1998–2011 and by three periods b) 1998–2002 c) 2003–2007 and d) 2008–2011. Results demonstrate NHB are significantly more likely to be diagnosed with late stage epithelial ovarian cancer than NHW overall; 1998–2011, in unadjusted (Model 1) and adjusted models (Models 2–4). Differences are decreasing over time being the highest in the: b) 1998–2002 period; and the lowest in d) 2008–2011 period. (National Cancer Database, 1998–2011) (n=148,668)

	Overall	Diagnosis Period			<i>P</i> _{trend} for Diagnosis Period ^e
	(a) 1998–2011 OR(95%CI)	(b) 1998–2002 OR(95%CI)	(c) 2003–2007 OR(95%CI)	(d) 2008–2011 OR(95%CI)	
Model 1^a	1.46 (1.39–1.52)	1.56 (1.43–1.69)	1.50 (1.38–1.62)	1.36 (1.25–1.47)	<.0001
Model 2^b	1.32 (1.25–1.39)	1.42 (1.29–1.55)	1.36 (1.25–1.49)	1.22 (1.11–1.34)	<.0001
Model 3^c	1.26 (1.19–1.33)	1.36 (1.23–1.49)	1.27 (1.16–1.39)	1.16 (1.06–1.27)	<.0001
Model 4^d	1.26 (1.19–1.33)	1.36 (1.23–1.49)	1.27 (1.15–1.39)	1.15 (1.05–1.27)	<.0001

^a Adjusted for age

^b Adjusted for age, histology and grade.

^c Adjusted for age, histology, grade, health insurance status, zip code-level income and zip code-level education

^d Adjusted for age, histology, grade, health insurance status, zip code-level income, zip code-level education, facility type, facility location and facility case-volume

^e The *P*_{trend} was reported from the effect of diagnosis period on diagnosis stage in the final fully adjusted non-stratified model.

Table 3

Results from sensitivity analyses. Adjusted Odds Ratios (OR) and 95%CI of late-stage diagnosis for non-Hispanic Black (NHB) versus non-Hispanic whites (NHW) by diagnosis period, stratified by covariates. (ie. The OR of racial differences in late stage diagnosis statistically decreases over time within each level of health insurance status). (National Cancer Database, 1998–2011) (n=148,668).

	Diagnosis Period			<i>P</i> value for Trend for Diagnosis Period ^d
	1998–2002 OR (95%CI)	2003–2007 OR (95%CI)	2008–2011 OR (95%CI)	
Diagnosis Stage				
Late (III, IV) versus Early (I, II)	1.36 (1.23–1.49)	1.27 (1.15–1.39)	1.15 (1.05–1.27)	<.0001
Socio-Demographic Variables				
<u>Diagnosis Age:</u>				
<50 yrs	1.43 (1.19–1.72)	1.25 (1.03–1.51)	1.21 (0.98–1.48)	<.0001
50 – 64 years	1.43 (1.22–1.69)	1.39 (1.19–1.62)	1.11 (0.95–1.29)	<.0001
65 – 74 years	1.38 (1.12–1.70)	1.22 (0.99–1.51)	1.15 (0.94–1.41)	<.0001
75+ years	1.12 (0.89–1.39)	1.11 (0.88–1.41)	1.19 (0.93–1.51)	0.002
<u>Income:</u> ^a				
\$46,000 +	1.56 (1.26–1.94)	1.51 (1.23–1.86)	1.12 (0.93–1.36)	<.0001
\$35,000 – \$45,999	1.15 (0.95–1.39)	1.20 (0.99–1.46)	1.01 (0.84–1.21)	<.0001
\$30,000 – \$35,000	1.23 (1.01–1.51)	1.15 (0.94–1.41)	1.22 (0.99–1.50)	0.0002
< \$30,000	1.50 (1.26–1.78)	1.30 (1.10–1.55)	1.22 (1.02–1.47)	<.0001
<u>Education:</u> ^a				
less than 14% without HS diploma	1.43 (1.11–1.84)	1.41 (1.09–1.81)	1.18 (0.94–1.47)	<.0001
14%–19.9% without HS diploma	1.63 (1.25–2.13)	1.20 (0.96–1.52)	1.06 (0.85–1.34)	<.0001
20% – 28.9% without HS diploma	1.26 (1.07–1.49)	1.34 (1.13–1.59)	1.15 (0.97–1.36)	<.0001
29% or more without HS diploma	1.36 (1.17–1.58)	1.23 (1.05–1.44)	1.18 (1.00–1.39)	<.0001
<u>Health Insurance</u>				
Private Insurance/Managed Care	1.45 (1.26–1.67)	1.31 (1.14–1.50)	1.14 (0.99–1.32)	<.0001
Medicare	1.23 (1.05–1.43)	1.24 (1.06–1.46)	1.19 (1.02–1.39)	<.0001
Medicaid	1.35 (0.97–1.88)	1.14 (0.83–1.56)	1.02 (0.77–1.35)	<.0001
Not insured	1.59 (1.11–2.28)	1.43 (0.99–2.06)	1.30 (0.89–1.91)	0.02
Tumor Characteristics				
<u>Histology:</u>				
Serous	1.08 (0.93–1.25)	1.06 (0.92–1.23)	0.97 (0.84–1.11)	<.0001
Endometrioid	1.31 (1.02–1.69)	1.22 (0.94–1.60)	1.18 (0.86–1.61)	<.0001
Mucinous	2.18 (1.67–2.84)	2.60 (1.97–3.44)	2.04 (1.50–2.78)	<.0001
Clear cell	2.08 (1.34–3.21)	1.28 (0.84–1.97)	1.95 (1.33–2.86)	0.10
Undifferentiated	1.46 (1.16–1.83)	1.21 (0.94–1.56)	1.11 (0.86–1.43)	0.02
Unclassified	1.30 (0.94–1.78)	1.27 (0.98–1.64)	1.11 (0.88–1.40)	0.001

	Diagnosis Period			<i>P</i> value for Trend for Diagnosis Period ^d
	1998–2002 OR (95%CI)	2003–2007 OR (95%CI)	2008–2011 OR (95%CI)	
<u>Grade:</u>				
Well/moderately differentiated	1.57 (1.33–1.86)	1.38 (1.15–1.66)	1.20 (0.98–1.47)	<.0001
Poorly differentiated, undifferentiated, anaplastic	1.18 (1.01–1.38)	1.21 (1.05–1.40)	1.15 (1.00–1.32)	<.0001
Not determined, not stated or not applicable, unknown primaries/high grade dysplasia	1.34 (1.13–1.59)	1.29 (1.08–1.55)	1.14 (0.95–1.36)	0.005
Institutional Variables				
<u>Facility Type:</u>				
Academic/Research Program	1.37 (1.18–1.60)	1.28 (1.11–1.48)	1.23 (1.07–1.42)	<.0001
Community Cancer Program	1.34 (0.95–1.89)	1.19 (0.83–1.71)	1.10 (0.73–1.65)	0.001
Other specified types of cancer programs	2.06 (1.42–3.03)	0.63 (0.31–1.28)	2.98 (0.30–29.9)	0.64
Comprehensive Community Cancer Program	1.30 (1.12–1.50)	1.31 (1.14–1.51)	1.07 (0.93–1.23)	<.0001
<u>Facility Location:</u>				
East North Central	1.15 (0.91–1.46)	1.17 (0.91–1.50)	1.41 (1.09–1.82)	<.0001
East South Central	1.70 (1.24–2.32)	1.28 (0.96–1.72)	1.33 (0.99–1.78)	<.0001
Middle Atlantic	1.41 (1.13–1.78)	1.55 (1.22–1.96)	1.14 (0.89–1.44)	<.0001
Mountain	1.96 (0.67–5.77)	1.24 (0.47–3.23)	0.72 (0.29–1.83)	0.004
New England	1.26 (0.58–2.73)	0.90 (0.52–1.57)	1.50 (0.74–3.04)	0.011
Pacific	1.69 (1.13–2.51)	1.06 (0.73–1.54)	1.02 (0.70–1.49)	<.0001
South Atlantic	1.28 (1.09–1.51)	1.30 (1.10–1.52)	1.08 (0.92–1.27)	<.0001
West North Central	1.84 (0.99–3.43)	1.67 (0.88–3.19)	1.18 (0.66–2.11)	<.0001
West South Central	1.54 (1.12–2.12)	1.19 (0.87–1.62)	1.02 (0.76–1.36)	0.0003
<u>Treatment Facility Case-Volume:</u> ^b				
Fourth Quartile	1.46 (1.16–1.84)	1.31 (1.07–1.60)	1.25 (1.03–1.52)	<.0001
Third Quartile	1.24 (1.02–1.50)	1.35 (1.12–1.63)	1.14 (0.95–1.36)	<.0001
Second Quartile	1.57 (1.29–1.90)	1.23 (1.02–1.48)	1.07 (0.88–1.30)	0.001
First Quartile	1.24 (1.04–1.47)	1.17 (0.97–1.42)	1.13 (0.93–1.39)	<.0001
Comorbidities: ^c				
0	N/A	1.25 (1.12–1.39)	1.13 (1.01–1.27)	<.0001
1	N/A	1.31 (1.04–1.65)	1.18 (0.95–1.46)	<.0001
2	N/A	1.25 (0.77–2.03)	1.23 (0.83–1.82)	0.1

^aMeasures estimated by matching the zip-code of the patient recorded at the time of diagnosis against files derived from year 2000 US Census data. Variables categorized as quartiles based on equally proportioned variable ranges within the NCDB, in all cancers and among all US zip codes.

^bQuartile distribution of cases per year: 1st = 0–7, 2nd = 8–16, 3rd = 17–28, 4th >29.

^cResults from sensitivity analysis; analysis restricted to cases diagnosed between 2003–2011; fully adjusted regression models stratified by patient comorbidities.

^dThe *P*_{trend} was reported from the effect of diagnosis period on diagnosis stage in the final non-stratified, fully adjusted model.