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Factors associated with delivery of neoadjuvant chemotherapy in women with advanced stage ovarian cancer

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HIGHLIGHTS

- Race, income level, center volume, and insurance were associated with neoadjuvant chemotherapy.
- Non-clinical factors were associated with treatment at a magnitude similar to clinical factors.
- Race was no longer predictive when women who received no surgery were excluded.

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ABSTRACT

Purpose. To identify clinical and non-clinical factors associated with utilization of primary cytoreductive surgery (PCS) or neoadjuvant chemotherapy (NACT) in women with advanced stage epithelial ovarian cancer (EOC).

Methods. Using the National Cancer Database, we identified women with stage IIIC and IV EOC diagnosed from 2012 to 2014. The primary outcome was receipt of NACT, defined in the primary analysis as utilization of chemotherapy as the first cancer-directed therapy, irrespective of whether interval surgery was performed. Univariable and multivariable associations between clinical and non-clinical factors and receipt of NACT were investigated using mixed-effect logistic regression models. A secondary analysis excluded women who received primary chemotherapy but did not receive interval cytoreductive surgery.

Results. Among 17,302 eligible women, 10,948 (63.3%) underwent PCS and 6354 (36.7%) received NACT. Older age, stage IV disease, high-grade, and serous histology were associated with receipt of NACT in univariate ($p < 0.001$) and multivariable analyses ($p < 0.001$). Analysis of non-clinical factors revealed that residency in the Northeast region and receipt of treatment closer to home were associated with NACT in univariate ($p < 0.05$) but not multivariable analysis ($p > 0.05$). In multivariable analysis, African-American race/ethnicity ($p = 0.04$), low-income level ($p = 0.02$), treatment in high-volume centers ($p < 0.01$), and insurance by Medicare or other government insurance ($p < 0.001$) were associated with receipt of NACT. When women who received no surgery were excluded, all factors that were independent predictors of NACT in the main analysis remained significant, except for race/ethnicity.

Conclusions. Non-clinical factors were associated with the use of NACT at a magnitude similar to that of clinically relevant factors.

1. Introduction

Practice guidelines document evidence-based, consensus-driven recommendations that aid clinical decision-making and decrease the use of unproven treatment strategies [1–3]. However, an analysis of national data revealed that only 44% of patients with advanced ovarian cancer received care consistent with the National Comprehensive Cancer Network guidelines [4]. Since 2011, these guidelines have

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recommended primary cytoreductive surgery (PCS) and adjuvant platinum-based chemotherapy as the preferred treatment for advanced ovarian cancer, with neoadjuvant chemotherapy (NACT) and interval cytoreduction reserved for patients who are not candidates for primary debulking surgery [5]. Similar criteria were recently endorsed by the Society for Gynecologic Oncology and the American Society for Clinical Oncology [6].

The use of NACT has increased substantially in the past decade, with recent literature reporting an increase from 8.6% to 22.6% between 2004 and 2013 [7]. The adoption of this treatment modality has particularly impacted certain patient populations, including elderly women and those with stage IV disease [7]. Ideally, the choice between NACT and PCS should depend only on factors related to a patient's disease burden and fitness for surgery. However, in the United States there is substantial geographic, racial, and socioeconomic variability in cancer treatment [8,9]. This study used a large national cancer registry to investigate how clinical and non-clinical factors contribute to treatment selection among women with advanced epithelial ovarian cancer in the United States.

2. Materials and methods

This study was granted exempt status by the Partners Human Research Committee. Data were obtained from the National Cancer Database (NCDB), a joint program of the American College of Surgeons and the American Cancer Society that captures >70% of newly diagnosed malignancies in the United States [10]. This national clinical surveillance oncology database includes information about patient demographics, tumor characteristics, cancer-directed treatments, and outcomes. We identified women with ovarian cancer diagnosed from 2012 through 2014 in the NCDB 2014 public use file. We used *International Classification of Disease for Oncology, 3rd Edition* (ICD-O-3) codes to identify women with epithelial ovarian histologies, including serous adenocarcinoma (8441, 8460–8463), mucinous adenocarcinoma (8470–8471, 8480, 8481), clear cell adenocarcinoma (8310, 8313), endometrioid adenocarcinoma (8380–8381), carcinosarcoma (8950, 8980, 8951, 8981), and other adenocarcinoma (8050, 8140, 8144, 8255, 8260, 8263, 8290, 8320, 8323, 8340, 8440, 8450, 8490, 8560, 8574, 8940) [11]. We included patients with American Joint Committee on Cancer (AJCC) 7th edition or FIGO stage IIIC or IV disease [12]. Because use of NACT could affect pathological stage, we defined stage using the AJCC clinical stage when this information was available.

The outcome of interest was primary treatment modality. In the primary analysis, all women whose first treatment was definitive surgery were categorized as having undergone PCS. Patients who received chemotherapy prior to, or to the exclusion of, surgery were categorized as having undergone NACT. In addition, we undertook an alternative analysis that excluded patients who received chemotherapy exclusively, because a subset of these patients may have received chemotherapy with palliative intent only.

We classified subject age as <40, 40–49, 50–59, 60–69, 70–79, and 80 years and older. Race/ethnicity was classified as non-Hispanic white, non-Hispanic African-American, Asian, Hispanic, and other/unknown. We classified patients as having or not having comorbidities using the Deyo adaption of the Charlson comorbidity index [13,14]. The geographic region of the treating facility was categorized according to census region (Midwest, Northeast, South, and West) [15]. Rural/urban status was determined using patients' county of residence and classified as metropolitan, adjacent to a metropolitan area, or nonmetropolitan, using the United States Department of Agriculture's Economic Research Service rural–urban continuum codes [16]. The median household income in the subject's ZIP code was used as a proxy for income, and categorized according to quartiles across all United States ZIP codes as estimated by the 2012 American Community Survey. Insurance status was categorized as privately insured, insured by Medicare, insured by another type of government insurance, or uninsured. The treating facility was categorized as an academic or research program, a community cancer program, an integrated network cancer program, or other/unknown. We calculated the annual average number of cases of advanced ovarian cancer treated in each facility during the study period and categorized into quartiles. Distance to the treating facility was estimated as the distance between the treating facility and the centroid of the patient's ZIP code and categorized into quartiles.

These variables were then classified as clinical or nonclinical factors. Clinical factors included age, comorbidity index, tumor stage, histology and grade. Demographic or nonclinical factors included race, education and income levels, insurance type, and geographic region, as well as hospital factors such as hospital proximity, volume, and facility type. Similar divisions of variables have been used in analyses of disparities in care for multiple other cancer types across multiple oncologic subspecialties [17–19].

2.1. Statistical analysis

We calculated the percentage of patients in each demographic and clinical category who underwent PCS and NACT. All p-values were obtained from mixed-effects models with a random intercept for the treating facility to account for hospital-level random effects. To test whether variables of interest were associated with receipt of NACT, we compared univariable mixed-effects logistic regression models with nested intercept–only models using the likelihood ratio test. To determine whether variables of interest were associated with receipt of NACT after adjusting for covariates, we constructed a multivariable mixed-effects logistic regression model including clinical and nonclinical variables that were a priori considered likely to affect treatment choice. We estimate adjusted odds of receiving NACT for variables of interest and Wald 95% confidence intervals. The significance of each covariate was estimated using the likelihood ratio test. Statistical analysis was performed using SAS 9.2 and Stata/MP version 14.2.

3. Results

The study sample consisted of 17,302 women with stage IIIC and IV epithelial ovarian cancer treated at a facility participating in NCDB between 2012 and 2014 who met the inclusion criteria. Of these women, 10,948 (63.3%) underwent PCS, whereas 6354 (36.7%) underwent primary chemotherapy. Of those who received primary chemotherapy, 1931 (30.4% of those receiving primary chemotherapy) did not have subsequent interval surgery and were therefore classified as having received chemotherapy only. Among all subjects, 10,327 (59.7%) had stage IIIC disease, and among patients with known tumor grade, 11,008 (63.6%) had grade 3 disease. Serous adenocarcinoma was the most common histology, identified in 13,066 patients (75.5%).

Patient characteristics and demographics, as well as univariable analysis of treatment modality, are reported in Table 1. In the entire population, we identified clinical factors that were associated with the selection of primary treatment modality. Women who had NACT were significantly older (mean age 65.7 vs. 61.6 years; $p < 0.001$), more likely to be diagnosed with stage IV disease (56% vs. 25.6%; $p < 0.001$), have serous histology (88.1% vs. 82.8%; $p < 0.001$), and have one or more comorbidities (14.4% vs. 11.3%; $p < 0.001$). Similarly, we examined associations between NACT and non-clinical factors. Primary chemotherapy was utilized more often in African-American patients compared with whites (41.9% vs. 36.5%; $p < 0.001$), residence in ZIP codes with median annual household income less than $63,000 (66.2% vs. 63.1%; $p < 0.001$), in patients without private insurance (42.2% vs. 29.5%; $p < 0.001$), in those treated in the Northeast compared with those in other regions (40.4% vs. 35.8%; $p = 0.01$), in those living within 5.8 miles of their treatment facility compared to those furthest away (39.2% vs. 35.3%; $p < 0.001$), and in those treated at high- or low-volume hospitals compared with intermediate volume hospitals (40.1% vs. 33.4%; $p = 0.001$).

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