Racial Disparities in the Ovarian Cancer Care Continuum: from the Symptomatic Period to the End of Life

by

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Dedication

This dissertation is dedicated to my dad, Larry Mullins. He taught me more than he will ever know, and I will carry him with me in all that I do.

gave me tennis, a love of nature and childlike joy--the things that have kept me sane and happy

in the last seven years. Thank you both from the bottom of my heart.

Preface

Chapter 2 (*Perceived Discrimination, Trust in Physicians, and Prolonged Symptom Duration Before Ovarian Cancer Diagnosis in the African American Cancer Epidemiology Study*) has been published in Cancer. The list of full authors is: Megan A. Mullins, Lauren C. Peres, Anthony J. Alberg, Elisa V. Bandera, Jill S. Barnholtz-Sloan, Melissa L. Bondy, Ellen Funkhouser, Patricia G. Moorman, Edward S. Peters, Paul D. Terry, Ann G. Schwartz, Andrew B. Lawson, Joellen M. Schildkraut and Michele L. Cote.

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Abstract

Ovarian cancer is the deadliest gynecologic cancer with less than half of women surviving five years after their diagnosis. At all stages of diagnosis and across histologic subtypes, black women have the poorest survival. Despite survival improvements among white women, survival in black women has declined. Evidence overwhelmingly points to differential care driving this disparity. This dissertation evaluates race and racially driven exposures in two phases of the ovarian cancer care continuum, the symptomatic window prior to diagnosis and end-of-life care.

In Aim 1, we evaluated the associations between everyday discrimination and trust in physicians with a prolonged interval between symptom onset and ovarian cancer diagnosis in the African American Cancer Epidemiology Study. Perceived everyday discrimination was associated with prolonged symptom duration whereas more commonly evaluated determinants of access to care and trust in physicians were not.

In Aim 2, we evaluated racial disparities in aggressive end-of-life care among older women with ovarian cancer in the Surveillance, Epidemiology and End Results linkage with Medicare. We also explored the association of care characteristics including source of evaluation and management, utilization of hospice/palliative care visits, and continuity of care. We found that nonwhite women were more likely to receive aggressive end-of-life care than white women. While the proportion of management done in oncology, receipt of a hospice or palliative

evaluation and management visit and continuity of care were associated with certain outcomes, they did not explain the racial variation that we see in these outcomes.

In Aim 3, we investigated physician variation in aggressive end-of-life care. We found substantial clustering in physicians for many aggressive end-of-life care indicators including chemotherapy, not enrolling in hospice, and multiple hospitalizations in the last month of life. Although physician characteristics did not meaningfully explain the racial differences seen in receipt of aggressive end-of-life care, nonwhite women tended to see different types of physicians, and seeing a physician with a more racially diverse patient base was associated with higher odds of not receiving hospice, having a stay in the ICU, receiving a life extending procedure, and having a terminal hospitalization.

Overall, this dissertation is one of the first to examine racial disparities across the care continuum for women diagnosed with ovarian carcinoma. Findings suggest that black women tend to receive different care for their ovarian cancer than white women, especially towards the end of life. Future studies must delve further into the effects of racism and patient care practices on ovarian cancer care in order to identify targets for intervention.

CHAPTER 1. Introduction

Ovarian Cancer Epidemiology

Disease Incidence and Risk Factors

In 2020, an estimated 21,750 new cases of ovarian cancer will occur in the US, and 13,940 women will die from the disease.[1] Ovarian cancer incidence is higher among white women, with 12.2 cases/100,000 women, compared to 9.4 cases/100,000 among black women.[2] There are several established risk factors for ovarian cancer. Exposures and behaviors known to be protective against ovarian cancer are parity, oral contraceptive use, breastfeeding and tubal ligation.[3] Alternatively, endometriosis, BRCA1 and BRCA2 mutation, first degree family history, obesity, talc use, mutations in BRIp1, RAD51C, RAD51D, and Lynch syndrome all increase risk of the disease.[4–9] Additionally, there are 35 epithelial ovarian carcinoma susceptibility alleles, with effect sizes ranging from odds ratios of 0.79 to 3.0 discovered in predominantly European ancestry populations.[10] Despite small effect sizes, these risk-conferring SNPs can make larger differences in risk when considered in aggregate such as in genetic risk scores. Differing prevalence of environmental risk factors among racial groups contributes to 31% of the lower incidence seen in African ancestry women compared to European ancestry.[11] Estimating the contribution of genetics to the racial difference in incidence is challenging given the very small number of non-European ancestry women genotyped.

Types of Ovarian Cancer

The majority of ovarian cancers arise from epithelial cells. Other types of ovarian cancer include sex-cord stromal, germ cell, or mixed cell tumors.[12] Within epithelial ovarian cancer, there are five major histologic subtypes of invasive disease that are increasingly recognized as distinct. High grade serous is the most common subtype (70%), followed by endometrioid (10%), clear cell (10%), mucinous (3%) and low grade serous (<5%). There are also borderline serous and mucinous subtypes, which are noninvasive.[13,14] High grade serous carcinoma begins in the fimbriated end of the fallopian tube, while endometrioid and clear cell carcinomas arise from borderline serous carcinoma and endometriosis.[15] Endometrioid carcinoma cells resemble normal cells in the uterine corpus, while mucinous cells resemble the epithelial cells in the endocervix, gastric pylorus and intestine. Clear cell tumors contain clear and hobnail cells, and have distinct tubulo-cystic growth.[16]

Symptoms and Diagnosis

Although ovarian cancer has been called the silent killer, there is increasing acknowledgement of a set of non-specific symptoms including: gas, nausea, indigestion, urinary frequency/urgency, bowel irregularity, abnormal menstrual/vaginal bleeding or discharge, pain during intercourse, ongoing fatigue, distended/hard abdomen, bloating/ feeling of fullness, unexplained weight gain/loss, pelvic/abdominal discomfort, and chest pain/ respiratory difficulties.[17–19] Compared to white women, black women with ovarian cancer are more likely to have co-morbid conditions including hypertension, renal disease and cardiovascular disease.[20] A previous analysis in black women with ovarian cancer found that women with higher body mass index (BMI) had longer symptom duration before diagnosis.[21]

The vague symptoms and rare incidence of ovarian cancer make it difficult to diagnose successfully. This is further complicated because there is currently no effective screening

mechanism for ovarian cancer.[22] On the patient level, women may think their ovarian cancer symptoms are due to stress or menopause, other benign conditions, or just overall not serious enough to investigate.[23] Physicians commonly misattribute symptoms to more common causes, and many women do not follow up when their symptoms persist.[23] A Danish study found that more than five visits to a general practitioner were needed before a woman was diagnosed with ovarian cancer.[24]

With no screening and vague symptoms, around 75% of women diagnosed with ovarian cancer are diagnosed with late stage disease.[25] Stages I and II are considered early stage, versus III and IV which are late stage. Stage I is confined to the ovary or fallopian tube. Stage II means cancer has spread to other organs within the pelvis. Stage III signifies spread to the lining of the abdomen or the lymph nodes at the back of the abdomen. Stage IV denotes spread to the inside of the spleen, liver, lungs or other organs outside the peritoneal cavity.[26] Because most women are diagnosed at stages III and IV, ovarian cancer is the most deadly gynecologic cancer, with an overall 5-year survival of 48%.[27]

Non-modifiable traits associated with survival

Race, age, and genetic drivers all have known associations with ovarian cancer survival. Across histologic subtypes and stages of diagnosis, non-Hispanic black women have the lowest five-year survival rates.[28] The greatest survival difference for black women is seen for distant disease, which is also the most commonly diagnosed stage.[28] The five-year survival rate is also twice as high for women below age 65 when compared to those over 65 (60% versus 31%).[27] A meta-analysis of 14 studies of ovarian cancer found that women with BRCA1 or BRCA2 mutations had better overall and progression free survival when compared to those without BRCA mutations. This was true across stage, grade and histologic subtype.[29]

Modifiable traits associated with survival

Although a minority of women are diagnosed with localized disease (15%), for these women 5 year relative survival is 92%.[27] After diagnosis, receiving National Comprehensive Cancer Network (NCCN) guideline adherent care is associated with improved survival, although less than half of women receive it.[30,31] Within guideline adherent care, maximal cytoreduction in surgical de-bulking is an important prognostic factor for ovarian cancer survival.[32,33] A meta-analysis of studies including women with advanced ovarian carcinoma found a 5.5% increase in median survival for every 10% increase in maximal cytoreduction.[33] Early discontinuation of chemotherapy and lower relative dose intensity are associated with ovarian cancer mortality.[20,34]

Racial differences in survival

Not only do black women have the worst ovarian cancer survival, it appears to be worsening over time.[35] In the Annual Report to the Nation 2017, between 1975 and 2012, survival rates increased for nearly all cancers. The exceptions were ovarian and cervical cancers, where survival improved for white women, but declined for black women.[36] With many outstanding questions regarding ovarian cancer etiology and carcinogenesis, we cannot rule out the possibility that black women have a more aggressive type of disease; however, most evidence suggests improved survival with guideline adherent care, and equal outcomes across races when they are given equal treatment.[31,37,38]

Gynecologic oncology group (GOG) trials have shown that with equal treatment, black women have the same overall and progression free survival outcomes as white women.[39,40] The Southwest Oncology Group (SWOG) did find poorer overall survival in black women compared to white women (HR 1.48 CI 1.03-2.11) after adjustment for education, income, age, stage, histology and performance status.[41] The SWOG trials only had 56 black participants, compared

to 97 and 112 in the GOG trials. SWOG found persistent racial disparities in other sex specific cancers (breast and prostate), but not in their other cancers such as lung and colorectal, so they suggest hormonal differences may be at work.[39,41] However, given their small numbers, and generally poor participation of black women in these trials, there may be a selection issue contributing to this difference. This is supported by observational studies also finding equal survival benefit with equivalent treatment.[30,42] A single-institution study found a higher risk of death among black women when controlling for receipt of surgery and chemotherapy; however, this study did not look at chemotherapy dosing or early discontinuation.[43] They found higher survival differential among women with more co-morbidities, but co-morbid conditions are also associated with lower chemotherapy dose intensity and early termination of chemotherapy, which could be an important confounder in this case.[20,43]

Guideline Treatment for Ovarian Cancer

Ovarian cancer survival is largely impacted by the care received.[30,44,45] Ovarian cancer care can be considered a shifting continuum. As a patient progresses from their diagnosis toward death, the balance of treatment efforts should shift. Initially, the curative treatment regimen for ovarian cancer includes intensive tumor de-bulking surgery followed by six rounds of chemotherapy. The NCCN guidelines specify bilateral salpingo-oophorectomy/laparotomy/ total abdominal hysterectomy plus staging and de-bulking as needed, followed by 6 cycles taxane and platinum chemotherapy.[46] They also specify that palliative care evaluation should occur at the beginning of treatment and be incorporated throughout the course of care.[47] While the intention of initial treatment is cure, maximal removal of diseased tissue and eradication of cancer cells, NCCN guidelines specify palliative care should begin when cancer treatment begins.[46] Palliative care is done with the goal of "relief from the symptoms and stress of serious illness" in order to

improve quality of life not only for patients, but also their families.[48] Patients with cancer who receive palliative care have shown reduced symptom burden, better quality of life, and improved survival.[49–52] Moreover, palliative care referral earlier in the disease course has been found to reduce cost, increase hospice utilization and result in less aggressive end-of-life care.[53–55] Although palliative care can and should be conducted concurrently with curative treatment, hospice treatment is for patients who are terminally ill. To use Medicare hospice benefits, a patient must waive coverage of curative treatment.[56]

Black Race Disparities in Curative Ovarian Cancer Care

Black/white racial disparities in ovarian cancer treatment have been well documented. Compared to white women, black women are less likely to receive lymph node dissection at both Stage I and later stages.[57,58] Black women are also less likely to have comprehensive surgical treatment for their ovarian cancer, receive care from a high volume surgeon, have surgical staging, receive guideline adherent care, or to complete chemotherapy without dose reduction, delay or early discontinuation.[20,30,31,37,44,45,58–63] These differences exist within the integrated care delivery system of Kaiser Permanente Northern California and among women with Medicare, suggesting traditional insurance and socioeconomic (SES) variables are not capturing the full picture of access to ovarian cancer care.[20,30]

Five studies have approached access to ovarian cancer care using area-based measures. A recent Surveillance, Epidemiology, and End Results (SEER) analysis was unable to account for individual level SES, but it did highlight that black women in counties with fewer doctors had higher odds of late stage diagnosis than black women in other areas (OR 1.86 CI 1.10-3.13).[64] These findings are in line with a California Cancer Registry analysis that found white women were more likely to travel more than 20 miles to receive ovarian cancer care than black women,

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and that travel distance to care was protective against non-guideline adherent care (OR 0.8 CI

0.69-0.92).[65] Three small studies in Cook County Illinois (includes Chicago), evaluated

neighborhood SES, affluence or disadvantage in association with ovarian cancer characteristics

and survival. These studies did not have individual level SES measurements, which makes it

difficult to say the neighborhood measures are more than a proxy for individual traits.

Interestingly, after adjusting for individual age and race, lower neighborhood SES was associated

with higher grade tumors.[66] This study only had independent pathology review for 55% of the

cases, and no comment about level of agreement with prior pathology, so it is difficult to say

whether this grade difference is real or an artifact of different pathologists.

End-of-life care for Ovarian Cancer

Guidelines for End-of-Life Care

End-of-life care is a relatively new area of research. The Institute of Medicine (IOM)

released its first report on end-of-life care in 1997, and there have been subsequent changes in

care guidelines and policy discussions.[67] Focus on value-based care sparked the National Quality

Forum (NQF) to create quality measures for end-of-life and palliative care in cancer patients.

These measures include: not receiving chemo in the last 14 days of life; no more than one

emergency room visit or hospitalization and no intensive care unit (ICU) visit in the last month

of life; not dying in an acute care setting, admitted to hospice before death; and not being

admitted to hospice for less than 3 days.[68] These indicators have been used as a metric for

defining non-aggressive end-of-life care.[69–72] Because it is not possible to measure the intention

of a treatment in medical claims data, treatments cannot reliably be classified as palliative or

curative. An alternative is using aggressive care metrics. If a patient is receiving aggressive care,

and requiring multiple ICU or emergency room visits, they are not receiving adequate palliative

treatment.[68] Counter to care recommendations, aggressive end-of-life care and low utilization of

palliative care are prevalent in population data. Despite the poor prognosis faced after disease

recurrence, utilization of palliative care and hospice remains low among cancer patients overall

and ovarian cancer patients specifically, and, 30-50% of patients are still receiving aggressive

care at the end of their lives.[69,73–75]

End-of-life Care and Ovarian Cancer

The literature on end-of-life care in ovarian cancer is limited, and consists of many single

institution studies. Despite improvements in hospice utilization, a 2014 study using SEER-

Medicare data found that most women with ovarian cancer experience some aggressive care at

the end of life, and it appears to be increasing over time.[69] However, this study only used data

through 2007, and these trends have not been assessed using more recent data up to 2016.

Palliative care involvement in treatment and discussions about end of life are happening too late

in the course of ovarian cancer care.[76] A Duke study of ovarian cancer patients found end-of-life

discussion at least 30 days before death was associated with lower incidence of aggressive care;

however, 30 days was only the median time of EOL discussion before death, suggesting women

were having the conversation too late.[77] Similarly, gynecologic cancer patients who had a

hospice discussion had shorter inpatient hospital stays and more palliative care utilization.[78]

Although determining a prospective prognosis for patients is not exact, there are significant

clinical events such as bowel obstruction, as well as metastasis to the liver or lungs that indicate

a patient is likely within six months of dying and should be referred to hospice.[79]

Unlike in curative care where high volume hospitals are established as producing the best

outcomes for patients with ovarian cancer, little is known about clinical care characteristics and

end-of-life care. What may reflect better quality curative care, may lead to poor quality end-of-

life care. For example, clinical trial enrollment is a hallmark of care at better quality institutions, but has been associated with a higher likelihood of aggressive care at the end of life in other cancers. A single institution study of gynecologic cancer patients found that clinical trial enrollment was associated with increased likelihood of chemotherapy at the end of life.[80] Among patients with other cancers, patients under oncologist care had higher likelihood of chemotherapy and hospice admission when compared to those managed by other physicians, though hospice admission was late.[71] Living in an area with more teaching hospitals, or receiving care at a teaching hospital was also associated with more aggressive end-of-life care.[71] Similarly, living in an area with more access to hospice was associated with more hospice use.[71]

Physicians and End-of-Life Care

Physicians are an important facet of the care a woman receives. Although not previously evaluated among women with ovarian cancer, physician preferences are associated with cost and intensity of end-of-life care received in other patient populations.[81–85] Among patients with poor prognosis cancer, seeing a physician who has had many patients go on hospice was the single largest predictor of hospice enrollment.[82] Unlike patient preferences for end-of-life care, physician preferences for aggressive end-of-life care are strongly associated with higher regional spending for enrollees during the last six months of life.[81,83,85] Although not in a cancer specific population, Cutler et al. found that after accounting for patient preferences, physician motivation by finances, and organizational factors, the biggest driver in regional spending was physician beliefs about whether aggressive treatments were effective despite being against evidence or guideline recommendations.[81] Echoing the role of physician beliefs, a multicenter survey of oncologists found uncertainty of treatment benefits was a barrier to having goal of care conversations with patients with advanced cancer.[86]

Types of oncologists have differing attitudes about end-of-life treatment.[87] For example hematologic oncologists value hospice, but feel it has inadequate resources for blood cancer patients.[88] A study comparing end-of-life care by physician specialty found that patients receiving care from medical oncologists were more likely to enroll in hospice, however the comparison groups were predominantly not oncologists.[82] A study in Taiwan found patients of medical oncologists were less likely to have more than one ED visit, stay in an ICU, receive life extending procedures.[89] These studies suggest physician specialty may be an important characteristic in end-of-life care.

Physician care patterns result from many different influences. A survey of physician end-of-life preferences found that personal family experience and patient interaction/observation were listed as influencing their end-of-life decision making almost as commonly as their training was.[90] Physicians surveyed about different patient preferences by race indicated that black patients were more likely to want to pursue treatment, have family participation, avoid hospice and favor being at home.[90] Physicians have beliefs about which groups of patients will and will not accept guideline adherent end-of-life care, which can impact their communication decisions about care options.[91] Perceived physician communication as unsupportive, or uninformative was more common among black cancer patients than white patients, and was associated with lower trust in the physician as a result.[92] Black patients also receive less information from their providers and are less active participants in visits.[93] As a result, nonwhite patients more often have discordant understanding of prognosis. [94] Oncologists cite unrealistic patient expectations and reduced patient trust as barriers to providing quality end-of-life care. [95,96] Among healthcare providers there is a belief that palliative care referral may be perceived as giving up or would signal that healthcare providers were giving up hope for the patient.[97] Echoing this belief,

gynecologic oncologists have indicated that patient trust is key for being willing to recommend palliative care or transition to end-of-life care.[98]

Race and End-of-Life Care

Racial differences in end-of-life care preferences are well known, but not well understood.[90,99] In the cancer literature, many studies of racial differences in end-of-life care received have used SEER-Medicare data.[61,100–103] These studies predominantly evaluate differences in hospice use because it is impossible to determine care preferences or goals from medical claim data, and hospice use is more clear.[61,100,101,103,103] Qualitative and hospital based studies have been able to delve more deeply into racial differences in patient preferences and end-of-life practices outside of hospice or claims based markers of aggressive care.

Several studies have evaluated components of advanced care planning, which is associated with less aggressive end-of-life care and race .[77,78,86,104–106] Among lung cancer patients at a single institution, white patients were more likely to have durable power of attorney and a living will than black patients. In a near-death state, black patients were more likely to prefer life preserving intervention than white patients. [106] In a multisite study, Black and Hispanic patients were less likely to acknowledge their terminal status than white patients; however, preferences for aggressive end-of-life care and acknowledging terminal status did not account for the racial disparity in having advanced care planning in place.[107]

A single institution study found that using spirituality to cope with illness was associated with a lower likelihood of having a living will and having a preference for life extending treatment.[105] In this study, black patients were more likely not to have a living will and to prefer life extending care.[105] In a multisite study, although black women had high religious coping, it was less predictive of care decisions than it was for white patients.[108] This study also found a

disconnect between black patients' stated preferences and the care they received, including a stated preferences for aggressive care but not receiving it.[108] Findings indicate that changes in care givers or care facility result in confusion around patients' end-of-life preferences, suggesting continuity of care is an important characteristic to evaluate with respect to end-of-life care.[108] Similarly, Mack et al. found that compared to white patients, black patients end-of-life care discussions were not associated with less aggressive end-of-life care, and those with do-not-resuscitate orders were not less likely to receive aggressive care.[109] The discordance between patient preferences and care received is not well understood. It may reflect a change in how a patient feels as the reality of death approaches, a fear of a physician giving up if the patient asks for comfort care, or less consistent communication.[108,110,111]

Despite some mixed findings, religious beliefs have been identified across studies as important drivers of end-of-life decision making for black and Hispanic women.[99] Those receiving more end-of-life support through religious communities were more likely to have aggressive end-of-life care and not enroll in hospice.[99] While this may be due to incompatible beliefs, when spirituality was incorporated by the medical care team, odds of aggressive care and no hospice use decreased.[112] This finding suggests the association of religiosity and aggressive end-of-life care may be due to misunderstanding or miscommunication rather than a true difference in beliefs and preferences.

Forgoing curative care to access hospice benefits may be another barrier to black patients' decision to elect hospice care. A single institution study in Pennsylvania found that black patients were more likely to prefer aggressive end-of-life treatment than white patients, and were also more likely to perceive need of hospice services, although not naming them as such.[113] This racial difference was no longer statistically significant after adjustment for the household

income.[113] The authors concluded that requiring patients to give up curative treatment, in order to access hospice benefits through Medicare is a barrier to accessing the hospice services that black families need.[113] This may indicate another area where more culturally appropriate communication regarding available care, and a patient's ability to leave hospice to use their curative benefits, may alleviate anxieties about entering hospice care.

Race and End-of-Life Care for Women with Ovarian Cancer

Race and end-of-life care have not been widely studied among women with ovarian cancer. A Texas study found end-of-life care was more aggressive among black women with ovarian cancer than white women.[75] In particular, compared to white women, black women had higher odds of more than one emergency room visit (OR 2.20 CI 1.53-3.16) and receiving a life extending procedure (OR 2.13 CI 1.49-3.04).[75] They also had lower odds of enrolling in hospice (OR 0.74 CI 0.55-0.98).[75] A single-institution study in Texas also found non-white women with gynecologic cancers were less likely to enroll in hospice, have a medical power of attorney or a living will than white women.[114]

End-of-life care has also been found to vary widely by region and institution.[115,116] Utilizing national data is imperative to fully understand the extent of the disparities by region and type of facility. In a national study in the Medicare population, non-white women with ovarian cancer had 44% higher odds of not receiving hospice care at the end-of-life than white women.[3] Although ovarian cancer is unique given its poor prognosis and relatively quick progression, this finding has also been seen in other cancers and other diseases.[99,108,117] A review of end-of-life care studies of racial minority cancer patients found that black patients were less likely to use hospice, to see the relevance of hospice but have less information regarding

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utilization and benefits for hospice, and to prefer more aggressive end-of-life care such as resuscitation.[99]

Summary

The most deadly gynecologic cancer, ovarian cancer has a five year survival of only 46.5% in the United States.[2] In 2020, an estimated 21,750 new cases of ovarian cancer will occur in the US, and 13,940 women will die from the disease.[1] Despite these poor numbers overall, the mortality burden is higher for black women. The National Cancer Institute Annual Report to the Nation 2017 highlights that between 1975 and 2012, ovarian cancer and cervical cancer were the only cancers without survival improvements for all groups, because survival decreased for black women.[36] Survival with ovarian cancer has worsened for black women in recent decades.[118] While there is little evidence of biologic reasons for this difference, this dissertation examines the numerous ways black women with ovarian cancer receive disparate treatment. As new technologies in care emerge, I hypothesize these racial gaps in treatment will only continue to grow. Clinical trials drive care forward, and considering incidence rates of ovarian cancer, black enrollment was 15 fold lower than what would be expected in Gynecologic Oncology Group trials, and black participation has waned over time.[119] A major obstacle in understanding the racial disparity in ovarian cancer survival is lacking insight into what is driving care differences. The goal of this work is to highlight new exposures associated with different care for black women so that as new technologies emerge we may better understand how to ensure more equitable care for all women throughout the ovarian cancer care continuum.

In Aim 1, we will evaluate acceptability, one facet of accessing care, which is the relationship of client and provider attitudes about the acceptability of the other, operationalized as study measures everyday discrimination and trust in physician, and their association with a

longer symptom duration prior to ovarian cancer diagnosis. [120] Aim 1 goes beyond the more commonly assessed affordability component of access to care, to include exposures that may be informative for improving access to ovarian cancer care.

The poor prognosis of ovarian cancer means end-of-life care is a phase of treatment most women with ovarian cancer will face as part of their cancer care. Black women with ovarian cancer are especially vulnerable to inappropriate treatment at the end of life because they are more likely than white women to have co-morbid conditions, higher care-taking burden, poverty, and spouses with very low life expectancy.[121–124] Limited research suggests that black women with ovarian cancer are less likely to enroll in hospice and more likely to receive overly aggressive end-of-life treatment.[61,75,114,125] However, little is known about the national patterns of utilization and disparities in the end-of-life care in women with ovarian cancer. Aim 2 will set a national baseline for end-of-life care differences between black and white women to highlight areas of need going forward. It will also evaluate the association of important care characteristics with receipt of aggressive end-of-life care, including care continuity, proportion of evaluation and management in oncology and use of palliative/hospice visits. We know that physicians are important drivers of end-of-life care,[81,82,85] but variation at the physician level has not been evaluated among women with ovarian cancer, or with regard to racial differences in end-of-life care. Aim 3 will quantify physician variation in aggressive end-of-life care among older women with ovarian cancer and evaluate the association of physician ovarian cancer volume, nonwhite patient volume and specialty with aggressive end-of-life care for patients.

Specific Aims and Hypotheses

The following are the specific aims and hypotheses for this dissertation:

Aim 1: To evaluate novel facets of access to care among black women with ovarian cancer.

Hypothesis 1: Given persisting disparities after adjusting for traditional SES characteristics, we hypothesize that social barriers will have a stronger association with symptom duration prior to diagnosis.

Aim 2: To describe national racial disparities in aggressive end-of-life care among women with ovarian cancer, and examine the association with individual care characteristics (e.g. types of evaluation and management visits, having hospice/palliative/pain visits, SEER region of care) for ovarian cancer patients in the last month of life.

Hypothesis 2: Compared to non-Hispanic white women, black women will receive more aggressive care in the last month of life, and that women with more oncology visits will receive less aggressive end-of-life care.

Aim 3: To quantify the proportion of variation in aggressive end-of-life care among women with ovarian cancer that is attributable to a woman's oncologist and evaluate physician characteristics (patient volume, racial patient mix, and specialty) that may be associated with this variation.

Hypothesis 3: We hypothesize that physicians will contribute a substantial proportion of the variation seen in aggressive end-of-life care, and this variation will be most explained by variation in a physician's ovarian cancer patient volume.

CHAPTER 2. Perceived Discrimination, Trust in Physicians and Prolonged Symptom Duration before Ovarian Cancer Diagnosis in the African American Cancer Epidemiology Study

Abstract

Background: Discrimination and trust are known barriers to accessing healthcare. Despite well documented racial disparities in the ovarian cancer care continuum, the role of these barriers has not been examined. This study evaluates the association of everyday discrimination and trust in physicians with a prolonged interval between symptom onset and ovarian cancer diagnosis (hereon referred to as prolonged symptom duration).

Methods: Subjects include cases enrolled in the African American Cancer Epidemiology Study, a multisite case-control study of epithelial ovarian cancer among black women. Logistic regression was used to calculate multivariable-adjusted odds ratios and 95% confidence intervals for associations between everyday discrimination and trust in physicians with a prolonged symptom duration (one or more symptom lasting longer than the median symptom-specific duration), controlling for access to care covariates and potential confounders.

Results: Among 486 cases in this analysis, 302 women had prolonged symptom duration. In the fully adjusted model, a one unit increase in frequency of everyday discrimination increased the odds of prolonged symptom duration 74% (OR 1.74 CI 1.22-2.49), but trust in physicians was not associated with prolonged symptom duration (OR 0.86 CI 0.66- 1.11).

Conclusions: Perceived everyday discrimination was associated with prolonged symptom duration whereas more commonly evaluated determinants of access to care and trust in physicians were not. These results suggest more research on the effects of interpersonal barriers impacting ovarian cancer care is warranted.

Introduction

Ovarian cancer is the most lethal gynecologic cancer with less than 50% of women surviving 5 years or longer after their diagnosis.[126] Compared to white women, black women have a lower five-year survival rate for all histologic subtypes of ovarian cancer at all stages of diagnosis.[28] Moreover, compared to 1975 rates, 5-year survival has improved about 10% for white women with ovarian cancer but declined about 5% for black women.[36]

Racial disparities in ovarian cancer care are well-documented at all stages of the care continuum.[127,128] Access to care is one key component of high quality cancer care that may explain differences in ovarian cancer treatment. While health insurance and socioeconomic status (SES) impact access to care, these factors alone fail to account for racial disparities in ovarian cancer treatment.[20,30] Trust in physicians and perceived discrimination are two interpersonal factors that could contribute to these racial differences. Previously unstudied among women with ovarian cancer, these factors are associated with lower healthcare utilization, less preventive screening, non-adherence to care recommendations, and delay in care-seeking in other patient populations.[129–131]

Here, we examine the association between everyday discrimination and trust in physicians with a prolonged interval between symptom onset and ovarian cancer diagnosis (hereon referred to as prolonged symptom duration) in the African American Cancer Epidemiology Study (AACES). As depicted in Figure 1, prolonged symptom duration

encompasses a series of events that must occur between a symptomatic change in the body and a woman receiving a diagnosis of ovarian cancer. This portion of the care continuum is particularly important for women with ovarian cancer because there is no screening or annual exam with clear guidelines on when to seek care, and ovarian cancer symptoms are non-specific. This places more burden on patients to initiate and continue seeking/accessing care when symptoms do not resolve (Figure 1).[23,24] We hypothesize that low trust in physicians and more frequent perceived discrimination contribute to prolonged symptom duration.

Methods

Study population

The AACES has been described in detail elsewhere.[132] In brief, AACES is a multisite population-based case-control study of ovarian cancer in black women. Study sites include Alabama, Georgia, Illinois, Louisiana, metropolitan Detroit, Michigan, North Carolina, New Jersey, Ohio, South Carolina, Tennessee, and Texas. Institutional review board approval was obtained from all participating sites. Cases were identified via rapid case ascertainment through state or Surveillance, Epidemiology and End Results cancer registries and hospital gynecologic oncology departments, and enrolled between December 2010 and December 2015. Self-identified black women between the ages of 20 and 79 who were newly diagnosed with histologically-confirmed invasive epithelial ovarian cancer and could complete an interview in English were eligible to participate.

Data collection

AACES participants completed a computer-assisted telephone interview. A short version was offered to women who would have otherwise refused to participate. Cases were excluded from this analysis if they had missing data (Figure 2). Confounding variables were selected *a*

priori based on published literature. Selected confounders included: age at diagnosis, geographic region, marital status, body mass index (BMI), Charlson Comorbidity Index, education, and income.

Independent Variables

Perceived discrimination was evaluated using the 5-question version of Williams' Everyday Discrimination Scale (Table 2).[133] We averaged each woman's responses (range 0-5) for the score such that a higher score reflects more frequent discrimination. Scale items were evaluated for internal consistency with Cronbach's alpha.

Trust in physicians was measured with the Trust in Physicians Scale (Table 3).[134] Questions were coded so that a higher score indicated higher trust, and responses were summed across the 11 questions (range 0-55). Scale items were evaluated for internal consistency with Cronbach's alpha.

Outcome

The primary outcome for this study was prolonged symptom duration. Given the lack of symptom specific durations in the literature, we defined prolonged symptom duration relative to other women in the AACES. Women were asked whether/how long in the year prior to diagnosis they had symptoms (Appendix 1). Because each symptom has unique meaning and urgency, and most women do not have all possible symptoms, a median duration was calculated for each symptom only among women who had the symptom. Women who had any symptom longer than the median symptom specific duration were classified as having prolonged symptom duration.

Statistical analyses

Demographic characteristics were summarized using t-tests, Mann Whitney U test (for everyday discrimination and income based on histogram distributions), or X^2 tests to compare

distributions between women who had prolonged symptom duration to those who did not. Unconditional multivariable logistic regression was performed to calculate odds ratios (ORs) and 95% confidence intervals (CI) for the associations between trust in physicians and everyday discrimination with prolonged symptom duration (greater than or equal to, ≥, median duration for any symptom).

The baseline model was adjusted for demographic covariates including age at diagnosis (years), region (North: Ohio, New Jersey, metropolitan Detroit, Michigan, Illinois, and South: Tennessee, Alabama, South Carolina, North Carolina, Georgia and Texas); BMI categories (< 25, 25 to< 30, 30 to <35 and 35+ (kg/m^2)), marital status (single, partnered, widowed/divorced); and modified Charlson comorbidity index (0, 1, 2, 3, 4+). [135] Model 2 was also adjusted for SES measures including education (high school or less, some post high school training, college or graduate degree), and income. Income data were collected using categorical ranges and modeled as the midpoint of each bounded category ($10,000, $17,500, $37,500, $62,500, $87,500, and $100,000). The final model also included measures of access to care including health insurance (Medicare, Medicaid, private, uninsured), not having a regular physician (yes/no), self-reported barrier to seeking care (yes/no), and primary care provider density (number of clinically active primary care providers in primary care referral area/ 100,000 population).[136]

Two sensitivity analyses were performed using different definitions of prolonged symptom duration. Overall median symptom duration and overall mean symptom duration were used as cut points to define the outcome indicator instead of symptom specific durations. Time to interview was also evaluated as a possible source of bias.

Statistically significant p-values were considered <0.05, and all analyses were performed using SAS version 9.4 (SAS Institute).

Results

Median symptom duration and symptom frequency are presented in Appendix 1. This resulted in 302 women who had prolonged symptom duration and 184 women who did not. On average, women had three symptoms lasting longer than the median duration.

Descriptive characteristics are presented in Table 1. On average, women were diagnosed in their late 50's and obese (BMI > 30 kg/m^2). Most women reported having a regular family physician and were insured by private health insurance or Medicare. The average supply of clinically active primary care providers in their primary care service area was about 70 providers/100,000 population, and 80% of women reported no barriers to seeking care (Table 1).

We observed measurable differences in the Charlson index, marital status, self-reported barriers to care-seeking, attitudes towards physicians, and perceived discrimination between women who did and did not experience prolonged symptom duration. The proportion of women with a Charlson index of four or more was three times greater among women with symptom delay compared to those without (Table 1).

Women with prolonged symptom duration had lower trust in physician scores, and both groups had response averages below "agree" (response sum=44) across the 11 questions. Women with prolonged symptom duration also had more frequent experiences of everyday discrimination. Both groups had average discrimination scores between zero and one, which reflects an average discrimination frequency between never and less than once a year (p<0.001).

The distribution of responses to the everyday discrimination scenarios in the interview are displayed in Table 2. Notably, 32% of women reported being treated with less courtesy or

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respect than other people, 33% perceived receiving poorer service than other people at restaurants or stores, and 32% felt people act as if they were not smart. Cronbach's alpha for the everyday discrimination scale was 0.73 in this analytic sample.

Table 3 presents the trust in physicians statements and responses. Generally responses more frequently indicated trust; however, several scenarios had substantial numbers of responses indicating low trust (Table 3). Cronbach's alpha for the trust in physicians scale was 0.92 in this analytic sample.

Table 4 presents the ORs (and 95% CI) from the multivariable logistic regression models for prolonged symptom duration. Model one is adjusted for demographic characteristics. A one unit increase in the everyday discrimination score (e.g., from never to almost monthly) was associated with 77% higher odds of prolonged symptom duration (OR 1.77 CI 1.25-2.52). Trust in physician was not associated with increased risk of symptom duration (OR 0.86 CI 0.67-1.11). Further adjustment for measures of socioeconomic status, including education and income, resulted in little change in the strength of the associations for discrimination and trust (Table 4, Model 2). Further, accounting for access to care covariates resulted in a negligible change in the magnitude of the association for discrimination (OR 1.74 CI 1.22- 2.49) and physician trust (OR 0.68 CI 0.45-1.20) (Table 4, Model 3).

Noteworthy associations for other variables included in the fully adjusted model were observed. Women with Charlson index 4+ had 4.6 times the odds of prolonged symptom duration compared to women with no co-morbid conditions (OR 4.62 CI 2.12-10.1). Compared to single women, divorced or widowed women had twice the odds of prolonged symptom duration (OR 2.09 CI 1.24-3.54). Having a self-reported barrier to going to the doctor increased the odds of prolonged symptom duration 96% (OR 1.96 CI 1.10- 3.50).

In sensitivity analyses, no meaningful changes to the results were observed with the different definitions of outcome, except for one covariate, self-reported barriers to care, where the previously observed association was no longer present (data not shown). There was no association between prolonged symptom duration and time to interview in models, nor did including time to interview as a covariate in models change results.

Discussion

In summary, in this sample of 486 black women with ovarian cancer, everyday discrimination, was associated with prolonged symptom duration. Particularly noteworthy was our finding that despite reflecting broader everyday life context, more frequent everyday discrimination increased the odds of prolonged symptom duration 74% in fully-adjusted models, but health system-specific trust in physicians was not associated with prolonged symptom duration. This finding is important because material components for accessing care have not been sufficient in explaining racial disparities in ovarian cancer care, and this is the first study to evaluate possible interpersonal contributions.

While perceived discrimination has not previously been evaluated in women with ovarian cancer, our results are consistent with findings in other populations.[137,138] Although our findings reflect a specific pre-diagnostic window, perceived discrimination has similarly been associated with delay in breast cancer diagnosis after an abnormal mammogram.[130] These results align with the Casagrande et al. study finding discrimination experiences were associated with prolonged symptom duration and non-adherence to medical recommendations.[131]

In contrast, other studies have not found an association between perceived discrimination and low healthcare engagement, or have found the opposite relationship.[137,139] These mixed findings are likely due to differences in the burden of comorbid conditions, racial identity of

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study participants, and measures of healthcare utilization. Many studies evaluate routine or preventive services with a clear guideline for care-seeking. However, seeking care for ovarian cancer symptoms relies more heavily on patient perception and often, persistence.[23,24] Although the individual symptoms are non-specific, combinations of symptoms, onset, and intensity of symptoms can be important indicators of disease.[140]

The Everyday Discrimination scale showed reasonable internal consistency in this analysis, particularly given that the scale has only five items. Although everyday discrimination was modeled as a mean score, to better understand these findings, each discrimination scenario was modeled separately (results not shown), and "people act as if I am not smart" was the only scenario associated with prolonged symptom duration. This suggests one mechanism of this relationship may be stereotype threat, defined as, "a disruptive psychological state that people experience when they feel at risk for confirming a negative stereotype associated with their social identity."[141] Stereotype threat is associated with increased stress, cognitive burden, avoidance of situations that induce the threat, and lower healthcare utilization.[141,142] It may also underlie increased distrust of physicians and lower healthcare satisfaction.[141,142]

Trust in physicians was not associated with prolonged symptom duration. It is well-established that black patients are more likely to mistrust the healthcare system compared to white patients.[143] Because this analysis was limited to black women, trust may contribute less variation. Other studies suggest trust in physicians is predicted by perceived discrimination.[144] In our analysis, bivariate tests did not support discrimination as a mediator of physician trust (data not shown), and trust was not highly correlated with everyday discrimination score (r=-0.11).

Finally, two confounders had significant associations with prolonged symptom duration. Having a 4+ Charlson index had the largest association with prolonged symptom duration in this

analysis. These findings are expected as many ovarian cancer symptoms overlap with a wide range of health issues. This association likely reflects a masking effect, in which poorer health makes it more difficult to identify symptoms attributable to ovarian cancer. Similarly, women who lost a spouse by either death or divorce were twice as likely as single women to have prolonged symptom duration. This may reflect a decline in mental health or a change in social support.[145]

This study has several strengths. The AACES provides an unprecedented sample size of black women with ovarian cancer. This study was uniquely positioned to analyze previously un-addressed exposures among women with ovarian cancer. Although several studies have documented disparities in ovarian cancer survival and treatment, most data have come from medical claims where studying interpersonal exposures was not possible. Also, our primary exposure measures were validated multi-item scales, which have been found to be more reliable than single item measures.[146] These measures also showed good internal consistency in this analytic dataset. Finally, we used a symptom specific approach which reflects the complexity of changes in the body and their different associated meanings.[147]

Limitations

Study participants were slightly younger and healthier than non-participants which may limit generalizability of these findings, though this is a common challenge in ovarian cancer studies.[132]

Prolonged symptom duration reflects several components (Figure 1). However, it would be nigh on impossible to disaggregate this outcome without a prospective design. Although our outcome cannot parse the individual contributions of this time period apart, it reflects a longer time period before diagnosis that could be acted upon. Despite steps in health system control

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such as timely appointment availability or misattribution of symptoms to other diseases, patient self-efficacy and persistence in pursuing resolution of symptoms are key drivers to navigating those barriers.[23,24]

The outcome measure also relied upon retrospectively reported symptoms. Though measurement error is possible, all participants were recalling symptoms from the recent past so this is unlikely to introduce bias. Including time to interview did not impact results and the duration of symptoms in our study are in line with previous findings.[140]

These data were collected cross-sectionally and could be subject to reverse causation. A woman who experienced a prolonged symptom duration despite prompt care-seeking may possibly perceive more discrimination due to her healthcare experience. Our hope is that the discrimination measure, which assessed specific everyday experiences rather than healthcare experiences, minimizes this possible bias.

Finally, discrimination and trust are sensitive topics to ask about in a research survey. These sections were placed towards the end of the survey to allow the interviewer and respondent to develop rapport before approaching them. Despite this, non-response to the trust in physicians section of the questionnaire was the largest exclusion after questionnaire length (Figure 2). These women had higher everyday discrimination scores, but they were not more likely to have prolonged symptom duration, suggesting any selection bias is likely to be minimal.

Conclusion

This work is a novel first step in understanding the relationship between interpersonal exposures and racial disparities in ovarian cancer care. More equitable access to ovarian cancer care necessitates women feeling comfortable to advocate for their needs and trusting their self-assessment of their symptoms. These results point to social context in daily life playing a role in

receiving optimal ovarian cancer care, and suggest more research is needed on the effects of

interpersonal barriers in the ovarian cancer care continuum.

Tables and Figures

Figure 2.1 Patient flow prior to ovarian cancer

Patient driven   Health system driven

| Symptom causes new bodily sensation | → | Woman perceives new bodily sensation | → | Woman recognizes sensation as a problem | → | Woman decides to seek care for this problem | → | Woman finds an available physician appointment, schedules and attends | → | Physician evaluates symptom(s) | → | Referral to a specialist | → | Correct diagnosis attained |

Woman persists with conviction that something is wrong ← Time spent with incorrect diagnosis ← Correct diagnosis not attained

Figure 2.2 Patient exclusion flow diagram
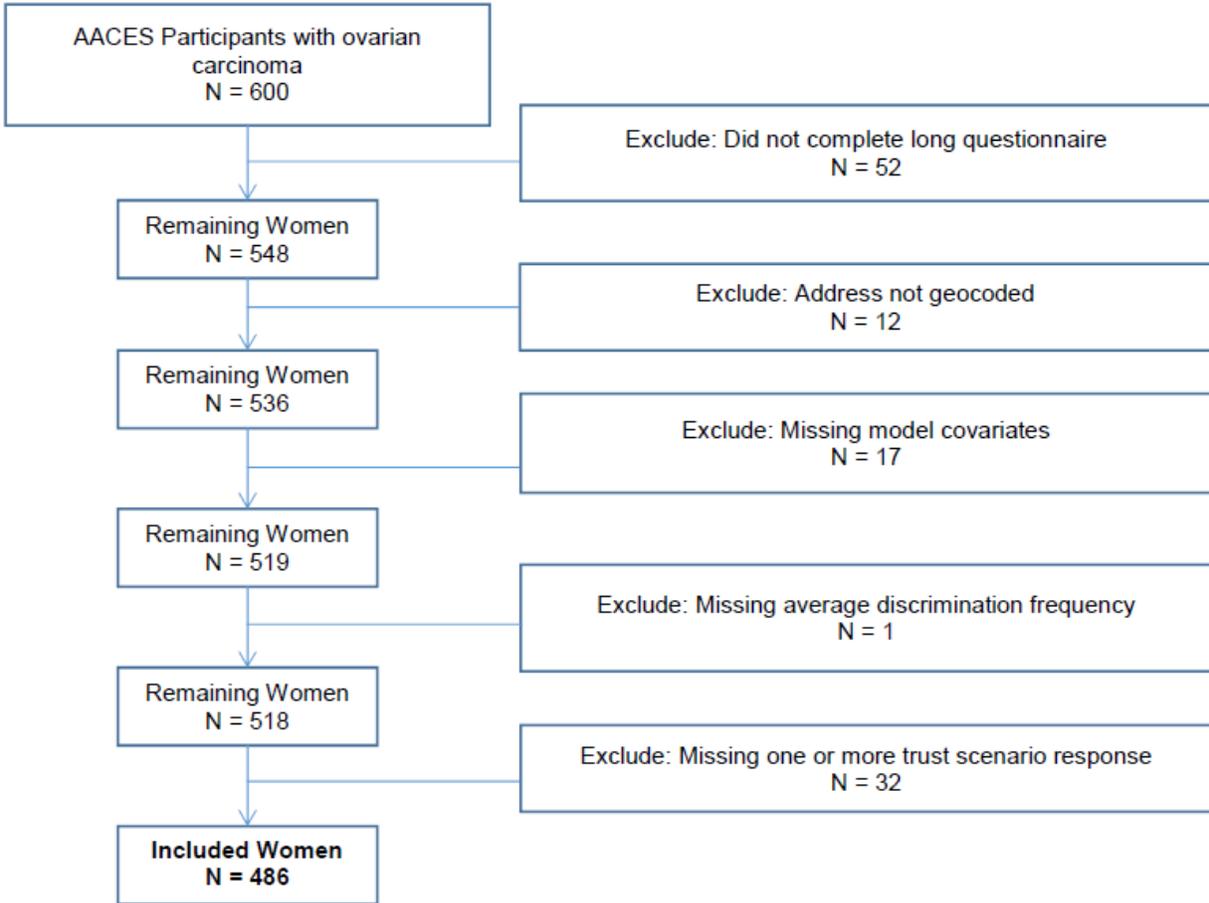
Table 2.1 Characteristics of women with and without a prolonged symptom duration in the African American Cancer Epidemiology Study (AACES)

	Prolonged symptom duration (n=302)	Non-prolonged symptom duration (n=184)	P-value
	N (%) or mean (SD)	N (%) or mean (SD)	
Charlson Index			<.001
0	92(30.5)	86(46.7)	
1	74 (24.5)	44 (23.9)	
2	51 (16.9)	25 (13.6)	
3	31 (10.3)	18 (9.8)	
4+	54 (17.9)	11 (6.0)	
Body mass index (kg/m^2)			0.15
<25	37 (12.3)	35 (19.0)	
25-<30	77 (25.5)	47 (25.5)	
30-<35	88 (29.1)	54 (29.4)	
35+	100 (33.1)	48 (26.1)	
Annual Household income ($10,000)	4.00 (3.0)	3.87 (2.8)	0.92[†]
Education			0.70
High school or less	126 (41.7)	84 (45.6)	
Some post high school training	79 (26.2)	45 (24.5)	
College or graduate degree	97 (32.1)	55 (29.9)	
Have regular physician			0.67
Yes	265 (87.7)	159 (86.4)	
No	37 (12.3)	25 (13.6)	

Self-reported barrier to seeking care			0.02
Yes	70 (23.2)	27 (14.7)	
No	232 (76.8)	157 (85.3)	
Primary care provider density (per 100,000 pop.)	70.9 (19.8)	69.8 (17.0)	0.52
Insurance			0.86
Private	116 (38.4)	75 (40.8)	
Medicare	90 (29.8)	49 (26.6)	
Medicaid	64 (21.2)	42 (22.8)	
Uninsured	32 (10.6)	18 (9.8)	
Total trust in physician score	41.3 (8.4)	42.7 (7.0)	0.06
Mean everyday discrimination score	0.53 (0.72)	0.31 (0.52)	< 0.001[†]

[†] Mann Whitney U test used due to distribution

Table 2.2 Everyday discrimination scenario frequencies in the AACES

Discrimination Scenario[†]	Number of AACES participants
You are treated with less courtesy or respect than other people.	
Almost everyday	13 (2.7)
At least once a week	5 (1.0)
A few times a month	17 (3.5)
A few times a year	38 (7.8)
Less than once a year	84 (17.3)
Never	329 (67.7)
You receive poorer service than other people at restaurants or stores.	
Almost everyday	0 (0.0)
At least once a week	4 (0.8)
A few times a month	11 (2.3)
A few times a year	54 (11.1)
Less than once a year	89 (18.4)
Never	326 (67.4)
People act as if they think you are not smart.	
Almost everyday	9 (1.9)
At least once a week	6 (1.2)
A few times a month	22 (4.5)
A few times a year	46 (9.5)
Less than once a year	74 (15.3)
Never	327 (67.6)
People act as if they are afraid of you.	
Almost everyday	9 (1.9)
At least once a week	4 (0.8)
A few times a month	10 (2.1)
A few times a year	22 (4.5)
Less than once a year	22 (4.5)
Never	418 (86.2)
You are threatened or harassed.	
Almost everyday	1 (0.2)
At least once a week	3 (0.6)
A few times a month	5 (1.0)
A few times a year	11 (2.3)
Less than once a year	25 (5.2)
Never	440 (90.7)

[†] May not sum to total due to missing responses on some discrimination scenarios

Table 2.3 Trust in physicians response frequencies in the AACES

Trust in physician scenario	Number of AACES Participants
I doubt that my doctor really cares about me as a person [†]	
Strongly disagree	168 (34.5)
Disagree	226 (46.5)
Neither agree nor disagree	30 (6.2)
Agree	48 (9.9)
Strongly Agree	14 (2.9)
My doctor is usually considerate of my needs and puts them first	
Strongly disagree	12 (2.4)
Disagree	34 (7.0)
Neither agree nor disagree	28 (5.8)
Agree	261 (53.7)
Strongly Agree	151 (31.1)
I trust my doctor so much I always try to follow his/her advice	
Strongly disagree	9 (1.8)
Disagree	31 (6.4)
Neither agree nor disagree	53 (10.9)
Agree	272 (56.0)
Strongly Agree	121 (24.9)
If my doctor tells me something is so, then it must be true	
Strongly disagree	15 (3.1)
Disagree	94 (19.3)
Neither agree nor disagree	98 (20.2)
Agree	227 (46.7)
Strongly Agree	52 (10.7)
I sometimes distrust my doctor's opinion and would like a second one [†]	
Strongly disagree	58 (11.9)
Disagree	218 (44.9)
Neither agree nor disagree	49 (10.1)
Agree	137 (28.2)
Strongly Agree	24 (4.9)
I trust my doctor's judgements about my medical care	
Strongly disagree	10 (2.1)
Disagree	35 (7.2)
Neither agree nor disagree	33 (6.8)

Agree	304 (62.5)
Strongly Agree	104 (21.4)
Trust in physician scenario	Number of AACES Participants
I feel my doctor does not do everything he/she should for my medical care †	
Strongly disagree	82 (16.9)
Disagree	272 (56.0)
Neither agree nor disagree	38 (7.8)
Agree	70 (14.4)
Strongly Agree	24 (4.9)
I trust my doctor to put my medical needs above all other considerations when treating my medical problems	
Strongly disagree	10 (2.1)
Disagree	35 (7.2)
Neither agree nor disagree	40 (8.2)
Agree	306 (62.9)
Strongly Agree	95 (19.6)
My doctor is a real expert in taking care of medical problems like mine	
Strongly disagree	16 (3.3)
Disagree	54 (11.1)
Neither agree nor disagree	57 (11.7)
Agree	264 (54.3)
Strongly Agree	95 (19.6)
I trust my doctor to tell me if a mistake was made about my treatment	
Strongly disagree	10 (2.1)
Disagree	59 (12.1)
Neither agree nor disagree	59 (12.1)
Agree	276 (56.8)
Strongly Agree	82 (16.9)
I sometimes worry that my doctor may not keep the information we discuss totally private †	
Strongly disagree	136 (28.0)
Disagree	293 (60.3)
Neither agree nor disagree	36 (7.4)
Agree	18 (3.7)
Strongly Agree	3 (0.6)

† Responses coded so a higher score indicates higher trust

Table 2.4 Adjusted ORs for the associations between trust in physicians and everyday discrimination with prolonged symptom duration in the AACES

	Model 1[†]	Model 2[‡]	Model 3[§]
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Trust in physician score (10 units)	0.86 (0.67, 1.11)	0.84 (0.65, 1.09)	0.86 (0.66, 1.11)
Mean discrimination score	1.77[**] (1.25, 2.52)	1.75[**] (1.23, 2.48)	1.74[**] (1.22, 2.49)
Age (years)	1.00 (0.98, 1.02)	1 (0.98, 1.02)	1 (0.98, 1.02)
Region			
South	1.0 (Reference)	1.00 (Reference)	1.00 (Reference)
North	0.82 (0.51, 1.32)	0.78 (0.48, 1.26)	0.7 (0.41, 1.21)
Marital Status			
Single	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Partnered	1.41 (0.84, 2.38)	1.29 (0.75, 2.22)	1.34 (0.77, 2.34)
Divorced/Widowed	2.06[**] (1.23, 3.46)	2.03[**] (1.21, 3.42)	2.09[**] (1.24, 3.54)
BMI (kg/m^2)			
<25	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
25-<30	1.48 (0.80, 2.73)	1.51 (0.81, 2.82)	1.55 (0.83, 2.93)
30-<35	1.33 (0.73, 2.44)	1.34 (0.73, 2.46)	1.31 (0.70, 2.44)
35+	1.52 (0.82, 2.80)	1.56 (0.84, 2.89)	1.55 (0.83, 2.90)
Charlson Index			
0	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
1	1.43 (0.87, 2.36)	1.46 (0.89, 2.40)	1.48 (0.89, 2.46)
2	1.73 (0.96, 3.11)	1.8 (0.99, 3.27)	1.73 (0.94, 3.18)
3	1.31 (0.66, 2.60)	1.39 (0.69, 2.78)	1.32 (0.65, 2.72)
4+	4.13[**] (1.96, 8.72)	4.45[**] (2.09, 9.47)	4.62[**] (2.12, 10.1)
Education			
College or graduate degree	--	1.00 (Reference)	1.00 (Reference)
Some post high school training	--	1.03 (0.60, 1.76)	1.07 (0.62, 1.85)
≤High school	--	0.82 (0.49, 1.40)	0.85 (0.49, 1.45)

	Model 1[†]	Model 2[‡]	Model 3[§]
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Income ($10,000)	--	1.04 (0.95, 1.13)	1.06 (0.97, 1.16)
Insurance			
Private	--	--	1.00 (Reference)
Medicare	--	--	1.08 (0.59, 1.96)
Medicaid	--	--	0.99 (0.53, 1.86)
Uninsured	--	--	1.15 (0.53, 2.48)
No Regular Physician	--	--	0.91 (0.48, 1.73)
Barrier to care seeking	--	--	1.96[*] (1.10, 3.50)
Primary care provider density (10 physicians per 100,000 population)	--	--	1.06 (0.94, 1.19)

[†]Model 1: trust in physician score, mean everyday discrimination score, age, region, marital status, BMI, Charlson co-morbidity index

[‡]Model 2: trust in physician score, mean everyday discrimination score, age, region, marital status, BMI, Charlson co-morbidity index, education, income

[§]Model 3: trust in physician score, mean everyday discrimination score, age, region, marital status, BMI, Charlson co-morbidity index, education, income, insurance, no regular physician, barrier to care-seeking, primary care provider density

[*]$p < 0.05$

[**]$p < 0.01$

CHAPTER 3. Aggressive End-of-Life Care among Women with Ovarian Cancer: A SEER-Medicare Analysis

Abstract

Background End-of-life care for women with ovarian cancer is understood to be aggressive overall, and more aggressive for nonwhite women. The association between race and aggressive end-of-life care among women with ovarian cancer has not been evaluated nationally, nor has the role of care characteristics been explored. This study evaluated the association of patient race, care continuity, proportion of oncology evaluation and management, and having a hospice/palliative evaluation and management visit with receipt of a set of established claims-based aggressive end-of-life care indicators.

Methods Subjects include women over age 66 with ovarian cancer who died between 2000 and 2016 and had continuous Medicare coverage. Generalized estimating equations adjusted for confounding and accounting for patient clustering within physicians were used to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) for associations of race, continuity of care, proportion of oncology evaluation and management, and having a hospice/palliative visit outside the hospice setting with aggressive end-of-life care indicators including: no hospice, late hospice enrollment, intensive care unit stay, terminal hospitalization, multiple hospitalizations, more than one emergency department (ED) visit, receiving an invasive or life prolonging procedure, or any chemotherapy in the last two weeks of life.

Results Among the 11,036 women in this analysis, aggressive end-of-life indicators were common. Black women had less management in oncology and lower continuity of care. They were also the most likely to have >1 ED visit, life extending procedures, multiple hospitalizations, and terminal hospitalization.

Conclusion Similar to other phases of the care continuum, black women with ovarian cancer are receiving different care than white women, but this does not explain the racial difference in the odds of aggressive end-of-life care. These results suggest detailed examination of care characteristics that may impact racial differences in end-of-life care are warranted.

Introduction

End-of-life care for women with ovarian cancer is aggressive.[69,114,125] Similar to many other areas on the ovarian cancer care continuum, studies suggest non-white women with ovarian cancer have higher odds of aggressive care at the end of life, and are less likely to enroll in hospice.[61,75,114] However, these studies are limited by either a hospice only scope, or data drawn from a single state or institution.[61,75,114] These limitations are critical because we know aggressive end-of-life care indicators measure distinct aspects of end-of-life care that are independent of hospice utilization,[70,71] and that end-of-life care has been found to vary widely by region and institution.[115,116]

Similarly, little is known about the end-of-life care characteristics of women with ovarian cancer. Only two single institution studies have evaluated care characteristics including palliative care consultation, end-of-life discussions, and advanced care planning. [77,125] Studies within this population are important because ovarian cancer is rare, and it is the most deadly gynecologic cancer.[148] Evidence shows that surgical care from physicians who manage a high volume of

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women with ovarian cancer results in superior outcomes.[149,150] However, the type of physician most involved in patient evaluation and management has not been evaluated with respect to end-of-life care. In this analysis, we will evaluate the association of the proportion of oncology management visits with receipt of aggressive end-of-life care.

Women with ovarian cancer are likely to experience disease recurrences and have complex healthcare needs for managing advanced incurable cancer and other co-morbid conditions.[151,152] In other populations, care continuity has been associated with improved quality of care, satisfaction, and lower healthcare utilization.[153–155] We evaluated the association of care continuity with receipt of aggressive end-of-life care among women with ovarian cancer. To our knowledge, this is the first study to evaluate racial disparities in aggressive end-of-life care with national data accounting for regional variation. It is also the first to take the important next step of drilling into whether care continuity or predominant evaluation and management within oncology contributes to aggressive end-of-life care.

Methods

Data

SEER-Medicare data links two large population-based data sources, Surveillance, Epidemiology and End Results (SEER) registry data, and Medicare claims data.[156] Medicare insures 97% of US population aged 65 or older, and this linkage includes 93% of SEER cases over the age of 65.[156] This analysis includes claims data from Medicare Parts A and B, and excludes individuals with HMO coverage. Part A covers inpatient care, home health and hospice. Part B covers physician services, outpatient care, durable medical equipment, and certain home health care. Medicare HMO supplemental plans are considered Part C coverage, or Medicare

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Advantage coverage.[157] Linked SEER-Medicare files include the Patient Entitlement and

Diagnosis Summary File (PEDSF), Medicare Provider Analysis and Review (MEDPAR) file for

inpatient services, Home Health Administration files, Hospice files, Hospital Outpatient

Standard Analytic Services (OUTSAF) file for outpatient services, physician/supplier files for

physician services (NCH), census tract files for census level variables, and durable medical file

for oral chemotherapies. Cause of death data is attained by a linkage with the National Death

Index.[158]

Given the tie to payment for services, Medicare data are reliable records of treatment

received.[159] An overview of SEER-Medicare data found that compared to the US population,

SEER-Medicare data has fewer white individuals, people living in poverty and a higher proportion

of urban residents than the elderly population in the United States. [156]

Cohort Selection

To avoid attributing receipt of therapy to another cancer, we included women who died

between 2000 and 2016, whose first and only cancer was invasive ovarian cancer. To facilitate

measurement of co-morbidity, we limited our sample to women over age 66 at the time of cancer

diagnosis (1 year of Medicare data prior to diagnosis to derive co-morbidity), who have complete

case information captured among one of the 18 SEER registries. To ensure we have complete

information on all treatments, we excluded patients who were not enrolled in both Part A and

Part B Medicare, or who were enrolled in an HMO plan in the 12 months prior to their diagnosis,

or at any point from the time of diagnosis through the end of study observation. We excluded

cases with unknown month of diagnosis or death, cases who died within 30 days of diagnosis or

did not die before December 2016, cases where SEER and Medicare birth or death dates were

more than 3 months different, women who were diagnosed at death or autopsy, women with non-

invasive disease, women without at least two claims after diagnosis, women who could not be classified as urban/rural and women whose hospice admission date predates their diagnosis.

Outcomes

The outcomes were assessed using binary claim-based metrics endorsed by the National Quality Forum that include: chemotherapy within 14 days of death, more than one emergency department (ED) visit in the last month of life, more than one hospital admission, an intensive care unit admission in the last month of life, failure to enroll in hospice, less than three days of hospice before death, life extending procedures (ventilation, resuscitation or feeding tubes) or death in an acute care hospital.[70–72,160] We also evaluated receipt of invasive procedures as these are uncomfortable and reduce quality of life.[75,160] These metrics have been successfully used in SEER-Medicare claims, and align with NQF guidelines for quality end-of-life care.[68,69,72] Using claim data from the PEDSF, NCH, OUTSAF and Hospice files, independent binary measures were created to indicate whether any of the aforementioned aggressive treatments occurred in the month before death.

Exposures

Care characteristics were ascertained based on evaluation and management (E/M) visits. Encounters were classified as E/M using current procedural terminology (CPT) codes beginning with 99 in the NCH Medicare claim file. Visits were further classified into a specialty using the CMS code specialty code for pricing the line-item on a claim for payment. Oncology was defined by codes '82', '83', '90' ,'91' ,'92' ,and '98'. Hospice/palliative care was defined by codes '17', '72', and '09'.

Provider assignment Each woman was assigned to an oncologist based on E/M visits after ovarian cancer diagnosis. Visits with specialty listed as hematology, hematology/oncology,

medical oncology, surgical oncology, radiation oncology, gynecologic (GYN)-oncologist were counted by provider ID, and the patient was assigned to the provider with whom she had the most visits.

Provider continuity was evaluated using the Boxerman and Bice Continuity of Care Index (COCI) to reflect the spread of visits across providers.[161] Having all visits with the same provider would result in an index of 1.0, and having all visits with a different provider would have an index value near zero. The index was calculated based upon evaluation and management visits occurring in the last 23 months of life. The final month of life was excluded from the calculation as that time period is used to determine the outcomes of interest. Although the usual provider of care index is most commonly used, it does not account for dispersion across multiple providers.[162] This index was selected to account for patients seeing multiple providers, which is expected for women with ovarian cancer. COCI was calculated for each woman based upon E/M encounters from providers in the 23 months prior to the final month of life. Visits with non-physician providers, (i.e. lab, podiatry, dentistry) or physician providers not driving patient care (anesthesiology, pathology, interventional radiology) were excluded. The last month of life was excluded from this calculation as that is when the outcomes were derived. This calculation requires women have at least two visits, otherwise the denominator is undefined.

Race (non-Hispanic white (NHW), non-Hispanic black (NHB), Hispanic, other) was our primary exposure of interest. Our secondary exposures of interest were care characteristics including: COCI, proportion of oncology E/M visits, and presence of hospice/palliative E/M visits. Each care characteristic was calculated for the 23 months prior to the last month of life.

Models were adjusted for confounding by patient year of death, urban/rural residence, SEER registry, age at death (66-74, 75-84, 85+), one year increase in time between diagnosis and

death, Charlson score (0,1,2,3+), and marital status. We calculated a modified Charlson Index

score for each patient from the 12 months prior to diagnosis. Marital status was classified as un-

partnered (single, separated, widowed, divorced), partnered (married, domestic partnership) or

unknown.

Statistical analysis

We tabulated decedent characteristics, end-of-life care events and care characteristics by

race. Bivariate associations were evaluated for statistical significance using chi-squared tests. We

then used generalized estimating equations to analyze the association between race, care

characteristics and aggressive end-of-life care events. Population averaged models allow for

potential correlation in outcomes among women who share the same physician and account for

this with robust standard error estimates. Final models were adjusted for year of patient death,

urban/rural status, time between diagnosis and death, age at death, Charlson co-morbidity score,

SEER registry and marital status. All analyses were conducted in SAS version 9.4.

We tested the validity of enumerating our cohort based on first and only ovarian cancer

diagnosis by conducting a sensitivity analysis restricted to women with first and only ovarian

cancer whose cause of death was specified as cancer.

Results

There were 11,036 women included in this analysis (Figure 3.1). Women were

predominantly NHW (84.9%), urban residents (97.8%), aged 75-84 (48.5%), un-partnered

(56.3%), with no co-morbid conditions (56.3%), diagnosed with distant spread disease (77.8%),

and with serous histology (73%) (Table 3.1). Tumors were largely high grade (44%) or not

graded (45%) (Table 3.1). Median survival was 1.6 years (range .9-19 years). The median

proportion of evaluation and management visits classified as oncology visits was 33.8%. The median continuity of care index was .198. Only 2% of women had a hospice/palliative evaluation and management visit.

Indicators of aggressive end-of-life treatment were often common in this population, and they varied significantly by race (Table 3.2). Other race women had the highest non-enrollment in hospice (42%), compared to 30% of NHW women did not enroll in hospice, and 38% of NHB and Hispanic women. Only 8% of NHW women had multiple hospitalizations, and the other groups had nearly double the proportion with 15% of NHB, 12% Hispanic and 13% other (p<.0001). Similarly, 9% of NHW women had a life extending procedure, compared to 16% NHB, 12% Hispanic, and 14% of women in the other race category (p<.0001). NHB women had the highest proportion of invasive procedures (29%), compared to 25% of Hispanic and Other women, and 21% of NHW women (p<.0001). All non-white groups of women had 26% of women stay in the ICU and around 25% of women died in the hospital (p<.0001). ED use was highest among NHB women (16%), which was nearly double the proportion of NHW women (8%). Although racial differences were not seen for late enrollment to hospice (p=0.1) and receiving chemotherapy (p=0.8), around 15% of women had a late enrollment to hospice and around 6% received chemotherapy.

The distribution of racial groups varied by SEER region. California contributed the largest proportion of each racial group, and the distribution of races varied significantly among SEER registries (p<.0001). Most NHB women lived in Detroit, Louisiana, Georgia, California and New Jersey. Hispanic women overwhelmingly lived in California (62.3%), as did other race women (56.1%).

The proportion of oncology E/M visits and the COCI varied by race. NHB women had the smallest proportion of women above the median number of E/M visits in oncology (37%), compared to the other groups that had closer to half of women above the cutoff (p<.0001) (Table 3.3). Similarly, NHB women had the least amount of women with a COCI above the median (43%), compared to 50% of NHW and Hispanics, and 52% in other race women (P<.01) (Table 3.3).

Results from the final fully adjusted model are shown in Table 3.4. Models were adjusted for year of death, age of death, survival, co-morbid conditions, marital status and SEER registry as potential confounders. Covariates were added in a stepwise manner and the included exposures did not meaningfully explain the race differences in the aggressive end-of-life indicators evaluated. After adjustment, non-white women had higher odds of almost all aggressive end-of-life indicators evaluated. NHB and Hispanic women both had about 40% increased odds of not enrolling in hospice compared to NHW ((OR 1.40 CI 1.18-1.65) and (OR 1.36 CI 1.13-1.62)), but other race women had 60% higher odds compared to NHW (OR 1.60 CI 1.26-2.02). The largest race effect sizes were for the ED outcome. NHB women had twice the odds of more than one ED visit compared to NHW women (OR 2.02 CI 1.61-2.53). Other race women had 1.9 times the odds of more than one ED visit compared to NHW women (OR 1.86 CI 1.34-2.56). All non-white women had about 40% higher odds of an ICU stay compared to white women. NHB women had 60% higher odds of receiving a life extending procedure compared to NHW (OR 1.64 CI 1.31-2.06) and other race women had 50% higher odds compared to NHW (OR 1.52 CI 1.09-2.11). NHB and Hispanics had 50% higher odds of dying in the hospital compared to NHW, and other race women had 60% higher odds than NHW (OR 1.63 CI 1.24-2.14). Hispanic women had 1.6 times the odds of more than one hospitalization

compared to NHW (OR 1.55 CI 1.16-2.07). NHB had slightly higher odds than Hispanic women (OR 1.73 CI 1.37-2.20), and other race women had nearly twice the odds of NHW (OR 1.91 CI 1.38-2.63).

Four outcomes showed less racial variation. Even in the race only model, receipt of chemotherapy never significantly differed by race. Hispanic women did not have different odds of more than one ED visit or receiving a life extending procedure when compared to NHW. After adjustment, the odds of late hospice enrollment and receipt of an invasive procedure did not vary by race.

COCI was associated with life extending and invasive procedures as well as chemotherapy. Women with a higher COCI had 14% lower odds of receiving either a life extending procedure or an invasive procedure (OR 0.86 CI .74-.99 and OR 0.86 CI .78-.95). Women with a COCI above the median cutoff had 32% higher odds of receiving chemotherapy in the last two weeks of life (OR 1.32 CI 1.12-1.55). Although COCI varied by race in univariate associations, adding the continuity variable did not make an appreciable difference in the race effects in the adjusted models (results not shown).

Having a higher proportion of E/M visits in oncology was associated with lower odds of not enrolling in hospice, late hospice enrollment, and ICU stay, receipt of a life extending or invasive procedure, terminal hospitalization or multiple hospitalizations (Table 3.4). In contrast, a higher proportion of oncology visits was also associated with higher odds of chemotherapy in the last two weeks of life (OR 1.37 CI 1.16-1.63).

Although not many women had evaluation and management visits classified as hospice or palliative care, for those who did, these visits were associated with lower odds of not enrolling in hospice (OR 0.70 CI 0.52-0.95) and terminal hospitalization (OR 0.77 CI 0.69-0.86).

Although not enrolling in hospice, receiving invasive procedure and terminal hospitalization varied by registry, adjusting for registry did not meaningfully change the race effects (results not shown). Compared to Utah, women in Detroit had twice the odds of more than one ED visit (OR 1.97 CI 1.17-3.31) and multiple hospitalizations (OR 1.93 CI 1.02-3.64). Similarly, women in Connecticut had nearly twice the odds of late hospice compared to those in Utah (OR 1.80 CI 1.11-2.90). The only outcome associated with rural residence was not enrolling in hospice. Rural women had 69% higher odds of not enrolling in hospice (OR 1.69 CI 1.27- 2.25).

Sensitivity analysis

We chose to enumerate our cohort based on first and only diagnosis of ovarian cancer rather than cause of death ovarian cancer because death certificate data has many known inaccuracies and limitations.[163–166] In contrast, SEER is considered the gold standard of cancer registry data, with quality checks and established rigor. [167,168] To verify the robustness of our results, we conducted a sensitivity analysis restricting the sample to women who had a cancer cause of death. Result patterns were very similar to our findings in the whole sample. The main difference was that the magnitude of the effect for black race increased, while the effects for Hispanic and other race generally decreased. Because non-cancer cause of death was more common for Hispanic women, other women, older women, and women with longer survival, these changes in results suggest a selection bias introduced by enumerating the cohort using cause of death. Using the cohort defined by diagnosis likely results in more conservative effect estimates.

Discussion

In summary, in this nationally representative sample of 11,036 women with ovarian cancer, racial differences in receipt of aggressive end-of-life care indicators persisted after adjustment for co-morbid conditions, care continuity, hospice/palliative visits, and proportion of management in oncology. Notably, a higher COCI and more evaluation and management in oncology were associated with lower odds of several aggressive end-of-life care indicators. These findings are important because racial differences in end-of-life care vary regionally, and this is the first study to evaluate care characteristics associated with aggressive end-of-life care for women with ovarian cancer.[169]

There are four other studies looking at race and end-of-life care aggressiveness indicators among women with ovarian cancer.[61,75,114,125] Three of these studies come from Texas, two of which are from the same single institution.[75,114,125] Similar to our study, half of ovarian cancer patients in the Brown et al. study received aggressive end-of-life care.[125] Overall, in this institution, patients had late hospice referrals and palliative care consultation. [125] At the same institution, another study found that among gynecologic oncology patients, nonwhite patients were more likely not to have a power of attorney or living will.[114] Those nonwhite patients who enrolled in hospice did so sooner than white patients, but they were overall less likely to enroll in hospice.[114] For the entire state of Texas, in the Medicare population, NHB were twice as likely to have more than one ED visit and to receive a life extending procedure. [75] These studies are limited by their scope within one state or institution. Racial differences in end-of-life care intensity are more pronounced in high expenditure areas.[169] Differences may also reflect regional variation, or physician preferences.[83,85,115] Our analysis used a population averaged model that

accounted for patient clustering within physicians to account for physician preferences. We were also able to adjust for regional variation and benefit from a geographically diverse sample.

The fact that nationally we see similar patterns of aggressive end-of-life care indicators suggests that more work is needed to understand what is driving racial differences in end-of-life care among women with ovarian cancer. This analysis took an important first step in evaluating the association of certain characteristics of care with receipt of aggressive end-of-life care indicators. Although the included care characteristics did not explain the racial differences in the odds of aggressive end-of-life care, they were associated with receipt of certain outcomes. Having more evaluation and management done in oncology as opposed to primary care or other specialties, was associated with lower odds of not enrolling in hospice, late hospice enrollment, ICU use, receipt of life extending/invasive procedures, terminal hospitalization and multiple hospitalizations. This may reflect increased familiarity with the disease process, comfortability in referring patients to hospice or offering palliative services.[170] More oncology evaluation and management was also associated with higher odds of receiving chemotherapy. The reasons for oncologists giving chemotherapy at the end of life are complex and can span from patient desires, inability of a physician to deliver a poor prognosis, or patient misunderstanding of the potential benefits of continued therapy.[171] Administering chemotherapy also drives revenue for many oncology practices.[172] It is also impossible to distinguish the reverse causation that may influence this effect. Women who want to continue chemotherapy would also have a higher proportion of oncology E/M visits because they prefer to receive chemotherapy. We attempted to mitigate this potential bias by using COCI and proportion of oncology visits in the last two years of life, not including the last month because that is the time when outcomes were ascertained.

Nonetheless, delivery of chemotherapy at the end of life is associated with poor outcomes and reduced quality of life, and reflects an opportunity for patient and provider education.[173–175]

Having higher care continuity was associated with lower odds of life extending and invasive procedures. However, women with a higher continuity of care were also more likely to have chemotherapy in the last two weeks of life. Higher COCI likely reflects closer relationships with physicians, which has been associated with overly optimistic prognosis on the part of the physician.[176] This is the first time the association of COCI and aggressive end-of-life care is being evaluated among women with ovarian cancer. Among other cancer patient populations, continuity with same place of healthcare service with coordination by a team was associated with less healthcare utilization at the end of life including aggressive care.[177] Similarly, continuity of care for lung cancer patients reduced odds of ICU usage by 25%.[178] This study defined continuity by a patient's usual outpatient care provider seeing them inpatient, which is likely why they found an association with ICU usage and we did not. [178] However, life extending and invasive procedures, which were associated with COCI in this analysis, are similarly inpatient events. Primary care continuity was associated with less ED use at the end of life in Canada. [179] However, study authors explain this association was found in an area where advanced cancer care is given by primary care providers, so this type of relationship would not be expected in our population. Continuity of care was identified as a contributor to quality of care by advanced cancer patients, and merits further investigation to better understand its relationship to receipt of aggressive end-of-life care.[180]

A key finding in our analysis is that NHB women are receiving a different type of care. While other racial groups had close to 50% of women over the median proportion of oncology visits for evaluation and management, NHB women only had 37% of women receiving that level

of management in oncology. Similarly, only 43% of NHB women had a care continuity index over the median. Although this is the first study to evaluate care characteristics associated with race and end-of-life care, this finding is in line with other phases of the ovarian cancer care continuum. A lower proportion of black women saw a high volume provider for first line treatment as well.[149] Black patients are also more likely to receive non-guideline-adherent care for their ovarian cancer, and they are less likely to travel for care compared to white women.[31,65] In our analysis, NHB had the highest likelihood of ED visits, also highest odds of life extending procedures, multiple hospitalizations, and tied with the other race group for the highest odds of terminal hospitalization. Taylor et al. had a similar finding.[75] These outcomes are likely not independent. A review of ED use by cancer patients suggests that more than half of emergency department visits result in an admission.[181] Future work evaluating patterns of care among women who have several aggressive outcomes, may highlight the most fruitful target for intervention.

As adjustment for the care characteristics evaluated in this study did not result in a meaningful change in race coefficients, what is driving racial differences warrants further investigation. Like this analysis, many studies evaluating racial differences in end-of-life care among populations with cancer utilize SEER Medicare data.[75,99] While these studies yield important data, they are limited in capturing patient preferences or patient characteristics contributing to those preferences.

Although several studies suggest that NHB prefer more aggressive end-of-life care, there is not consensus as to why.[105,107,108,113,182] A multisite study found that although many black patients with advanced cancer prefer aggressive end-of-life care, their preferences did not align

with the care they received.[108] Continuity of care could contribute to this difference, as could differential communication.[108,109]

Physicians also have preconceived ideas of what certain patients will accept for end-of-life care, including that black patients prefer more aggressive care.[91] This is an important area for future qualitative studies, specifically among women with ovarian cancer, because ovarian cancer and its pattern of recurrence and loss of sensitivity to chemotherapy is unique. [183] Management of worry is an unmet need of women with recurrent ovarian cancer.[184] Death anxiety has been associated with not having end-of-life preference conversations with family, which could contribute to a disconnect in care received versus what a patient prefers.[185] In another study, patients with clinical anxiety had less trust in physician recommendations, felt less likely to understand clinical information, and felt less comfortable asking questions. [186] Future work understanding how death anxiety may have similar impacts on clinical interactions and end-of-life decision making could have important implications for more informed end-of-life care decision making.

Limitations

These data are retrospective and claims based. We cannot determine the intention behind procedures received, nor the patient's preferences in receiving them. However, the markers for aggressive care that we used are well established as indicative of quality of end-of-life care. Ovarian cancer has clinical hallmarks such as malignant bowel obstruction, pleural effusion or a metastasis to the liver should signal to healthcare providers that end-of-life measures are appropriate.[79]

Medicare coverage begins at age 65, and the median age of diagnosis for ovarian cancer is 63.[1] Our findings are not generalizable to the younger women diagnosed with ovarian cancer.

In addition, NHB are diagnosed at earlier ages so NHB in our sample may be healthier or better resourced than women who are not included.[28] This would result in our race effects being a conservative estimate of racial differences.

We were unable to account for socioeconomic status (SES) in this analysis. The best SES measures available were census tract poverty averages from the year a woman was diagnosed. Neighborhood SES is not necessarily equivalent to individual SES. For example, Trupin et al. found that only 17% of individuals whose household income is below 125% of the federal poverty threshold live in high poverty areas.[187] Studies have also shown that individual and neighborhood SES have distinct health effects, highlighting their lack of exchangeability.[188,189] In another study evaluating these outcomes among women with ovarian cancer, income and education were not associated with differences in aggressive end-of-life care.[75] Women in this analysis also had the same health insurance coverage, which is one key element in the relationship between SES and utilizing healthcare.

Strengths

This analysis also had several strengths. This is the first national look at a comprehensive set of end-of-life care quality measures among women with ovarian cancer that evaluates an association with race. End-of-life care varies regionally, so it is important to have a nationally representative sample.[169,190] It is also known that physician preferences play a role in the aggressiveness of end-of-life care received.[85] Our analysis accounted for potential correlation between women sharing the same physician by using population average models. Finally, this analysis looked at novel individual care characteristics to drill into what could be contributing to the racial differences seen in end-of-life care for older women with ovarian cancer. Our finding

that black women have differing care characteristics related to end-of-life care is an important first step toward understanding the differences we see.

Conclusion

In conclusion, our results show that after accounting for regional variation, care characteristics and clustering within physicians, nonwhite women are more likely to receive aggressive end-of-life care. While care characteristics were associated with certain outcomes, they did not explain the racial variation that we see in these outcomes.

Tables and Figures

Table 3.1 Characteristics of the Analytic Cohort of Women Dying with Ovarian Cancer between 2000 and 2016 in SEER-Medicare

	N	%
Race		
Non-Hispanic White	9,374	84.9
Non-Hispanic Black	711	6.4
Hispanic	568	5.1
Other	383	3.5
SEER Registry		
Connecticut	742	6.7
Detroit	733	6.6
Hawaii	88	0.8
Iowa	764	6.9
New Mexico	267	2.4
Seattle	714	6.5
Utah	285	2.6
Kentucky	651	5.9
Louisiana	611	5.5
New Jersey	1,686	15.3
Georgia	1,328	12.0
California	3,167	28.7
Urban/Rural		
Urban	10,790	97.8
Rural	246	2.2
Age		
66-74	2,934	26.6
75-84	5,347	48.5
85+	2,755	25.0
Charlson Score		
0	6,215	56.3
1	2,662	24.1
2	1,125	10.2
3+	1,034	9.4
Marital status		
Not partnered	6,199	56.2
Partnered	4,424	40.1
Unknown	413	3.7
Any hospice/palliative visits		
No visits	10,772	97.6
At least one visit	264	2.4

SEER Stage		
Localized	388	3.5
Regional	1,178	10.7
Distant	8,583	77.8
Un-staged	887	8.0

Table 3.2 Racially Stratified Proportions of Aggressive End-of-Life Care Received by Women Dying with Ovarian Cancer between 2000 and 2016 in SEER-Medicare

Race	No Hospice	Late Hospice	Terminal Hosp.	Multiple Hosp.	Life Ext. Procedure	Invasive	ICU	ED	Chemo
NHW	29.8%	14.0%	16.9%	7.9%	8.8%	21.3%	18.2%	8.1%	6.6%
NHB	38.0%	17.9%	25.3%	14.5%	15.9%	28.7%	26.3%	16.3%	6.3%
Hispanic	38.4%	12.6%	24.1%	12.1%	12.0%	25.0%	26.4%	10.9%	6.3%
Other	42.3%	15.8%	25.6%	13.1%	13.8%	24.8%	26.1%	13.6%	7.8%
p	<.0001	0.1	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	0.8

Table 3.3 Racially Stratified Care Characteristics of Women in SEER-Medicare Dying with Ovarian Cancer between 2000 and 2016

	NHW		NHB		Hispanic		Other		p-value
	N	%	N	%	N	%	N	%	
Region									
Connecticut	695	7.4%	24	3.4%	21	3.7%	2	0.5%	
Detroit	591	6.3%	118	16.6%	15	2.6%	9	2.3%	
Hawaii	13	0.1%	--	0.0%	4	0.7%	--	0.0%	
Iowa	753	8.0%	3	0.4%	8	1.4%	71	18.5%	
New Mexico	187	2.0%	2	0.3%	63	11.1%	15	3.9%	
Seattle	650	6.9%	11	1.5%	13	2.3%	40	10.4%	<.0001
Utah	275	2.9%	--	0.0%	8	1.4%	2	0.5%	
Kentucky	626	6.7%	21	3.0%	3	0.5%	1	0.3%	
Louisiana	489	5.2%	114	16.0%	7	1.2%	1	0.3%	
New Jersey	1482	15.8%	123	17.3%	61	10.7%	20	5.2%	
Georgia	1131	12.1%	179	25.2%	11	1.9%	7	1.8%	
California	2482	26.5%	116	16.3%	354	62.3%	215	56.1%	
Any Hosp/Pall									
	226	2.4%	17	2.4%	14	2.5%	7	1.8%	0.91
>Median % Onc.									
	4806	51.3%	263	37.0%	273	48.1%	179	46.7%	<.0001
>Median COCI									
	4729	50.4%	306	43.0%	285	50.2%	199	52.0%	0.002

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Table 3.4 Adjusted Odds Ratios for Association of Aggressive End-of-Life Care with Race and Patient Care Characteristics for Women in SEER-Medicare Dying with Ovarian Cancer between 2000 and 2016

	ED	No Hospice	Late Hospice	Chemo	ICU	Life Extending	Invasive	Terminal Hospit.	Multiple Hospit.
	OR (CI)	OR (CI)	OR (CI)	OR (CI)	OR (CI)	OR (CI)	OR (CI)	OR (CI)	OR (CI)
Race/Eth.									
NHB	2.02[*]	1.40[*]	1.24	0.95	1.42[*]	1.64[*]	1.21	1.50[*]	1.73[*]
	(1.61,2.53)	(1.18,1.65)	(0.96,1.60)	(0.68,1.33)	(1.18,1.72)	(1.31,2.06)	(0.99,1.47)	(1.25,1.82)	(1.37,2.20)
Hisp	1.29	1.36[*]	0.75	0.95	1.39[$]	1.28	1.17	1.54[*]	1.55[*]
	(0.97,1.72)	(1.13,1.62)	(0.54,1.04)	(0.66,1.36)	(1.13,1.69)	(0.98,1.68)	(0.95,1.43)	(1.26,1.88)	(1.16,2.07)
Other	1.86[*]	1.60[*]	1.14	0.95	1.40[†]	1.52[†]	1.15	1.63[*]	1.91[*]
	(1.34,2.56)	(1.26,2.02)	(0.78,1.68)	(0.60,1.52)	(1.08,1.83)	(1.09,2.11)	(0.89,1.50)	(1.24,2.14)	(1.38,2.63)
NHW	1.00 Ref	1.00 Ref	1.00 Ref	1.00 Ref	1.00 Ref	1.00 Ref	1.00 Ref	1.00 Ref	1.00 Ref
> Med. COCI	0.93	1.07	0.93	1.32[*]	0.90	0.86[†]	0.86[$]	1.12[†]	1.05
	(0.80,1.08)	(0.98,1.17)	(0.81,1.07)	(1.12,1.55)	(0.81,1.00)	(0.74,0.99)	(0.78,0.95)	(1.00,1.25)	(0.91,1.22)
>Med. % Onc.	0.89	0.66[*]	0.85[†]	1.37[*]	0.70[*]	0.8[$]	0.75[*]	0.77[*]	0.80[$]
	(0.77,1.04)	(0.61,0.73)	(0.74,0.98)	(1.16,1.63)	(0.63,0.78)	(0.7,0.93)	(0.68,0.83)	(0.69,0.86)	(0.69,0.93)
Any Hosp/ Pall visit	0.84	0.7[†]	0.76	0.94	0.81	1.03	1.26	0.6[†]	0.83
	(0.54,1.32)	(0.52,0.95)	(0.49,1.17)	(0.54,1.63)	(0.59,1.11)	(0.69,1.56)	(0.95,1.69)	(0.40,0.91)	(0.51,1.35)

Figure 3.1 Analytic Cohort Exclusion Flow

Invasive epithelial ovarian cancer cases died 2000-2016, age ≥66 (N = 35,233)	
	Second primary cancer N=7,853
Remaining Cases N =27,380	
	Missing diagnosis/death date N =219
Remaining Cases N = 27,161	
	Died within 30 days of diagnosis or still alive N = 5,144
Remaining Cases N = 22,017	
	Did not have continuous Medicare coverage N = 7695
Remaining Cases N = 14,322	
	SEER and Medicare birth/death dates do not reasonably agree N= 21
Remaining Cases N = 14,301	
	Diagnosed at death or autopsy N= 698
Remaining Cases N = 13,603	
	Non-invasive disease N= 340
Remaining Cases N = 13,263	
	Enrolled in hospice before diagnosis N= 52
Remaining Cases N = 13,211	
	No claims after dx N= 23
Remaining Cases N = 13,188	
	Could not ascertain oncologist N= 2,012
Included Cases N = 11,176	
	Could not be coded as urban/ rural N= 9
Included Cases N = 11,167	
	<2 E/M visits in last 2 years N= 131
Included Cases N = 11,036	

CHAPTER 4. Physician Variation in Aggressive End-of-Life Care for Women with Ovarian Cancer

Abstract

Background Physicians are important drivers of end-of-life spending and hospice use. We do not know which physician practice characteristics may be associated with more aggressive end-of-life care, or how they may contribute to racial differences in aggressive end-of-life care. In this analysis, we determined the variation in aggressive end-of-life care attributable to physicians. We then evaluated the association of ovarian cancer patient volume, nonwhite patient volume and physician specialty with claims based aggressive end-of-life outcomes.

Methods Subjects included women over age 66 with ovarian cancer who died between 2000 and 2016 and had continuous Medicare coverage. Multilevel logistic models with random intercepts for physicians were adjusted for confounding and used to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) for associations of race and physician characteristics with aggressive end-of-life care including: no hospice, late hospice enrollment, intensive care unit stay, terminal hospitalization, multiple hospitalizations, more than one emergency department (ED) visit, receiving an invasive or life prolonging procedure, or any chemotherapy in the last two weeks of life.

Results In summary, in this sample of 11,167 women with ovarian cancer, physician level variation accounted for substantial variation in aggressive end-of-life care indicators including 15% of variation in receipt of chemotherapy in the last two weeks of life, 11% of variation in

undergoing multiple hospitalizations in the last 30 days of life, and 9% of variation in not enrolling in hospice. A provider's nonwhite patient volume was associated with increased odds of a woman not receiving hospice (OR 1.15 CI 1.04- 1.28), having a stay in the ICU (OR 1.25 CI 1.12-1.40), receiving a life extending procedure (OR 1.18 CI 1.01-1.37), and having a terminal hospitalization (OR 1.17 CI 1.05- 1.31).

Conclusion Although physician variation does not explain why nonwhite women are more likely to have aggressive care at the end of life, our findings suggest nonwhite women may be seeing providers with lower ovarian cancer patient volume and higher nonwhite patient volume. Future work including qualitative interviews of patients and more comprehensive physician characteristics is an important next step.

Introduction

Ovarian cancer is an aggressive and rapidly fatal cancer, with less than half of women surviving five years after they are diagnosed.[191] As such, end-of-life care is an important segment of the ovarian cancer care continuum. Despite a poor prognosis with few curative options, we know that many women with ovarian cancer receive aggressive end-of-life care, a likelihood that increases for non-white women with ovarian cancer.[61,75,125]

Studies suggest physicians are important drivers of end-of-life care intensity and hospice use.[81,82] To our knowledge, no one has evaluated to what extent physician variation is associated with aggressive end-of-life care for women with ovarian cancer, or how this may contribute to racial variation in the aggressiveness of care received.

Although ovarian cancer patient volume and racial mix of patients have not been previously evaluated, past work suggests that high volume surgical providers of ovarian cancer surgery have better outcomes.[149] Similarly, providers who have more training and experience

with end-of-life discussions feel more prepared and have less aggressive care outcomes.[192–194]

We also know personal and clinical experiences inform physician decision making.[90] Serving a more racially diverse patient base may influence physician choices about end-of-life care and impact the aggressiveness of the care their patients receive. Finally, different specialties have different beliefs about end-of-life care that may be associated with more aggressive care.[88,95] We will evaluate the association of physician ovarian cancer patient volume, nonwhite patient volume, and specialty with patient receipt of aggressive care as defined by a commonly used set of claims based indicators derived from National Quality Forum measures.[69,71,75,160]

Methods

Cohort Ascertainment

Surveillance Epidemiology and End Results (SEER) is a National Cancer Institute (NCI) program of 18 population-based cancer registries that collect patient information on cancer cases who reside within the geographic catchment area of the registry. SEER data collection includes patient demographics, tumor characteristics, treatment, and survival. SEER records can be linked to Medicare data, providing detailed data for approximately 25% of elderly patients diagnosed with cancer in the US. The linkage to Medicare includes women from SEER catchment areas including Atlanta, Connecticut, Hawaii, Iowa, New Mexico, Utah, Rural Georgia, Detroit, Seattle-Puget Sounds, Los Angeles, San Jose-Monterey, San Francisco-Oakland, Greater California, Kentucky, Louisiana and New Jersey. Alaska Native and Arizona Indians special population registries are not included in this data linkage.[156] Data are from the linkage of SEER registry data with Medicare claims for women who died between 2000 and 2016. The Wayne State University institutional review board determined this study was exempt.

A detailed cohort enumeration can be found in Figure 4.1. Included were women whose first and only cancer was invasive ovarian cancer, and who were aged 66 and older in order to ensure availability of 12 months of claims prior to diagnosis for determining co-morbidities. Patients lacking continuous enrollment in Medicare Parts A and B, or patients who enrolled in a health maintenance organization (HMO) in the period including 12 months before cancer diagnosis to death or the end of our analytic time period (December 31, 2016), were excluded as HMO claims are not included in this dataset and could lead to missing treatment information. Patients were also excluded for the following: missing date of diagnosis or death, birth or death date did not reasonably agree between SEER and Medicare records, diagnosed at death, surviving less than 30 days after diagnosis, enrolled in hospice before diagnosis, no claims (inpatient, outpatient, carrier, hospice) after diagnosis, no claims with an oncology provider listed as well as women who were unable to be classified as urban or rural.

Physician characteristics In order to obtain the most information possible, physician characteristics were derived from the entire sample of women with ovarian cancer, regardless of vital status. Women were included who had the same inclusion criteria as the analytic cohort in this analysis, with the exception of having died. Physician characteristics are derived from all women with complete Medicare coverage diagnosed between 1997 and 2016 with invasive ovarian cancer.

Provider assignment Each woman was assigned to an oncologist based on evaluation and management (E/M) visits after ovarian cancer diagnosis. Encounters were classified as E/M using current procedural terminology (CPT) codes beginning with 99 in the NCH Medicare claim file. Visits with specialty listed as hematology, hematology/oncology, medical oncology,

surgical oncology, radiation oncology, gynecologic (GYN)-oncologist were counted by provider ID, and the patient was assigned to the provider with whom she had the most visits.

Provider specialty assignment Oncologists were classified into the specialty where they billed the most E/M visits. If the specialty was not GYN-oncology or medical oncology they were classified as miscellaneous.

Provider volume Patient volume was determined by counting the number of women with ovarian cancer who had an E/M encounter with each provider. A median cutoff was determined based on physicians with patients in the analytic sample.

Provider non-white volume The number of patients in each racial ethnic group was calculated for each provider. Non-Hispanic black, Hispanic and other classified patients were combined into a non-white category and the proportion of non-white patients was calculated. As 15% of physicians only saw one patient, proportions were shrunk toward the sample distribution of 15% non-white patients. Median non-white volume was determine based on physicians with patients in the analytic sample.

Outcomes

The outcomes were assessed using binary claim-based metrics endorsed by the National Quality Forum that include: chemotherapy within 14 days of death, more than one emergency visit in the last month of life, more than one hospital admission in the last month of life, an intensive care unit admission in the last month of life, failure to enroll in hospice, less than three days of hospice before death, life extending procedures (ventilation, resuscitation or feeding tubes) or death in an acute care hospital.[70–72,160] We also evaluated receipt of invasive procedures as these are uncomfortable and reduce quality of life.[75,160] These metrics have been successfully used in SEER-Medicare claims, and align with NQF guidelines for quality end-of-life care.[68,69,72]

Using claim data from the PEDSF, NCH, OUTSAF and Hospice files, independent binary measures were created to indicate whether any of the aforementioned aggressive treatments occurred in the month before death.

Model Covariates

Apart from physician clustering and characteristics, our primary exposure of interest was race. Patients were classified as non-Hispanic white, non-Hispanic black, Hispanic or other. Models were adjusted for confounding by patient year of death, age at death (66-74, 75-84, 85+), one year increase in time between diagnosis and death, Charlson Score (0,1,2, 3+), and marital status. We calculated a modified Charlson Index score for each patient from the 12 months prior to diagnosis. Marital status was classified as un-partnered (single, separated, widowed, divorced), partnered (married, domestic partnership) or unknown.

Statistical Analyses

We tabulated patient and provider characteristics. Bivariate associations were assessed with chi-squared tests. We then developed multilevel logistic models for each outcome with a random intercept for oncologist. The intraclass correlation coefficient (ICC) was calculated for each model to determine the percent variation in each outcome attributable to the oncologist, and evaluate how that variation changes with the addition of oncologist characteristics. Models for evaluating the ICC did not include patient characteristics due to the fixed level one variation. Models for evaluating the association of race with each outcome were also multilevel logistic models with a random intercept for oncologist. All analyses were conducted in SAS version 9.4.

We conducted two sensitivity analyses. The first evaluated the robustness of results when inclusion of women in the analytic cohort was restricted to those having a cancer cause of death.

The second analyzed the characteristics of women who were excluded from the main analysis because they did not have an identifiable oncologist.

Results

There are 11,167 women in this analytic cohort. Detailed cohort enumeration is presented in Figure 4.1. The majority of the sample was NHW (85%), dying between ages 75 and 84 (48%), had no co-morbid conditions (56%), were not partnered (56%), and had the most evaluation and management done by a medical oncologist (73%) (Table 4.1). The median cutoff for proportion of non-white patient volume was 12.5%. The median cutoff for volume of ovarian cancer patients was 12 patients. Median survival was 1.6 years (range 0.9 to 19 years).

Many of the aggressive end-of-life care indicators evaluated in this study were common, and their occurrence varied by race (Table 4.2). Women of other race/ethnicity had the highest non-enrollment in hospice (43%), compared to 30% of NHW women who did not enroll in hospice, and 38% of NHB and Hispanic women. Only 8% of NHW women had multiple hospitalizations, and the other groups had nearly double the proportion with 16% of NHB, 11% Hispanic and 14% other ($p<.0001$). Similarly, 9% of NHW women had a life extending procedure, compared to 16% NHB, 12% Hispanic, and 14% of women in the other race category ($p<.0001$). NHB women had the highest proportion of invasive procedures (29%), compared to 25% of Hispanic and Other women, and 22% of NHW women ($p<.0001$). All non-white groups of women had 26% of women stay in the ICU and around 25% of women die in the hospital ($p<.0001$). ED use was highest among NHB women (16%), which was nearly double the proportion of NHW women (8%). Although racial differences were not seen for late enrollment to hospice ($p=0.1$) and receiving chemotherapy ($p=0.8$), around 15% of women had a late enrollment to hospice and around 6% received chemotherapy.

All physician characteristics had different distributions across racial groups (Table 4.3).

NHB and other race women had around 2% more women who saw an oncologist other than

medical or GYN-oncology most often, and about 3% more women seeing a GYN-oncologist

most often (P=0.1). For both NHB and other race women, 93% saw a physician who had a larger

proportion (higher than 12.5%) nonwhite ovarian cancer patients with Medicare (p<.001) (Table

4.3). A larger proportion of NHW women saw an oncologist who had a higher ovarian cancer

patient volume (53%) versus less than half of women in the other racial ethnic groups (P<.001)

(Table 4.3).

With the exception of having more than two ED visits in the last month of life, the

likelihood of each aggressive end-of-life care indicator varied significantly across physicians

(Table 4.4). The most provider level variation was seen in chemotherapy (14%), multiple

hospitalizations (10%), no hospice (8%), life extending procedures (7%) and ICU stay (6%).

Seeing more ovarian cancer patients, seeing more nonwhite patients, and billing more in a certain

specialty did not explain more than 1% of the physician driven variation in any of the outcomes

(Table 4.4).

The magnitude of the odds ratio for each race/ethnic group did not change meaningfully

as covariates were added to the model. Results shown are from the fully adjusted model

controlling for year of death, time from diagnosis to death, age at death, and Charlson Score,

while also conditioning on physician via the random intercept (Table 4.5). The odds of

chemotherapy and enrolling in hospice during the last three days of life did not differ by

race/ethnic group (Table 4.5). All nonwhite women had 40% higher odds of a stay in the ICU

when compared to NHW women. Other race women had the highest odds of no hospice use (OR

1.59 CI 1.27-2.00), whereas NHB and Hispanic women had closer to 30% higher odds than

NHW (OR 1.29 CI 1.09-1.54 for NHB, OR 1.36 CI 1.12-1.65 for Hispanic). Similarly, other race women had the highest odds of terminal hospital stay (OR 1.57 CI 1.23-2.01). NHB had the highest odds of receiving a life extending procedure (OR 1.75 CI 1.39-2.21), receiving an invasive procedure (OR 1.33 CI 1.11-1.59) and multiple hospitalizations (OR 1.74 CI 1.36-2.22) (Table 4.5). The model of more than two ED visits in the last month of life did not have enough variation at the physician level for the model to successfully converge upon addition of patient level characteristics.

Seeing a provider with a larger volume of nonwhite patients was associated with a higher odds of no hospice enrollment (OR 1.15 CI 1.04-1.28), an ICU stay (OR 1.25 CI 1.12-1.40), receipt of life extending procedure (OR 1.18 CI 1.01-1.37), and a terminal hospitalization (OR 1.17 CI 1.05- 1.31). Seeing a provider with a higher volume of ovarian cancer patients was not associated with any of the aggressive end-of-life care indicators.

Compared to women who had most evaluation and management with a gynecologic oncologist, women who saw medical oncologists were less likely to have a life extending procedure (OR 0.74 CI 0.62-0.88), but were more likely to have a terminal hospitalization (OR 1.26 CI 1.10-1.46).

Sensitivity analysis

2,007 women were excluded because their oncologist could not be ascertained from claim data. Upon sensitivity analysis, these women were more likely to be in the oldest age category, survive less than one year after diagnosis, to be un-partnered, and to have no co-morbid conditions identified by claims. Not having an identified oncologist was also more common in women who died closer to the year 2000, and the proportion decreased over time. Importantly race was not associated with not having an oncologist. These findings support excluding these

women from our analytic cohort. They are women who did not follow the usual course of treatment for ovarian cancer, and likely are not engaged with the healthcare system.

We chose to enumerate our cohort based on first and only diagnosis of ovarian cancer rather than cause of death ovarian cancer because death certificate data has many known inaccuracies and limitations.[163–166] In contrast, SEER is considered the gold standard of cancer registry data, with quality checks and rigor.[167,168] To verify the robustness of our results, we did a sensitivity analysis restricting the sample to women who had a cancer cause of death. Result patterns were very similar to our findings in the whole sample. The main difference was that the magnitude of the effect for black race increased, and the ICCs for variation attributable to physicians increased. Because non-cancer cause of death was more common for Hispanic women, other women, older women, and women with longer survival, these changes in results suggest a selection bias introduced by enumerating the cohort using cause of death. Using the cohort defined by diagnosis likely results in more conservative effect estimates for each racial/ethnic group.

Discussion

In summary, in this sample of 11,167 women with ovarian cancer, physician level variation accounted for substantial variation in aggressive end-of-life care indicators including 15% of variation in receipt of chemotherapy in the last two weeks of life, 11% of variation in undergoing multiple hospitalizations in the last 30 days of life, and 9% of variation in not enrolling in hospice. This finding is important because while previous studies have shown end-of-life care for ovarian cancer is aggressive, our results highlight a potential mechanism for intervention and improving the quality of end-of-life care.[61,69,75,125] Physicians with special training in palliative care make less aggressive end-of-life care decisions.[192] Similarly, oncologist

training in shared decision making around palliative treatment improved observed and patient reported shared decision making.[193] Caring for dying women is a topic that 97% of gynecologic oncology trainees identified as important, yet only 34% identified it as important to their attendings.[194] Having more end-of-life discussions and receiving feedback on said discussions increased gynecologic oncology fellows perceived preparedness to have end-of-life discussions; however, during their training, many had never been observed having these conversations (46%) or given feedback on them (56%). [194]

Similar to our findings, physician preferences account for intensity of care received in other patient populations.[81–85] Among patients with poor prognosis cancer, seeing a physician who has had many patients go on hospice was the single largest predictor of hospice enrollment.[82] Unlike patient preferences for end-of-life care, physician preferences for aggressive end-of-life care are strongly associated with higher regional spending for enrollees during the last six months of life.[81,83,85] Although not cancer specific, Cutler et al. found that after accounting for patient preferences, physician motivation by finances, and organizational factors, the biggest driver in regional spending was physician beliefs about whether aggressive treatments were effective despite being against evidence or guideline recommendations.[81] Echoing the role of physician beliefs, a multicenter survey of oncologists found uncertainty of treatment benefits was a barrier to having goal of care conversations with patients who have advanced cancer.[86]

Types of oncologists have differing attitudes about end-of-life treatment.[87] For example hematologic oncologists value hospice, but feel it has inadequate resources for blood cancer patients.[88] Despite potential differences in beliefs about end-of-life care by specialty, our results showed minimal differences by oncology specialty (Table 4.5). Similarly, we found no

significant differences in the odds of aggressive end-of-life indicators among patients of providers who saw more patients with ovarian cancer. One reason we may fail to see associations with aggressive end-of-life indicators and these differences in physician characteristics is that they were defined by a limited segment of the physician's overall patient population. Likewise, all of these physicians were treating women with ovarian cancer, which may make them more similar than physicians who were randomly surveyed and focus on different cancers. A study comparing end-of-life care by physician specialty found that patients receiving care from medical oncologists were more likely to enroll in hospice, however the comparator groups were predominantly non oncologists.[82] Another study in Taiwan found patients of medical oncologists were less likely to have more than one ED visit, stay in an ICU or receiving life extending procedures.[89] We also found patients managed by medical oncologists were less likely to receive a life extending procedure (OR 0.74 CI 0.62-0.88). Similar to our study where medical oncologist care was associated with terminal hospitalization (OR 1.26 CI 1.10-1.46), they were more likely to have prolonged hospitalization.[89] Differences in our findings may reflect using GYN-oncology as a comparison group instead of other specialists as was done by Liu et al. They may also result from different healthcare access and utilization in the Taiwanese healthcare system.

The physician characteristic more widely associated with markers of aggressive end-of-life care was having a higher proportion of nonwhite ovarian cancer patients. After adjusting models for patient race, a provider's nonwhite patient volume was associated with increased odds of a woman not receiving hospice, having a stay in the ICU, receiving a life extending procedure, and having a terminal hospitalization. Perhaps having a more racially diverse patient population influences a physician's beliefs about patient understanding, desires and willingness

to transition to hospice or less aggressive care. A survey of physician end-of-life preferences found that personal family experience and patient interaction/observation were listed as influencing their end-of-life decision making almost as commonly as their training was.[90] Physicians surveyed about different patent preferences by race indicated that black patients were more likely to want to pursue treatment, have family participation, avoid hospice and favor being at home.[90] Physicians have beliefs about what groups of patients will and will not accept, which can impact their communication decisions about care options.[91] Perceived physician communication as unsupportive, or uninformative was more common among black cancer patients, and was associated with lower trust in the physician as a result.[92] Black patients also receive less information from their providers and are less active participants in visits.[93] As a result, nonwhite patients more often have discordant understanding of prognosis.[94] Oncologists cite unrealistic patient expectations and reduced patient trust as barriers to providing quality end-of-life care.[95,96] Among healthcare providers there is a belief that palliative care referral may be perceived as giving up or would signal that healthcare providers were giving up hope for the patient.[97] Echoing this belief, gynecologic oncologists have indicated that patient trust is key for being willing to recommend palliative care or transition to end-of-life care.[98]

Limitations

This study has certain limitations. Physician characteristics are based solely on women with ovarian cancer who have Medicare insurance. We cannot say that the Medicare population a physician sees is representative of their overall patient population. This misclassification could be contributing to the lack of association between physician characteristics and the outcomes, as well as the inability to explain much of the physician driven variation in outcomes with the addition of physician characteristics. The associations we found are likely conservative

estimates, and suggest more work evaluating physician characteristics is warranted. As this is retrospective claims-based data, we are limited in the intention driving the procedures we see. However, the outcomes we evaluate are a commonly accepted set of measures reflecting aggressive end-of-life care that are not reflective of optimal care.[68–71,160]

Strengths

This is the first study to look at the physician driven contribution to racial variation in end-of-life care aggressiveness for women with ovarian cancer. Physicians are an important point of intervention as they have indicated interest in improving their end-of-life treatment of patients, and evidence suggests training and familiarity with end-of-life discussions can improve outcomes in this area.[192–194] This study is also the first to use national data to evaluate racial disparities in aggressive end-of-life care for women with ovarian cancer. Other studies have been limited to single states or institutions, which are not generalizable.[75,114,125]

Conclusion

In conclusion, physicians are driving a meaningful amount of variation in aggressive end-of-life care for women with ovarian cancer. Although this does not explain why nonwhite women are more likely to have aggressive care at the end of life, our findings suggest nonwhite women may be seeing different types of providers. Future work evaluating the relationship of physician beliefs/characteristics and aggressive end-of-life care is an important next step in ensuring women with ovarian cancer receive less aggressive end-of-life care.

Tables and Figures

Figure 4.1 Analytic Cohort Exclusion Flow
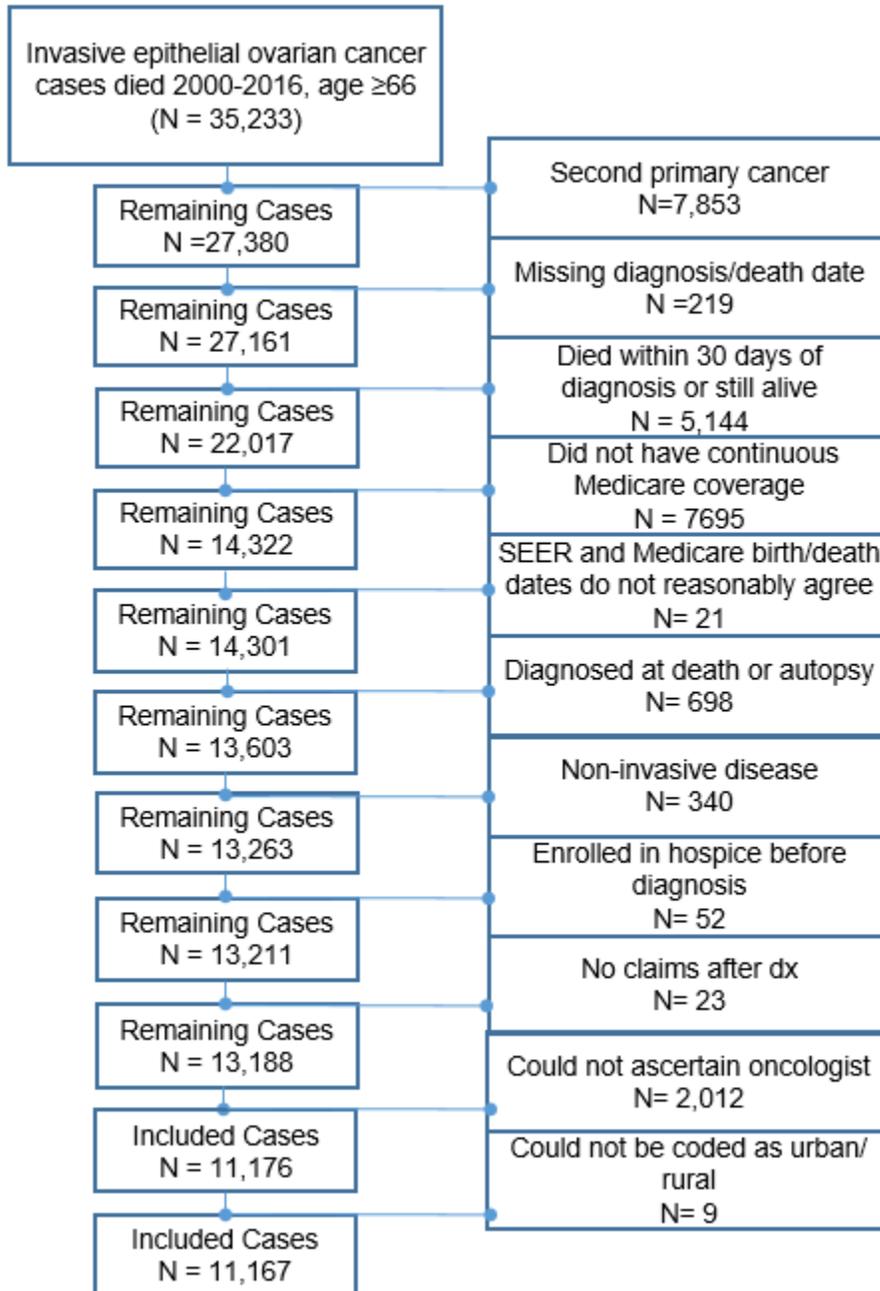
Table 4.1 Characteristics of the Analytic Cohort of Women Dying with Ovarian Cancer between 2000 and 2016 in SEER-Medicare

	N	%
Race		
Non-Hispanic White	9,490	85
Non-Hispanic Black	716	6.4
Hispanic	573	5.1
Other	388	3.5
Age		
66-74	2,970	26.6
75-84	5,395	48.3
85+	2,802	25.1
Charlson Score		
0	6,290	56.3
1	2,690	24.1
2	1,140	10.2
3+	1,047	9.4
Marital Status		
Partnered	4,461	40
Not-partnered	6,290	56.3
Unknown	416	3.7
Oncologist Type		
Gyn-Onc	2,483	22.2
Medical Onc	8,194	73.4
Misc. Onc	490	4.4

Table 4.2 Racially Stratified Proportions of Aggressive End-of-Life Care Received by Women Dying with Ovarian Cancer between 2000 and 2016 in SEER-Medicare

	No Hospice	ED	Late Hospice	ICU	Life Ext	Invasive	Chemo	Terminal Hospitalization	Multiple Hospitalization
NHW	30.1	8.1	14.1	18.3	8.9	21.5	6.7	17.1	8.0
NHB	38.3	16.3	17.9	26.7	16.1	29.1	6.4	25.6	14.4
Hispanic	38.7	11.0	12.5	26.5	11.9	25.3	6.3	24.3	12.2
Other	42.5	13.7	16.1	26.0	14.2	25.3	7.7	25.8	13.1
P	<.0001	<.0001	0.1	<.0001	<.0001	<.0001	0.8	<.0001	<.0001

Table 4.3 Physician Characteristics Grouped by Race of Women in SEER-Medicare Dying with Ovarian Cancer between 2000 and 2016

	NHW		NHB		Hispanic		Other		p
Provider specialty	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
Gyn-Oncology	2,089	22	180	25	115	20.1	99	25.5	0.01
Medical Oncology	6,996	73.7	494	69	438	76.4	266	68.6	
Miscellaneous	405	4.3	42	6	20	3.5	23	5.9	
Non-white patient volume									
<Median	4,970	52.4	54	8	64	11.2	28	7.2	<.001
>Median	4,520	47.6	662	93	509	88.8	360	92.8	
Ovarian cancer patient volume									
<Median	4,503	47.5	385	54	317	55.3	217	55.9	<.001
>Median	4,987	52.5	331	46	256	44.7	171	44.1	

Table 4.4 Physician Variation in Aggressive End-of-Life Care among Women in SEER-Medicare Dying with Ovarian Cancer between 2000 and 2016

	ICC 0	p	ICC 1	p	ICC 2	p	ICC 3	p
No Hospice	8.6%	0.00	8.3%	0.00	8.1%	0.00	7.9%	0.00
ED	2.6%	0.20	1.9%	0.27	1.6%	0.29	1.5%	0.30
Late Hospice	6.5%	0.01	6.1%	0.01	6.1%	0.01	6.1%	0.01
ICU	6.0%	0.00	5.7%	0.00	5.0%	0.00	5.0%	0.00
Life Extending	7.6%	0.01	7.5%	0.01	6.9%	0.01	7.0%	0.01
Invasive	3.9%	0.00	3.8%	0.00	3.7%	0.00	3.7%	0.00
Chemo	14.6%	0.00	14.0%	0.00	14.0%	0.00	13.7%	0.00
Terminal	5.0%	0.00	4.7%	0.00	4.1%	0.00	3.5%	0.01
Multiple	10.8%	0.00	10.6%	0.00	9.9%	0.00	9.9%	0.00

Model 0: No covariates

Model 1: over patient median

Model 2: over patient median, over nonwhite patient median

Model 3: over patient median, over nonwhite patient median, specialty

Table 4.5 Adjusted Odds Ratios for Association of Aggressive End-of-Life Care with Patient Race and Physician Characteristics among Women in SEER-Medicare Dying with Ovarian Cancer between 2000 and 2016

	No hospice OR(CI)	Late hospice OR(CI)	ICU OR(CI)	Life extending OR(CI)	Invasive OR(CI)	Chemo OR(CI)	Terminal OR(CI)	Multiple OR(CI)
Race/Ethnicity								
NHW	1.00 Ref	1.00 Ref	1.00 Ref	1.00 Ref	1.00 Ref	1.00 Ref	1.00 Ref	1.00 Ref
NHB	1.29 (1.09, 1.54)	1.26 (0.96, 1.66)	1.40 (1.16, 1.69)	1.75 (1.39, 2.21)	1.33 (1.11, 1.59)	0.94 (0.67, 1.31)	1.49 (1.23, 1.80)	1.74 (1.36, 2.22)
Hispanic	1.36 (1.12, 1.65)	0.81 (0.58, 1.13)	1.36 (1.11, 1.67)	1.23 (0.93, 1.62)	1.13 (0.92, 1.39)	0.90 (0.63, 1.31)	1.41 (1.15, 1.74)	1.48 (1.12, 1.95)
Other	1.59 (1.27, 2.00)	1.18 (0.81, 1.74)	1.40 (1.09, 1.79)	1.50 (1.09, 2.06)	1.16 (0.91, 1.49)	1.10 (0.73, 1.67)	1.57 (1.23, 2.01)	1.65 (1.19, 2.29)
Provider Non-White Patient Volume								
> Median	1.15 (1.04, 1.28)	1.00 (0.86, 1.16)	1.25 (1.12, 1.40)	1.18 (1.01, 1.37)	1.06 (0.95, 1.18)	0.95 (0.79, 1.14)	1.17 (1.05, 1.31)	1.00 (0.85, 1.18)
Provider Patient Volume								
> Median	0.96 (0.86, 1.06)	0.87 (0.75, 1.02)	1.01 (0.91, 1.13)	0.94 (0.81, 1.10)	1.01 (0.91, 1.13)	0.92 (0.77, 1.11)	1.02 (0.91, 1.14)	0.97 (0.83, 1.13)
Provider Specialty								
	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

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Gyn Oncologist	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Misc. Oncologist	0.95 (0.74, 1.23)	0.96 (0.67, 1.39)	0.77 (0.57, 1.02)	0.60 (0.41, 0.89)	1.02 (0.79, 1.32)	0.90 (0.55, 1.46)	1.08 (0.82, 1.43)	0.97 (0.66, 1.42)
Med. Oncologist	1.10 (0.97, 1.26)	1.01 (0.83, 1.21)	1.05 (0.92, 1.21)	0.74 (0.62, 0.88)	1.05 (0.92, 1.20)	1.21 (0.96, 1.53)	1.26 (1.10, 1.46)	1.01 (0.83, 1.23)

*** Models adjusted for: year of death, age at death, time between death and diagnosis, marital status, Charlson score, random intercept for physician.

CHAPTER 5. Conclusions

Summary and Implications of Main Findings

Ovarian cancer was one of two cancers in the 2017 NCI Report to the Nation that showed improved survival for white women, and worsening survival for black women.[36] This runs counter to national trends in nearly all cancers where patients are experiencing improved survival rates.[36] Knowing that differences in care received are associated with differing outcomes for black women with ovarian cancer, the goals of this dissertation were to: i) evaluate novel facets of access to care, ii) describe national racial disparities in aggressive end-of-life care and examine the relationship with individual care characteristics, and iii) quantify physician variation in aggressive end-of-life care and examine related physician characteristics. In fulfillment of these goals, the results presented here further our knowledge about racial differences at the beginning and end of the ovarian cancer care continuum.

In Chapter 2 we focused on the symptomatic period prior to ovarian cancer diagnosis. Ovarian cancer symptoms are non-specific and commonly require repeated healthcare encounters before a clinician suspects ovarian cancer. We evaluated two potential barriers to receiving an ovarian cancer diagnosis, everyday discrimination and trust in physicians, and their association with having a prolonged symptom duration prior to diagnosis. Our study found that an increase in the frequency of perceived everyday discrimination was associated with higher odds of prolonged symptom duration, but trust in physicians was not associated with prolonged symptom duration.

These findings inform future cancer care health disparities research. Particularly in studies of ovarian cancer where populations are generally small, low trust in the healthcare system is cited as an explanation for differences in care received; however, no studies have done qualitative work to understand whether this is true, or what other drivers of difference may be.[75,114] The AACES collected an unprecedented amount of data from black women with ovarian cancer that was not generated from medical claims. These results suggest the permeating impact of racism is important to consider in healthcare settings. They also highlight a distinction in perspective. Racism is understood to be perpetuated by people outside the black community, whereas low trust in physicians is commonly described as a characteristic of the black community. This distinction shifts the burden of responsibility off of black patients to the broader healthcare community. These findings also highlight the importance of continuing to create population based case-control studies like AACES because so many of the keys to the racial disparities in the ovarian cancer care continuum cannot be gleaned from medical claim data where most disparity studies take place.

In Chapters 3 and 4, we evaluated the opposite end of the care continuum, end-of-life care. In Chapter 3 we had the goal of understanding whether the racial disparities found among women with ovarian cancer in Texas were the same nationally. We also sought to determine whether continuity of care or management by different physician specialties would explain some of these racial differences. Black women had significantly less management in oncology and lower continuity of care than white women. They were also the most likely to have more than one ED visit, life extending procedures, multiple hospitalizations, and terminal hospitalization in the month prior to death.

In Chapter 4, we sought to quantify the physician variation in aggressive end-of-life care and evaluate the associations with physician ovarian cancer patient volume, nonwhite patient volume and oncology specialty. We found that a provider's nonwhite patient volume was associated with increased odds of a woman not receiving hospice, having a stay in the ICU, receiving a life extending procedure, and having a terminal hospitalization. Physician level variation also accounted for substantial variation in aggressive end-of-life care indicators including 15% of variation in receipt of chemotherapy in the last two weeks of life, 11% of variation in undergoing multiple hospitalizations in the last 30 days of life, and 9% of variation in not enrolling in hospice. This significant, overlooked variation in care practices at the provider level offers new opportunities to address care disparities at the physician level. Although physician variation did not explain racial differences in receiving aggressive care, it was substantial for several outcomes and can be an important point of intervention. Physicians have indicated a willingness to improve end-of-life discussions, and more training and experience have been associated with improved comfort in having the discussions and increasing shared decision making with patients.[192–194] It is likely that more racial variation could be explained at the physician level if we had physician characteristics drawing from a physician's entire practice instead of just women with Medicare and ovarian cancer. Nonetheless, this work is an important first step in understanding one component driving aggressive end-of-life care for women with ovarian cancer.

Findings in Chapter 3 and 4 have important implications for our understanding of aggressive end-of-life care among women with ovarian cancer. Similar to other phases of care, black women are receiving different care at the end of life. This analysis was restricted to older women who have the same health insurance, so evaluating these differences in populations with

younger women who have more variation in insurance may yield important insights into care differences. More importantly, future inquiries require data collection outside of healthcare claims to better understand decision making by providers, patients, and families.

Strengths and Limitations

This work had several notable strengths. First, each aim of this dissertation evaluated possible mechanisms driving racial disparities in ovarian cancer care. To date, most work in racial disparities in ovarian cancer care has simply identified disparities. In particular, highlighting different care characteristics among women with ovarian cancer and variation in end-of-life care at the physician level are important preliminary findings warranting further study. Despite these strengths there are several limitations that merit discussion. First, in Chapter 2 our outcome was limited to the symptoms experienced in the year prior to diagnosis. Many women likely had symptoms for a longer period of time that we were not able to capture. This would reduce the variation in our outcome, making comparison groups more similar, which would result in smaller observed effect estimates. We were also unable to link this symptomatic period to care seeking. Although women had symptoms that were memorable enough to report, having symptoms does not equate to care seeking. More research is needed to understand the symptomatic period before ovarian cancer diagnosis as well as the relationship between racism and the quality of care women with ovarian cancer receive. Given that our findings were likely underestimates, results suggest exploring barriers to care such as discrimination are fruitful areas for cancer care quality improvement.

Ovarian cancer is a rare and rapidly fatal cancer.[28] As such, survival from the disease influences selection into research studies. In Chapter 2, women who were sicker opted not to complete the longer AACES survey and were excluded from analysis. As a result, study

participants were slightly younger and healthier than non-participants which may limit

generalizability of these findings, though this is a common challenge in ovarian cancer studies.[132]

In Chapters 3 and 4, analyses included women who were diagnosed at age 66 or older. A larger

proportion of nonwhite women are diagnosed with ovarian cancer before age 66.[28] This means

that nonwhite women included in these analyses are probably healthier and less disadvantaged

than those who did not survive long enough for inclusion. This is likely to result in racial

differences reported in this dissertation being an understatement of the true associations for each

racial group.

Finally, each of these analyses required women to have an ovarian cancer diagnosis in

order to be included. This may differentially select women who were more engaged with the

healthcare system into our analyses. In Chapter 2, this would mean differentially selecting

women who had fewer barriers to accessing care in their symptomatic window. Again, this

would result in an underestimate of the associations we see. In Chapters 3 and 4, this may result

in underestimating the magnitude of healthcare characteristics and physician variation because

the comparisons are being made between women who are more similar with respect to healthcare

utilization. If this engagement with healthcare was also differential by race, it could lead to

differential misclassification bias in our findings. A sensitivity analysis suggested that having an

identifiable oncologist was not associated with race, so we would expect an underestimate of the

magnitude of associations with healthcare characteristics among all racial groups.

Public Health Significance

This work makes several important public health contributions. First, it builds upon

findings from single-state and single-institution studies to evaluate important national racial

differences in end-of-life care among women with ovarian cancer.[75,114,125] Improving quality of

care at the end of life is critical for both the patient and the US healthcare system. Treatment at the end of life drives substantial healthcare cost, increases likelihood of physical toxicity, and is associated with lower quality of life.[117,175,195–197]

Although this body of work highlights important areas for better understanding racial disparities in ovarian cancer care, perhaps its most valuable contribution is its conceptualization of race and what that means for cancer care. We consider race from a structural viewpoint where black women are systematically disadvantaged because of their race. Although limited in our ability to measure indicators of structural racism given the data, this understanding informed our selections of exposures to evaluate in this work, and pushed our analyses beyond where the racial disparity literature in ovarian cancer care has ventured. While many studies have understood access to care as SES or health insurance, we explored beyond this to look at interpersonal barriers including trust in physicians and everyday discrimination. Similarly, we used this lens to interpret the findings in Chapters 3 and 4. Although patients may receive the same care on paper, the dynamics taking place within a visit may prevent the same outcome from occurring. This is an important step forward considering many studies about cancer and cancer care still reduce race down to co-morbid conditions, or simply genetic ancestry.[127]

Future Work

We know that racial disparities exist throughout the ovarian cancer care continuum. This work has explored some possible exposures that could be related to these disparities, but it is critical that future work in this area has a qualitative component. Although claim and survey data give us important metrics for evaluating care received or individual characteristics, better understanding of black women's experience seeking care from diagnosis through the end of life, and the experiences or characteristics that led to making certain care decisions, is critical for

informing future studies. Ovarian cancer is unique from other cancers in its ambiguous path to diagnosis, vague symptoms, recurrence and rapid fatality, so it is important to specifically evaluate these experiences in this population.

It is also important that future work also focus on physicians as key drivers of care received. Chapters 3 and 4 highlight the association of management in oncology, a physician with a more racially diverse patient base, and overall variation in end-of-life aggressiveness at the physician level. Future work drawing from a physician's complete patient base to understand their practice characteristics is important to better understanding these associations.

Conclusion

The intention of this work was to shift the conversation about racial disparities in the ovarian cancer care continuum and to inform future studies for more meaningful inquiries. Now that we know racial disparities in end-of-life care persist nationally we can shift the focus to better understanding why and how best to intervene.

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