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Examination of Racial/Ethnic Disparities in Ovarian Cancer Stage of Diagnosis, Surgery Treatment and Survival: Multilevel Analysis of 2001-2012 SEER Data

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EXAMINATION OF RACIAL/ETHNIC DISPARITIES IN OVARIAN CANCER STAGE OF DIAGNOSIS, SURGERY TREATMENT AND SURVIVAL: MULTILEVEL ANALYSIS OF 2001—2012 SEER DATA

by

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ABSTRACT

Context. Racial/ethnic disparities in cancer outcomes are major public health concerns. Ovarian cancer is the tenth most common cancer and the fifth leading cause of cancer-related deaths among women. Identifying individual- and contextual-level factors contributing to racial/ethnic disparities in ovarian cancer stage of diagnosis, surgery treatment, and survival is necessary for reducing and eliminating these disparities.

Objective. The study aims to examine racial/ethnic disparities in ovarian cancer diagnosis, surgery treatment and survival outcomes; to explore individual- and contextual-level factors contributing to these disparities, and to examine the trend of ovarian cancer racial/ethnic disparities from 2001 to 2012.

Methods. The study was based on the Surveillance, Epidemiology, and End Results data. Multilevel binary logistic regressions were used for the analysis of racial/ethnic disparities in late stage diagnosis and receipt of surgery adjusted for both individual- and county-level factors, respectively. Multilevel Cox-proportional hazards models were applied to analyze the racial/ethnic disparities in ovarian cancer-cause specific mortality. Joinpoint regression models were used to analyze the trend of ovarian cancer racial/ethnic disparities over time.

Result. Adjusting for age at diagnosis, marital status, tumor pathological characteristics,

metro/nonmetro residence, and indicators of socioeconomic status of county residents, compared to Non-Hispanic white (NHW) patients, non-Hispanic black (NHB) patients have significantly higher probability of advanced stage diagnosis (75.44% vs. 69.52%; p=0.001), but this difference is only significant for patients living in counties with the employment rate ranked in the highest quartile. NHW patients have the highest adjusted probability of receiving surgery treatment (83.40%, 95%CI: 83.04% - 83.76%), whereas Hispanic patients (81.96%, 95%CI: 81.16% - 82.76%) and NHB patients (77.65%, 95%CI: 76.73% - 78.58%) have the lowest adjusted probability ($p < 0.05$). Compared to NHW patients, NHB patients have 24% increased hazards of ovarian cancer death (95% CI: 1.18 – 1.30, $p<0.001$). Both individual- and contextual-level factors contribute to racial/ethnic disparities in ovarian cancer. From 2001-2012, the extent of racial/ethnic disparities in ovarian cancer remained stable (p's<0.05).

Conclusion. The associations between individual- and contextual-level factors and ovarian cancer outcomes vary by race/ethnicity and should be examined separately. Multilevel culturally tailored efforts are required to decrease racial/ethnic disparities in ovarian cancer.

INDEX WORDS: Ovarian cancer, Diagnosis, Surgery, Survival, Racial/ethnic disparities, multi-level, SEER

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CHAPTER 1

BACKGROUND

Being the deadliest of gynecologic cancers, ovarian cancer is the eleventh most common cancer and the fifth leading cause of cancer-related deaths among women (Ovarian Cancer National Alliance, 2014a). According to the Surveillance, Epidemiology, and End Results (SEER) statistics, based on 2008-2012 cancer cases and deaths, the number of new cases of ovarian cancer was 12.1 per 100,000 women per year, and the number of deaths was 7.7 per 100,000 women per year (National Cancer Institute, 2015a). In 2011, there were approximately 188,867 women alive who had a history of ovarian cancer (National Cancer Institute, 2015a). It is estimated that, in 2015, 21,290 women (i.e. 1.3% of all new cancer cases) will be diagnosed with and 14,180 women (i.e. 2.4% of all cancer deaths) will die of ovarian cancer (National Cancer Institute, 2015a).

Ovarian cancer is often diagnosed at a later stage due to vaguely presented symptoms and lack of reliable screening tests for general female population. Certain tests are available for assisting with diagnosis of women with high risk; however, the only way for definitive diagnose is through surgery and biopsy. Upon diagnosis, the treatment plan usually depends on the cancer stage and histology type. Surgery, chemotherapy and radiotherapy are the main treatments for ovarian cancer.

Several genetic risk factors are associated with the development of ovarian cancer. For example, women with a family history of ovarian cancer are at increased risk (US Preventive Services Task Force [USPSTF], 2014a). Mutations in BRCA1 and BRCA2 genes are responsible for most inherited ovarian cancers, and the mutations in those two genes are also linked with high risk of inherited breast cancer (American Cancer Society, 2014c; Holschneider & Berek, 2000).

Behavioral factors also contribute to the development of ovarian cancer. For example,

being obese and use of postmenopausal estrogen are associated with increased ovarian cancer risk (American Cancer Society, 2014c; National Cancer Institute, 2014). Because the development of ovarian cancer is associated with the number of lifetime ovulations, factors that reduce ovulation, such as pregnancy, breast feeding, and use of oral contraceptive pills, and previous hysterectomy or sterilization are associated with reduced ovarian cancer risk (Edmondson & Todd, 2008; Holschneider & Berek, 2000; National Cancer Institute, 2014).

In addition to the genetic and behavioral risk factors, socioeconomic environment is an important factor which may influence ovarian cancer diagnosis, treatment and prognosis through differences in healthcare accessibility. Research has demonstrated a strong relationship between socioeconomic environment and healthcare accessibility (Breen & Figueroa, 1996; Coughlin, Leadbetter, Richards, & Sabatino, 2008; Kirby & Kaneda, 2005, 2006; Litaker, Koroukian, & Love, 2005; Prentice, 2006). Management of ovarian cancer and related complications requires a long-term and systematic approach. Living in a community with majority of residents characterized by low socio-economic status (SES) or rural communities where the allocation of medical resources is limited, may constrict people's individual accessibility for healthcare services (Hendryx, Ahern, Lovrich & McCurdy, 2002; Kirby & Kaneda, 2005).

SES has long been linked with race/ethnicity. There is also a significant interaction effect of race and SES on health outcomes. For example, based on the US National Health and Nutrition Examination Survey, Farmer and Ferraro found that the racial disparity between white and black adults in self-rated health was largest at the higher levels of SES. The finding may indicate that improvements in SES does not necessarily translate into improvements in health outcomes of people from different racial groups (Farmer & Ferraro, 2005). Despite improvements in cancer care during the past two decades, racial/ethnic disparities in ovarian cancer still exist in the United

States. According to the Centers for Disease Control and Prevention (CDC) 2011 statistics, white women had the highest incidence rate of ovarian cancer, followed by Hispanic, Asian/Pacific Islander, Black, and American Indian/Alaska Native women. White women also had the highest death rate of ovarian cancer, followed by Black, Hispanic, Asian/Pacific Islander, and American Indian/Alaska Native women (Centers for Disease Control and Prevention [CDC], 2014). Racial disparities in ovarian cancer have been documented with respect to stage of diagnosis, treatment, and survival outcomes (Farley, Risinger, Rose, & Maxwell, 2007; Tammemagi, 2007; Terplan, Schluterman, McNamara, Tracy, & Temkin, 2012). However, the extent to which these disparities reflect unequal access to health care and whether the disparities can be explained by individual-level, contextual-level characteristics or a combination thereof remains unclear.

Further research is needed to identify contextual-level factors associated with racial/ethnic disparities in ovarian cancer outcomes. Lack of such knowledge is an important barrier to decreasing the health disparities in the United States. For other cancer diseases, contextual level SES has been found to be associated with disparities in cancer outcomes (Ward et al., 2004; Breen & Figueroa, 1996; Coughlin, et al., 2008; Robert et al., 2004). However the contribution of socioeconomic characteristics of community in ovarian cancer outcomes is not understood.

Variations in US ovarian cancer outcomes by rurality is also unknown, especially based on national level data. With the rapid urbanization, urban environments are more likely to see large disparities in socioeconomic status (Unite For Sight, 2014). Also, with the growth of minority population in rural areas, part of the health disparities may also be attributed to lifestyle differences (Unite For Sight, 2014). As a result, although generally speaking, people living in rural areas are more likely to be of lower SES than their urban counterparts, the health disparity by rural/urban residence may not be fully explained by SES differences. Rural counties can have communities

with high SES, and rural/urban difference in health outcomes may also be attributed to factors such as differences in life styles and living environment. Examining rural/urban differences in health outcomes can provide insights on the development of policies to targeting rural areas.

The effects of socioeconomic environment, rural/urban residence, and individual-level factors on development and prognosis of ovarian cancer disease are unknown. Study based on examination of individual-level factors have limited health policy and intervention development implications. Failure to consider potential interaction effects between multilevel factors may lead to unwise recommendation for policy development (e.g. inefficient allocation of medical resources) which may slow down the progress of health promotion. This study relies on constructs of a social ecological model which integrates multilevel factors and provides conceptual framework for studying the interaction effects of those factors on ovarian cancer health outcomes (Glanz, Rimer, & Viswanath, 2008). The main hypotheses of the study are (i) there are racial/ethnic disparities in ovarian cancer stage of diagnosis, receipt of surgery treatment and survival outcome, and (ii) both individual-level characteristics (such as age, marital status, and pathological characteristics) and contextual-level factors (such as county-level SES and metro/nonmetro residence) contribute to these racial/ethnic disparities.

The study aims to examine racial/ethnic disparities in ovarian cancer diagnosis, surgery treatment and survival outcomes; explore individual- and contextual-level factors contributing to these disparities and examine trend in ovarian cancer racial/ethnic disparities from 2001 to 2012. The study findings are expected to provide insights into mechanisms through which ovarian cancer racial/ethnic disparities are developed; inform policy-makers about the subpopulation which suffers an excessive ovarian cancer burden, and update knowledge on the trend of ovarian cancer racial/ethnic disparities based on a national level cancer registry data.

CHAPTER 2

LITERATURE REVIEW

Ovarian Cancer: Symptoms, Diagnosis and Treatment

The development of ovarian cancer can be accompanied by several symptoms. Some of the potential symptoms include pelvic mass, such as urinary frequency, pain, and constipation. There are also symptoms related to other intra-abdominal disease, including disease of or invading the bowel, such as rectal bleeding or altered bowel habit; or the presence of ascites, leading to abdominal dissension; or some other general symptoms related to cancer, such as nausea, vomiting, anorexia, and cachexia (Edmondson & Todd, 2008). However, because the symptoms often are not acute or intense and present vaguely, particularly in the early stages, most women are not diagnosed until the disease had been progressed to the advanced stage (National Ovarian Cancer Coalition, 2014a).

When ovarian cancer is found early at a localized stage, about 94% of patients live longer than 5 years after diagnosis (American Cancer Society, 2014a). For women with high risks, such as those showing ovarian cancer symptoms, a strong family history, or a genetic predisposition, several screening tests are performed to help with diagnosis, including a complete pelvic exam, a transvaginal or pelvic ultrasound, or a CA-125 blood test (Ovarian Cancer National Alliance, 2014b). However, screening tests for ovarian cancer are not recommended for general asymptomatic women by major medical and public health organizations including the U. S. Preventive Services Task Force (USPSTF), the American Congress of Obstetricians and Gynecologists, and the American Cancer Society (American Cancer Society, 2014a; Committee Opinion No. 477: The Role of The Obstetrician-Gynecologist in The Early Detection of Epithelial Ovarian Cancer, 2011; USPSTF, 2014a). The positive predictive value (PPV) of screening for

ovarian cancer is low due to the low prevalence of the diseases (with an age-adjusted incidence of 13 cases per 100,000 women), as a result, most women with a positive screening test result are false-positive (USPSTF, 2014a). According to the Health Technology Assessment's review of 16 cohort studies on ovarian cancer screening among asymptomatic, average-risk women, using annual ultrasound screening, only 0.6 percent of those recalled for abnormal results, and 3 percent underwent surgery, have cancer. The PPV for CA 125-based multimodal screening (CA 125 followed by ultrasound if CA 125 levels are high) was estimated as 1 percent for initial recall and 15 percent for surgery. An estimated 3 percent to 12 percent of screened women will be recalled for further testing and assessment, resulting in potential distress and anxiety to otherwise healthy women. Approximately 0.5 percent to 1 percent of women will suffer a significant complication because of surgery (USPSTF, 2014b). Besides the potential harms of unnecessary surgery or repeated testing, based on a randomized controlled trial of 78,216 women in the U.S. population, simultaneous screening with CA-125 and transvaginal ultrasound does not reduce ovarian cancer mortality (Buys, Partridge, Black, & et al., 2011).

Although the aforementioned tests can improve ovarian cancer diagnosis among women with symptoms or high risks, when used individually, these tests are not definitive. Currently, the only definitive way for ovarian diagnose is through surgery and biopsy (Ovarian Cancer National Alliance, 2014b).

Once diagnosed with ovarian cancer, the stage of a tumor can be determined during surgery. Depending on whether the cancer spreads outside the ovaries, ovarian cancer can be classified into four stages: from Stage I (early disease) to Stage IV (advance disease) (National Ovarian Cancer Coalition, 2014c). According to the type of cell from which the cancer starts, ovarian cancer is classified into three types: (1) surface Epithelium-cells covering the lining of the ovaries, (2) germ

cell-cells destined to form eggs, and (3) stromal cells releasing hormones and connecting the different structures of the ovaries (National Ovarian Cancer Coalition, 2014c). Epithelial ovarian tumor, which accounts for 90% of the ovarian neoplasms and 70% of all ovarian malignancies is further classified as serous (30-70%), endometrioid (10-20%), mucinous (5-20%), clear cell (3-10%), and undifferentiated (1%) (Rosen et al., 2009).

Treatment plan usually depends on the kind of ovarian cancer and how far it has spread (CDC, 2014c). Currently, there are three types of ovarian cancer treatment: (1) surgery to remove the cancerous growth; (2) chemotherapy to deliver chemicals through the bloodstream to destroy cancer cells or stop them from growing both in and outside the ovaries, and (3) radiation therapy to use high-energy X-rays to kill cancer cells and shrink tumors. Chemotherapy is used in the majority of cases as a follow-up therapy to surgery, and radiation therapy is only rarely used in the treatment of ovarian cancer in the United States (National Ovarian Cancer Coalition, 2014b).

Factor Influencing Ovarian Cancer Diagnosis, Treatment and Survival

Literature suggests that multilevel factors can influence ovarian cancer diagnosis, treatment and survival outcomes.

Individual-level Factors:

Pathological Factors

Ovarian cancer stage at diagnosis, histology type, and grade of disease have been found to be important prognostic factors for survival (Chan, et al., 2008; Holschneider & Berek, 2000; Tingulstad, Skjeldestad, Halvorsen, & Hagen, 2003). Based on the statistics from the National Cancer Institute, SEER Data 2004-2010, the relative 5-year survival rates by ovarian cancer stage are as follows: 90% for stage I, 70% for stage II, 39% for stage III, and 17% for stage IV (American

Cancer Society, 2014b). Based on a systematic review of ovarian cancer pathology and biology, the survival outcome also vary by ovarian cancer histology type. The 5-year survival rates are 20-35% for serous type, 40-63% for endometrioid type, 40-69% for mucinous type, 35-50% for clear cell type, and 11-29% for undifferentiated type (Rosen, et al., 2009). Furthermore, the treatment plan also greatly depends on cancer pathology (National Ovarian Cancer Coalition, 2014b). Hence, pathological factors need to be controlled for in modeling ovarian cancer disparities.

Race/Ethnicity:

Race/ethnicity is an important contributor to health disparities. A broad range of factors such as social, behavioral, nutritional, psychological, residential, occupational can lead to racial and ethnic disparities in health. The interaction between biological factors and social/natural environmental factors could be complex. The reasons for racial disparities in health outcomes are multifactorial. Emerging studies suggest that the effects of unequal access to treatment have amplified racial disparities in survival from ovarian cancer (Chan et al., 2008; Terplan, et al., 2012; Terplan, Smith, & Temkin, 2009).

Previous studies yield inconsistent results on racial/ethnic disparities in ovarian cancer diagnosis. For instance, a study based on 1995-2007 SEER Medicare-linked data showed black women were more likely to present with stage IV disease compared to white women (42.1% versus 33.5%) (Howell et al., 2013). This result is consistent with another study based on earlier SEER data (1988-2001), suggesting a significantly higher proportion of African Americans diagnosed at stages III and IV disease compared to whites (74.8% versus 70.1%) (Chan, et al., 2008). However, another study based on SEER-Medicare linked 1992-1999 data found the percentage of ovarian cancer late stage diagnose (stage III and IV) was slightly higher in whites than African Americans (71.6% versus 69.7%) (Du, et al., 2008). Furthermore, a case-control study based on data collected

in Illinois in 1994-1998 showed no significant difference in stage at diagnosis between African American and Caucasian women (Kim, Dolecek, & Davis, 2010).

Emerging studies also indicate racial disparities in ovarian cancer treatment. For example, analysis of 1992-1999 SEER-Medicare linked data showed that compared with Caucasians, significantly lower percentage of African-Americans received chemotherapy for ovarian cancer treatment (Du, et al., 2008). According to a meta-analysis, white women are 1.17 times more likely to receive any form of surgical treatment for ovarian cancer than African Americans (Terplan, et al., 2009).

Although ovarian cancer mortality rates are slightly higher for white women than for African-American women (Ovarian Cancer National Alliance, 2013), one study suggests that the 5-year disease-specific survival of whites is significantly higher (44.1% versus 40.7%) than African-Americans (Chan, et al., 2008). According to an analysis of the SEER 1973-2008 database the disparities in ovarian cancer survival outcome has increased over the past three decades (Terplan, et al., 2012). However, an earlier study based on the 1992-1999 SEER data found no significant racial disparities in survival outcome between African-American and Caucasian women after adjusting for tumor characteristics, treatment, and socio-demographic factors (Du, Sun, Milam, Bodurka, & Fang, 2008).

When examining racial disparities in ovarian cancer diagnosis, treatment, and survival outcomes, most previous studies mainly focused on comparison between African American and Caucasian subpopulations. Very few studies included Hispanics, the largest and fastest growing minority ethnic group in the U.S. One study based on the 2000-2004 SEER data indicated that compared to non-Hispanic whites (NHWs) and non-Hispanic blacks (NHBs), Hispanic women were more likely to be diagnosed with ovarian cancer at a younger age and earlier stage, and had

a statistically significantly longer median survival (Ibeanu & Diaz-Montes, 2013). However, given the rapid growth of Hispanic population, especially in rural areas and small town (The Housing Assistance Council, 2012), it remains unknown whether Hispanic patients still have better survival outcomes than NHWs and NHBs.

Age

Age can also contribute to health disparities. Poorer prognosis and worse health outcomes among older persons may be attributed to several reasons. First, financial concerns might be one of the barriers to accessing needed healthcare services, because the majority of elderly population lives on fixed income and may not be able to cover their unanticipated healthcare costs. Second, increasing risks of comorbidities and complications may inhibit elderly to choose or adhere to required invasive therapies such as surgery and chemotherapy. Thirdly, they may also face some physical challenges (e.g., due to impaired mobility, disordered cognition, or lack of transportation) for accessing or asking for necessary healthcare services. Additionally, compared to younger population, older people may have fewer opportunities to access necessary health information via different media channels, such as Internet. Thus, older people are at a disadvantage in terms of accessing health related information in order to identify symptoms and to seek appropriate healthcare services.

Regarding ovarian cancer disparities by age, the receipt of cancer treatment is influenced by patients' age. For example, based on 2005 Australian Cancer Registries records, increasing age is associated with non-receipt of chemotherapy, and one possible explanation is that older women may have higher rates of toxicity with chemotherapy compared with younger women (Jordan et al., 2013). A retrospective cohort study conducted in Denmark in 2005-2006, found that compared with patients less than 70 years, elderly patients were also less likely to receive primary surgery

(Jørgensen et al., 2012). Based on an analysis of the 1988-2001 SEER data, compared with older ovarian cancer patients (i.e. those aged > 60 years), younger patients (i.e. those aged < 30 years) had a significantly higher 5-year cancer survival rate (78.8% versus 35.3%), and this survival advantage remained even after adjusting for race, stage, grade, and surgical treatment (Chan et al., 2006). In another study based on a statewide Maryland hospital discharge data, no significant differences in the number of comorbidities and intensive care unit length of stay were found between women aged over 80 years and their younger counterparts. However, the 30-day mortality rate was found to be 2.3 times higher for the older group compared with the younger group (Díaz-Montes et al., 2005).

Insurance Status

Insurance status is another important contributor to ovarian cancer disparities. Lack of health insurance has long been linked to negative outcomes for many diseases. According to a study of cancer outcomes based on the National Cancer Database with records from 12 sites, patients who were uninsured or had Medicaid insurance were diagnosed with more advanced disease than privately insured patients (Halpern et al., 2008). In another study, patients from counties with lower uninsured rates had longer median survival, and county uninsured rate was also associated with the stage at diagnosis for all cancers (Smith et al., 2013).

Additionally, there is a difference in insurance status by race/ethnicity. Compared to white ovarian cancer patients, African-American patients were more likely to have Federal payer status (Medicaid or Medicare) and less likely to have commercial insurance payer status (Bristow, Zahurak, & Ibeanu, 2011). Previous studies also reported higher mortality for Medicare and Medicaid patients compared to privately insured patients (LaPar et al., 2010). According to the 2012 NHIS data, Hispanic persons aged less than 65 years (32%) were more than twice as likely

as non-Hispanic persons in the same group (14%) to be uninsured (CDC, 2014).

However, despite the association between insurance status and race/ethnicity, to what extent the insurance status can contribute to the racial disparities in ovarian cancer remains unknown. For instance, based on the 1998-2004 US National Cancer Database, for general cancer patients, irrespective of insurance status, black and Hispanic patients had an increased risk of advanced stage disease (stages III or IV) at diagnosis (Halpern, et al., 2008). While in another study, public insurance was found to be associated with an increased hazard of ovarian cancer mortality and disease recurrence independent of race (Mishka Terplan, Temkin, Tergas, & Lengyel, 2008).

Marital Status

Being married has long be linked with improved health status and decreased mortality (Johnson, Backlund, Sorlie, & Loveless, 2000; Sorlie, Backlund, & Keller, 1995). According to a study focusing on the impact of marital status on cancer outcomes, based on the 2004-2008 SEER data, for cancer patients of the top 10 lethal cancer diseases (including ovarian cancer), unmarried patients were at significantly higher risk of presentation with metastatic cancer, undertreatment, and death resulting from their cancer (Aizer et al., 2013).

Few studies have reported the effect of marital status on ovarian cancer disparities in diagnosis, treatment and survival outcomes. A study based on 1988-2006 SEER data indicated that being married was independently associated with improved survival in women with ovarian cancer, with adjustment for race, age, histology, stage, grade, and surgical treatment (Mahdi et al., 2013). However, it is uncertain whether the effects remain after controlling for socioeconomic environment.

Contextual-level Factors

Rural/Urban Residence

The population in rural and small town America increased by roughly 3.5 million between 2000 and 2010. More than half of all rural and small town population growth in the last decade is attributable to Hispanics. In rural and small town areas, the Hispanic population increased by 1.9 million or 46 percent between 2000 and 2010, surpassing African Americans (8.2 percent) as the largest minority group in rural and small town areas (The Housing Assistance Council, 2012).

With the rapid increase of minority population in rural areas, it is important to analyze the rural-urban and racial patterns in ovarian cancer disparity. Such analysis allows us to quantify and potentially reduce ovarian cancer-related health disparities between the least and most burdened subpopulations.

The rural/urban disparity in health may be related to different lifestyles leading to different levels of exposure to risk factors, unequal access to healthcare services, and different quality of healthcare services and availability of the diagnostic tools and treatment required. Compared with people who live in urban areas, people who live in rural areas may have lower accessibility to health care and face longer travel times and lower access to specialized care (Chan, Hart, & Goodman, 2006).

Previous research yield inconsistent results on influence of rural and urban residence on ovarian cancer outcomes. A study conducted in Poznan, Poland during 2004-2011, suggest urban disadvantage. According to this study, compared with women who live in small towns and rural areas, several ovarian cancer risk factors, such as lower median parity and experienced menarche at an earlier age, were found to be more common among women in large cities. However, no rural/urban differences in stage at diagnosis or tumor type and size were found (Szpurek,

Moszynski, Szubert, & Sajdak, 2013). Several other studies suggested opposite results. One study in Denmark found greater risk of long diagnostic delays in rural areas (Robinson, Christensen, Ottesen, & Krasnik, 2011); and a study conducted in Australia suggested that rural residence was associated with non-receipt of chemotherapy (Jordan, et al., 2013). None of the studies to date have focused on ovarian cancer disparities by rural/urban residence in the U.S.

Socioeconomic Status

Socioeconomic Status (SES) is defined as a composite measure that typically incorporates economic, social, and work status. Economic status is measured by income. Social status is measured by education, and work status is measured by occupation (CDC, 2014a). Individual-level socioeconomic status has long be associated with disparities in health outcomes and healthcare accessibility. For example, a person with more education is more likely to get a well-paid job and have health insurance, and people who have higher incomes and health insurance are more likely to get preventive services and the right treatment (CDC, 2014b). However, emerging studies suggest the independent effects of contextual-level (such as county-level and community-level) socioeconomic status on health disparity. This may imply that the higher contextual-level SES can confer risk of diseases and reduce healthcare accessibility regardless of individuals' own SES. For instance, according to a longitudinal survey based on nationally representative households sampling, living in disadvantaged neighborhood (characterized as high percentage of residents below poverty line, high percentage of unemployment, and high percentage of residents with no high school diploma or GED) reduced the likelihood of having a usual source of care and increased the likelihood of having unmet medical need. This association remained to be statistically significant after controlling for individual-level characteristics (Kirby & Kaneda, 2005). According to a longitudinal study conducted in Netherlands, living in a neighborhood with

a high percentage of unemployed/disabled or poor persons was associated with increased mortality, and the effects remained even after controlling for individual socioeconomic status (Bosma, van de Mheen, Borsboom, & Mackenbach, 2001).

As it relates to cancer, based on an analysis using SEER 1975-2000 data, for several major types of cancers combined (but not including ovarian cancer), residents of poorer counties (with greater or equal to 20% of the population below the poverty line) had higher age-adjusted death rate and lower 5-year survival rate compared with more affluent counties (Ward et al., 2004). The contextual effect of SES on disparities in breast cancer and cervical cancer have been well established (Breen & Figueroa, 1996; Coughlin, et al., 2008; Robert et al., 2004). However, few studies focused on the association between contextual-level SES and ovarian cancer disparities in diagnosis, treatment, and survival outcomes. Furthermore, based on systematic review of previous studies, the pattern of association between cancer mortality and SES (measured at individual or contextual levels) may vary for specific cancers (Singh, Williams, Siahpush, & Mulhollen, 2012). For instance, higher SES was found to be associated with lower rates of lung, stomach, cervical, esophageal, oropharyngeal, and liver cancer mortality and higher rates of breast cancer and melanoma (Singh, et al., 2012). As a result, it remains uncertain whether high contextual-level SES has positive effect on ovarian cancer diagnosis, treatment, and survival.

To the best of my knowledge, racial/ethnic disparities in ovarian cancer diagnosis, treatment and survival outcome using up to date national level cancer registry data have not been examined. It also remains uncertain whether racial/ethnic disparities in ovarian cancer have changed over the last decade. There is lack of studies focusing on contribution of both individual- and contextual-level factors on ovarian cancer disparities. Previous studies have produced inconsistent results on the association of the aforementioned factors with ovarian cancer outcomes.

Findings from the current study will narrow the gap in ovarian cancer research by identifying social factors and mechanisms contributing to disparities in health care access and health outcomes. By identifying the subpopulations which suffer an excessive ovarian cancer burden, the study may provide insights on how to modify currently existing health policies (e.g., on medical resource allocation and public insurance reimbursement and coverage) and to develop health promotion programs specifically targeting hard-to-reach populations (e.g., women living in disadvantaged neighborhoods or minority groups with language barriers).

CHAPTER 3

METHODOLOGY

Study Design

This was an observational, retrospective, cross-sectional study of a population-based cancer registry database. Demographic, pathological, diagnosis, treatment, and survival information from women diagnosed with malignant ovarian cancer from 2001 to 2012 was extracted from the SEER Program of the National Cancer Institute (NCI). Patients diagnosed before age of 18, had a prior malignancy, and those not diagnosed with microscopic confirmation or have unknown diagnostic confirmation were excluded. The information obtained was not individually identifiable, and as a result, the study was exempt from the Georgia Southern Institutional Review Board approval.

Secondary Data Source

The SEER program collects cancer incidence and survival data from 18 population-based cancer registries that represent approximately 27.8% of the U.S. population and is a premier source for cancer statistics in the United States (National Cancer Institute, 2015e). The geographic areas (registries) which are covered include San Francisco-Oakland SMSA, Connecticut, Detroit (Metropolitan), Hawaii, Iowa, New Mexico, Seattle (Puget Sound), Utah, Atlanta (Metropolitan), San Jose-Monterey, Los Angeles, Alaska Natives, Rural Georgia, California excluding SF/SJM/LA, Kentucky, Louisiana, New Jersey and Greater Georgia (National Cancer Institute, 2015e). The SEER 18 Regs Research data include adjustments for areas impacted by hurricanes Katrina and Rita (National Cancer Institute, 2015e). United States Census 2000 and 2007-2011 data were used for county-level SES variables (US Census Bureau 2007-2011).

Study Variables

Main outcome variables included the stage of ovarian cancer at diagnosis, receipt of surgery treatment, and survival time. The stage of ovarian cancer at diagnosis was classified according to the American Joint Committee on Cancer classification system as stage 0 (in situ), I (cancer is limited to the ovary or ovaries), II (growth of the cancer involves one or both ovaries with pelvic extension), III (the cancer has spread beyond the pelvis to the lining of the abdomen or the cancer has spread to lymph nodes), IV (the cancer has spread to organs located outside of the peritoneal cavity) (National Cancer Institute, 2013). For the purposes of this study, the stage of diagnosis was further dichotomized into non-advanced stage (stages 0, I, II) and advanced stage (stages III and IV). Surgery treatment information was measured as receipt of surgery (yes/no). The event in the time-to-event/survival analyses was ovarian cancer-cause specific death within 5 years since ovarian cancer diagnosis, and survival time was defined as the time from the time of ovarian cancer diagnosis till the ovarian cancer-cause specific death or the cutoff time for follow-up (Dec 31, 2012). Ovarian cancer patients who died of other causes, or died of ovarian cancer but after more than 5 years since ovarian cancer diagnosis were treated as censored cases. The survival outcome was measured as 5-year ovarian cancer-cause specific mortality and reported as Hazard Ratio (HR).

Other individual-level factors obtained from SEER included age at diagnosis which was categorized into five categories (18-45 years/46-55 years/56-65 years/66-75 years/older than 76 years), race/ethnicity (NHW/ NHB/Hispanic/Other), marital status (married/not married), insurance status (insured/ uninsured) and tumor pathological characteristics. According to the International Classification of Diseases O-2 codes, tumor grade providing clinic-pathologic information, was classified as well- differentiated, moderately differentiated, poorly

differentiated, undifferentiated and unknown (National Cancer Institute, 2013). Major histology types were classified as clear cell, mucinous, serous, endometrioid, other, or not otherwise specified (NOS), based on the International Classification of Diseases O-3 codes.

Contextual-level variables included residence in a metro/nonmetro county and county-level SES status. According to the rural-urban continuum code (RUCC) classification system (United States Department of Agriculture, 2013), counties were classified as metro or nonmetro, using the Federal Information Processing Standards [FIPS] codes. Based on the RUCC classification system, counties with RUCC codes ≤ 3 (counties in metro areas of fewer than 250,000 population, 250,000 population or more) were defined as metro counties, and counties with RUCC codes 4-9 (counties adjacent or not adjacent to a metro area and with urban population of 2,500 or more or with completely rural or less than 2,500 urban population) were defined as nonmetro counties (United States Department of Agriculture, 2013). County-level SES variables included education, employment and poverty level. They were accessed through the SEER*Stat Datasets measured at ratio level, and were calculated based on 2000 Census Data and 2007-2011Census American Community Survey (ACS) 5-year files (National Cancer Institute, 2015c).The county-level Census data were matched with the individual-level SEER data by county FIPS codes. Patients diagnosed from the year of 2000-2006 were matched with the 2000 census data, and those diagnosed from the year of 2007-2011 were matched with the 2007-2011 census data. The county-level SES measurements include county education (i.e. percentage of a county population with less than 9th grade education); county employment (i.e. percentage of persons aged 16 and over who are unemployed in a county), and county poverty (i.e. percentage of persons in a county whose incomes are below the 100% federal poverty level threshold (U.S. Department of Health & Human Services, 2013). Each of these county SES percentage measures were sorted

and categorized into quartiles (highest/upper-middle/lower-middle/lowest) when included into models for analysis. For each of the three county SES quartile measures, counties in a higher quartile have a superior county level SES. Collinearity among contextual-level factors was assessed, its lack was confirmed with VIFs < 2.5.

Data Analysis

All individual- and contextual-level data were extracted using the 8.2.1 SEER*Stat Software (National Cancer Institute, 2015f). Statistical analyses were performed using the Stata SE 14.0 statistical software (College Station, TX) and Joinpoint trend analysis software version 4.2.0.1. (National Cancer Institute, 2015d). Descriptive statistics were used to describe the distribution of individual-level socio demographic and tumor pathological characteristics, and contextual-level factors. X-square tests of independence and analysis of variance (ANOVA) were applied to assess the difference in distribution of each of these characteristics among selected cases by race/ethnicity.

Multilevel binary logistic regression analyses were used to assess the effect of race and ethnicity on stage diagnosis and receipt of surgery adjusted for individual-level and county-level variables. Models included a random intercept for a county of residence; while the rest of the variables were included as fixed effect. To identify factors contribute to the racial/ethnic disparities, sub analysis using multilevel binary logistic regression were then conducted stratified by race/ethnicity subgroups (NHW, NHB, and Hispanic). Average predicted margins and marginal effects were calculated from multilevel logistic regression analysis with adjustment for random effect and interaction effect. Adjusted probability estimates for advanced stage diagnosis and receipt of surgery treatment were reported based on each of the logistic regressions.

The Cox proportional hazards model with shared frailty (i.e. multilevel model) was used to assess racial/ethnic disparities in ovarian cancer-cause specific mortality and to identify factors contributing to the disparities. The proportional hazards assumption was assessed by graphing the scaled Schoenfeld residuals on function of time, and testing the significance of interaction between the variables of interest and time.

Because insurance status information was only available for patients diagnosed in and after 2007, when insurance status was added into each of the logistic regression and Cox proportional hazards models, only cases diagnosed in 2007 and later were included in the analyses. For all the logistic regression and Cox proportional hazards models, significance of interaction terms between race/ethnicity and variables of interest were checked, and significant interaction terms were included in the final models.

To test whether the racial/ethnic disparities in stage at diagnosis, receipt of surgery treatment and ovarian cancer-cause specific mortality have changed over time, cases were grouped into 12 cohorts by year of diagnosis, and for each of the cohorts, logistic regressions were used to estimate odds ratios for advanced stage diagnosis and receipt of surgery, and survival analysis was used to estimate hazard ratios for ovarian cancer cause-specific death. The odds ratios and hazard ratios were estimated comparing each of the two racial/ethnic groups (NHW vs. NHB, NHW vs. Hispanics, and NHB vs. Hispanics), while adjusting for individual- and contextual-level confounders. The estimated odds ratios and hazard ratios for the 12 cohorts were then analyzed using the Joinpoint trend analysis software. This software takes trend data (odds ratios and hazard ratios) as dependent variables, year of diagnosis as independent variable, and fits the simplest Joinpoint model that the data allow. This analysis was applied to test whether an apparent change in trend was statistically significant. The test of significance applies

a Monte Carlo Permutation method (National Cancer Institute, 2015d). All tests were two-tailed. A significant level was set at $P < 0.05$.

CHAPTER 4
RESULTS

Descriptive Characteristics

There were 69,444 women diagnosed with malignant ovarian cancer between 2001 and 2012. Among those ovarian cancer patients, 669 cases were excluded because of age (less than 18 years old at diagnosis); 5,316 cases were excluded because of having no microscopic or unknown diagnostic confirmation; 8,686 cases were excluded because of prior malignancy diagnosis, and 193 cases were eliminated due to unknown race/ethnicity status. The final study sample included 54,580 ovarian cancer patients, of whom 39,726 (72.78%) were NHWs, 4,295 (7.87%) were NHBs, 6,256 (11.46%) were Hispanic, and 4,303 (7.88%) were of other race/ethnicity (e.g. American Indian/Alaska Native and Asian or Pacific Islander).

Descriptive characteristics are presented in Table 1 by race/ethnicity. NHW patients were diagnosed at an older age (mean age=62.55, $p<0.001$) compared with NHBs (mean age=59.57), Hispanics (mean age=55.63) and patients of other race/ethnicity (mean age=55.88). The prevalence of ovarian cancer by groups of age at diagnosis also significantly varied across race/ethnicity groups ($p<0.001$). NHW (25.06%) and NHB (24.05%) patients were more likely to be diagnosed at age of 55-64 compared with other age groups, but Hispanics were more likely to be diagnosed at the age of 18-45 (25.69%). NHW (54.24%) patients had a larger proportion of married women compared with NHBs (31.18%) and Hispanics (49.30%), but the proportion of being married was the highest in patients from Other racial/ethnic groups (58.62%) ($p<0.001$). NHW patients had the highest health insurance coverage rate (96.80%), followed by patients from Other racial/ethnic groups (95.36%), NHB (92.83%) and Hispanic patients (90.44%) ($p<0.001$). NHB patients (72.60%) were more likely to be diagnosed at advanced stage compared

with patients from NHW (71.29%), Hispanic (66.66%), and Other racial/ethnic groups (61.10%) ($p<0.001$). Patients from Other racial/ethnic groups (85.65%) had the highest rate of receiving surgery treatment, followed by Hispanics (82.29%), NHW (81.63%), and NHBs (69.18%) had the lowest rate for surgery treatment ($p<0.001$). Regarding tumor pathological characteristics, the prevalence of tumor grade and histology also significantly varied by race/ethnicity ($p<0.001$).

In terms of contextual-level characteristics, higher percentage of NHW patients (13.10%) lived in nonmetro areas compared to patients in NHB (9.39%), Hispanic (3.96%) and Other racial/ethnic groups (5.06%) ($p<0.001$). More Hispanic patients (48.91%) lived in counties with lowest quartile rank of county-level education compared to patients in NHW (19.54%), NHB (21.86%), and Other racial/ethnic groups (27.96%) ($p<0.001$). NHB patients were more likely to live in counties characterized as lowest SES when measured by unemployment (NHB: 37.81%, NHW: 18.72%, Hispanic: 24.34%, other: 12.53, $p<0.001$) and poverty rate (NHB: 35.51%, NHW 19.58%, Hispanic: 28.23%, other: 15.64%, $p<0.001$).

Table 1

Characteristics of Ovarian Cancer Cases, 2001-2012, SEER (N=54,580)

Characteristics	Non-Hispanic White (n=39,726) %[a]	Non-Hispanic Black (n=4,295) %	Hispanic (n=6,256) %	Other (n=4,303) %	p-value
Age at diagnosis (mean)	62.55	59.57	55.63	55.88	<0.001
Age at diagnosis (Group)					<0.001
18-45	11.37	17.88	25.69	23.66	
45-54	20.22	20.58	23.91	27.70	
55-64	25.06	24.05	21.44	22.08	
65-74	21.63	20.88	17.04	14.85	
>=74	21.73	16.60	11.92	11.71	
Marital status					<0.001
Not married	45.76	68.82	50.70	41.38	
Married	54.24	31.18	49.30	58.62	
Insurance [b]					<0.001
Uninsured	3.20	7.17	9.56	4.64	
Insured	96.80	92.83	90.44	95.36	
Stage					<0.001
Non-advanced	28.71	27.40	33.34	38.90	
Advanced	71.29	72.60	66.66	61.10	
Surgery					
No	18.37	30.82	17.71	14.35	<0.001
Yes	81.63	69.18	82.29	85.65	
Grade					<0.001
Well differentiated	6.60	5.77	8.07	7.81	
Moderately differentiated	13.42	11.06	13.16	14.06	
Poorly differentiated	34.29	29.29	30.66	33.07	
Undifferentiated	12.97	8.87	10.55	13.15	
Unknown	32.72	45.01	37.56	31.91	
Histology					<0.001
Serous	46.19	37.30	36.69	35.77	
Mucinous	5.48	6.38	7.18	7.90	
Endometrioid	9.59	6.10	10.10	11.85	
Clear cell	5.14	2.51	4.51	11.71	
Other or unspecified	33.60	47.71	38.52	32.77	
Contextual-level Factors					

Characteristics	Non-Hispanic White (n=39,726) %[a]	Non-Hispanic Black (n=4,295) %	Hispanic (n=6,256) %	Other (n=4,303) %	p-value
Metro/nonmetro Residence [c]					<0.001
Metro	86.90	90.61	96.04	94.94	
Nonmetro	13.10	9.39	3.96	5.06	
County education [d]					<0.001
Highest	30.12	16.07	7.24	13.87	
Upper-middle	26.35	37.46	13.63	19.38	
Lower-middle	23.98	24.61	30.21	38.79	
Lowest	19.54	21.86	48.91	27.96	
County employment [e]					<0.001
Highest	29.58	14.41	12.18	26.63	
Upper-middle	25.87	17.63	20.46	23.38	
Lower-middle	25.83	30.15	43.01	37.46	
Lowest	18.72	37.81	24.34	12.53	
County poverty [f]					<0.001
Highest	28.20	13.13	13.20	27.28	
Upper-middle	27.11	17.97	19.17	33.35	
Lower-middle	25.10	33.39	39.40	23.73	
Lowest	19.58	35.51	28.23	15.64	

Notes: [a] Unadjusted percentage [b] Only for cases diagnosed in 2007 and after. [c] Metro vs. nonmetro categories are based on the Rural-Urban Continuum Codes (RUCC Codes: 1-3 vs. 4-9) from the Economic Research Service, U.S. Department of Agriculture. [d] Sorted by percentage of a county population with less than 9th grade education in ascending order, and categorized into quartiles. [e] Sorted by percentage of persons aged 16 and over who are unemployed in a county in ascending order, and categorized into quartiles. [f] Sorted by percentage of persons in a county whose incomes are below the 100% federal poverty level threshold in ascending order, and categorized into quartiles.

Advanced Stage Diagnosis

Racial/Ethnic Disparities in Advanced Stage Diagnosis

As shown in Table 2 (Odds Ratios are presented in Appendix F: Table 2.2), adjusting for all the variables listed in Table 1, year of diagnosis, county random effect, and interaction effect of race/ethnicity and county-level employment, significant racial/ethnic disparities in advanced stage diagnosis only exist in counties with county-level employment rate ranked in the highest

and lower-middle quartiles. Significant differences in advanced stage diagnosis between NHB and NHW patients were only observed in counties with the employment rate ranked in the highest quartile, and in such counties, NHB patients (75.44%, 95%CI: 72.35% – 78.53%) were significantly more likely to present with advanced ovarian cancer at the time of diagnosis compared to NHW patients (69.52%, 95%CI: 68.58% - 70.46%). For patients living in counties that ranked in lower-middle quartile for employment rate, patients from Other racial/ethnic groups (66.91%, 95%CI: 64.80% - 69.01%) had significantly lower probability of advanced stage diagnosis compared with their NHW counterparts (70.65%, 95%CI: 69.76% - 71.54%). The prevalence of advanced stage diagnosis among Hispanic patients did not significantly differ from the prevalence in NHW patients.

Table 2

Adjusted Prevalence of Advanced Stage Diagnosis and Receipt of Surgery [a]

Study Variables	Advanced Stage Diagnosis (N=54,580) % [b] (95%CI)	Receipt of Surgery (N=54,580) % [b] (95%CI)
Race/ethnicity		
Non-Hispanic White	–	83.40 (83.04 – 83.76) [ref]
Non-Hispanic Black	–	77.65 (76.73 – 78.58)*
Hispanic	–	81.96 (81.16 – 82.76)*
Other	–	81.94 (80.92 – 82.97)*
Age at diagnosis		
18-45	55.73 (54.64 – 56.83) [ref]	93.81 (93.20 – 94.41) [ref]
46-55	65.85 (65.01 – 66.69)*	88.79 (88.16 – 89.42)*
56-65	71.94 (71.18 – 72.69)*	85.26 (84.68 – 85.84)*
66-75	75.77 (74.97 – 76.57)*	81.51 (80.88 – 82.13)*
>=76	79.41 (78.60 – 80.22)*	71.86 (71.11 – 72.62)*
Marital status		
Not married	70.70 (70.15 – 71.26) [ref]	81.13 (80.70 – 81.56) [ref]
Married	69.81 (69.28 – 70.33)*	84.31 (83.89 – 84.72)*

Study Variables	Advanced Stage Diagnosis (N=54,580) % [b] (95%CI)	Receipt of Surgery (N=54,580) % [b] (95%CI)
Stage		
Non-advanced	–	94.29 (93.84 – 94.74) [ref]
Advanced	–	79.32 (78.88 – 79.75)*
Grade		
Well differentiated	43.97 (42.21 – 45.74) [ref]	91.91 (90.34 – 93.47) [ref]
Moderately differentiated	60.95 (59.84 – 62.06)*	92.59 (91.78 – 93.40)*
Poorly differentiated	74.85 (74.19 – 75.50)*	91.93 (91.50 – 92.37)*
Undifferentiated	73.93 (72.85 – 75.00)*	94.21 (93.60 – 94.83)*
Unknown	73.88 (73.21 – 74.56)*	68.57 (67.83 – 69.32)*
Histology		
Serous	82.57 (82.04 – 83.09) [ref]	89.40 (88.98 – 89.83) [ref]
Mucinous	51.69 (49.84 – 53.55)*	84.11 (82.78 – 85.45)*
Endometrioid	46.12 (44.61 – 47.62)*	92.00 (90.70 – 93.29)*
Clear cell	39.93 (38.16 – 41.69)*	92.83 (91.64 – 94.03)*
Other or unspecified	69.70 (68.96 – 70.43)*	74.02 (73.40 – 74.64)*
Interaction: race/ethnicity * county employment		
County employment: highest		
Non-Hispanic White	69.52 (68.58 – 70.46) [ref]	–
Non-Hispanic Black	75.44 (72.35 – 78.53)*	–
Hispanic	67.82 (64.75 – 70.88)	–
Other	71.28 (68.84 – 73.72)	–
County employment: upper-middle		
Non-Hispanic White	70.52 (69.63 – 71.40) [ref]	–
Non-Hispanic Black	72.22 (69.34 – 75.11)	–
Hispanic	70.64 (68.39 – 72.90)	–
Other	69.29 (66.71 – 71.86)	–
County employment: lower-middle		
Non-Hispanic White	70.65 (69.76 – 71.54) [ref]	–
Non-Hispanic Black	71.33 (69.06 – 73.61)	–
Hispanic	71.13 (69.51 – 72.76)	–
Other	66.91 (64.80 – 69.01)*	–
County employment: lowest		
Non-Hispanic White	69.91 (68.76 – 71.06) [ref]	–
Non-Hispanic Black	70.55 (68.37 – 72.73)	–
Hispanic	70.83 (68.67 – 73.00)	–
Other	69.71 (66.10 – 73.31)	–
Contextual-level factors:		
Metro/nonmetro residence [c]		

Study Variables	Advanced Stage Diagnosis (N=54,580) % [b] (95%CI)	Receipt of Surgery (N=54,580) % [b] (95%CI)
Metro	70.27 (69.84 – 70.70) [ref]	82.66 (82.29 – 83.02) [ref]
Nonmetro	69.88 (68.73 – 71.02)	82.16 (81.37 – 82.95)
County education [d]		
Highest	70.91 (69.98 – 71.83) [ref]	82.50 (81.77 – 83.23) [ref]
Upper-middle	69.90 (69.06 – 70.73)	82.76 (82.11 – 83.41)
Lower-middle	70.41 (69.59 – 71.22)	82.40 (81.70 – 83.11)
Lowest	69.67 (68.72 – 70.62)	82.73 (82.06 – 83.40)
County employment [e]		
Highest	–	82.80 (82.15 – 83.46) [ref]
Upper-middle	–	82.74 (82.11 – 83.37)
Lower-middle	–	82.78 (82.22 – 83.34)
Lowest	–	81.98 (81.21 – 82.74)
County poverty [f]		
Highest	69.00 (67.96 – 70.04) [ref]	83.17 (82.35 – 84.00) [ref]
Upper-middle	69.72 (68.85 – 70.58)	82.41 (81.70 – 83.13)
Lower-middle	70.93 (70.12 – 71.75)*	82.50 (81.88 – 83.11)
Lowest	71.34 (70.37 – 72.30)*	82.34 (81.65 – 83.04)
Random effect		
County variance	0.0070	0.0451*

Notes: [a] Adjusted for all the variables listed in the table, year of diagnosis, interactions between race/ethnicity and county employment, and county random effects. [b] Average adjusted predicted probabilities. [c] Metro vs. nonmetro categories are based on the Rural-Urban Continuum Codes (RUCC Codes: 1-3 vs. 4-9) from the Economic Research Service, U.S. Department of Agriculture. [d] Sorted by percentage of a county population with less than 9th grade education in ascending order, and categorized into quartiles. [e] Sorted by percentage of persons aged 16 and over who are unemployed in a county in ascending order, and categorized into quartiles. [f] Sorted by percentage of persons in a county whose incomes are below the 100% federal poverty level threshold in ascending order, and categorized into quartiles.

CI, confidence interval. [ref] reference group. * $p<0.05$

Factors Associated with Disparities in Advanced Stage Diagnosis

Based on adjusted analysis, the probability of advanced stage diagnosis significantly increased by age. On average, women being diagnosed at the ages of 76 or older had a 23.68% increased probability of being diagnosed at advanced stage compared to women being diagnosed between the ages of 18 to 45 ($p<0.05$). On average, a significantly smaller percentage of married

women (69.81%, 95%CI: 69.28% - 70.33%) were diagnosed at advanced stage compared to unmarried women (70.70%, 95%CI: 70.15% - 71.26%) ($p<0.05$).

With respect to contextual-level factors, although not statistically significant, patients living in nonmetro counties (69.88%, %95CI: 68.73% – 71.02%) had lower probability of being diagnosed at advanced stage, compared to patients living in metro counties (70.27%, 95%CI: 69.84% – 70.70%). The average probability of advanced stage diagnosis also did not significantly vary by county-level education. Interaction between race/ethnicity and county-level employment was found to be significantly associated with advanced stage diagnosis. The effect of county-level employment rate varied by race/ethnicity. When considering the county-level poverty status, patients from the lower-middle (70.93%, 95%CI: 70.12% – 71.75%) and lowest quartile counties (71.34%, 95%CI: 70.37% – 72.30%) had a significantly increased probability of advanced stage diagnosis compared to patients from the highest quartile counties (69.00%, 95%CI: 67.96% – 70.04%). Based on the results of a sub analysis, when adding insurance status to the original model, and only including cases diagnosed in 2007-2012, on average, the probability of advanced stage diagnosis did not significantly differ by insurance status (uninsured: 69.24% vs. insured: 68.74%) (Appendix A: Table 2.1). The average probability of advanced stage diagnosis also did not vary significantly across counties (variance: 0.0068, p=1.0000). However, when comparing model (results not shown) adjusted for individual-level factors only with the full model (i.e., the one with both individual- and contextual-level factors), county random effect (variance) decreased from 0.0087 to 0.0068.

Factors Contributing to Racial/Ethnic Disparities in Advanced Stage Diagnosis

Results based on the sub analysis stratified by race/ethnicity group are shown in Table 3 (Odds Ratios are presented in Appendix G: Table 3.2). Age at diagnosis was positively

associated with advanced stage diagnosis for patients in all three racial/ethnic groups. The association between marital status and advanced stage diagnosis was statistically significant for NHW patients (married: 71.04% vs. unmarried: 72.00%, $p<0.05$), but not for NHB and Hispanic patients. Insurance status was not significantly associated with advanced stage diagnosis for patients in either of the three groups (Appendix B: Table 3.1). For patients in all three groups, probability of being diagnosed at advanced stage did not significantly vary by metro/nonmetro residence or county-level education status. County-level employment was significantly associated with advanced stage diagnosis in NHB patients, but not in NHW and Hispanic patients. NHB patients from counties with employment rate ranked in the lower-middle (72.19%, 95%CI: 69.63% – 74.75%) and lowest quartiles (70.93, 95%CI: 68.41% – 73.45%) had a significantly lower probability of being diagnosed at advanced stage compared with their counterparts from the highest quartile counties (77.45, 95%CI: 73.98% – 80.92%). However, while not statistically significant, NHW and Hispanic patients from counties with lower employment rate had higher prevalence of advanced stage diagnosis compared with their counterparts in the highest quartile counties. NHW patients from poorer counties were more likely to be diagnosed with advanced stage compared with their counterparts from less poorer counties. However, this association was not significant in NHB and Hispanic patients. Stage of diagnosis did not significantly differ by counties for all three racial/ethnic groups.

Table 3

Factors Contributing to Racial/Ethnic Disparities in Advanced Stage Diagnosis and Receipt of Surgery, by Race/Ethnicity [a]

Study Variables	Advanced Stage Diagnosis % [b] (95%CI)			Receipt of Surgery % [b] (95%CI)		
	Non-Hispanic White (n=39,726)	Non-Hispanic Black (n=4,295)	Hispanic (n=6,256)	Non-Hispanic White (n=39,726)	Non-Hispanic Black (n=4,295)	Hispanic (n=6,256)
Age at diagnosis						
18-45	56.29[ref] (54.88 – 57.7)	58.85 [ref] (55.42 – 62.27)	53.60 [ref] (51.13 – 56.07)	94.28 [ref] (93.46 – 95.10)	85.07 [ref] (82.50 – 87.64)	94.00 [ref] (92.74 – 95.27)
46-55	66.58[*] (65.6 – 67.57)	69.16 (66.20 – 72.12)	64.71[*] (62.28 – 67.14)	90.21[*] (89.46 – 90.97)	77.50[*] (75.05 – 79.94)	85.98[*] (84.33 – 87.62)
56-65	72.29[*] (71.44 – 73.13)	75.60[*] (72.99 – 78.21)	72.04[*] (69.61 – 74.47)	86.30[*] (85.63 – 86.98)	71.15[*] (68.88 – 73.43)	85.01[*] (83.43 – 86.58)
66-75	76.03[*] (75.14 – 76.92)	78.25[*] (75.50 – 81.01)	75.61[*] (72.96 – 78.26)	82.89[*] (82.18 – 83.6)	65.54[*] (63.08 – 67.99)	80.33[*] (78.54 – 82.13)
>=76	79.73[*] (78.85 – 80.61)	82.84[*] (80.02 – 85.67)	77.40[*] (74.28 – 80.52)	73.40[*] (72.56 – 74.240)	56.35[*] (53.31 – 59.39)	69.00[*] (66.31 – 71.70)
Marital status						
Not married	72 .00 [ref] (71.37 – 72.63)	73.42 [ref] (71.91 – 74.94)	67.06 [ref] (65.41 – 68.71)	81.36 [ref] (80.84 – 81.87)	69.35 [ref] (68.07 – 70.62)	82.97 [ref] (82.01 – 83.93)
Married	71.04[*] (70.47 – 71.62)	71.24 (68.92 – 73.56)	65.84 (64.16 – 67.52)	84.74[*] (84.26 – 85.22)	73.95[*] (72.03 – 75.88)	84.93[*] (83.89 – 85.97)
Stage						
Non-advanced	-	-	-	94.12 [ref] (93.56 – 94.68)	89.11 [ref] (87.14 – 91.08)	96.44 [ref] (95.45 – 97.44)
Advanced	-	-	-	80.14[*] (79.64 – 80.65)	65.12[*] (63.76 – 66.49)	79.43[*] (78.42 – 80.43)

Study Variables	Advanced Stage Diagnosis % [b] (95%CI)			Receipt of Surgery % [b] (95%CI)		
	Non-Hispanic White (n=39,726)	Non-Hispanic Black (n=4,295)	Hispanic (n=6,256)	Non-Hispanic White (n=39,726)	Non-Hispanic Black (n=4,295)	Hispanic (n=6,256)
Grade						
Well differentiated	45.97 [ref] (43.87 – 48.06)	42.15 [ref] (35.52 – 48.78)	39.43 [ref] (34.72 – 44.14)	90.86 [ref] (88.94 – 92.78)	93.05 [ref] (87.16 – 98.95)	94.88 [ref] (91.07 – 98.70)
Moderately differentiated	62.05* (60.77 – 63.32)	64.22* (59.94 – 68.50)	60.21* (56.92 – 63.49)	92.43 (91.47 – 93.40)	88.26* (84.78 – 91.75)	93.61 (91.47 – 95.74)
Poorly differentiated	75.79* (75.06 – 76.52)	76.18* (73.77 – 78.60)	71.66* (69.52 – 73.81)	92.20 (91.69 – 92.71)	84.70* (82.75 – 86.64)	92.69 (91.55 – 93.83)
Undifferentiated	74.78* (73.58 – 75.98)	76.93* (72.48 – 81.37)	72.03* (68.46 – 75.61)	94.86* (94.17 – 95.56)	86.11* (82.75 – 89.48)	93.04 (91.20 – 94.88)
Unknown	75.39* (74.61 – 76.16)	76.29* (74.31 – 78.28)	69.12* (67.10 – 71.14)	68.51* (67.59 – 69.43)	54.06 (51.96 – 56.16)	71.72* (70.09 – 73.35)
Histology						
Serous	83.19 [ref] (82.62 – 83.77)	83.68 [ref] (81.83 – 85.52)	80.26 [ref] (78.54 – 81.98)	89.65 [ref] (89.15 – 90.15)	80.73 [ref] (78.97 – 82.50)	90.33 [ref] (89.28 – 91.38)
Mucinous	51.76 (49.50 – 54.03)	60.76* (54.88 – 66.65)	50.79* (45.93 – 55.64)	84.42* (82.79 – 86.04)	72.04* (66.71 – 77.37)	86.24* (82.97 – 89.50)
Endometrioid	45.38* (43.63 – 47.14)	49.80* (43.48 – 56.12)	45.73* (41.50 – 49.96)	91.85* (90.31 – 93.39)	83.11 (76.79 – 89.43)	94.59* (91.35 – 97.82)
Clear cell	39.53* (37.42 – 41.63)	50.66* (41.61 – 59.71)	39.91* (34.39 – 45.43)	93.60* (92.21 – 95.00)	79.64 (71.42 – 87.86)	91.37 (87.99 – 94.74)
Other or unspecified	71.36* (70.50 – 72.22)	70.03* (67.91 – 72.16)	64.08* (61.92 – 66.23)	74.25* (73.50 – 75.00)	61.69* (59.87 – 63.52)	75.52* (74.07 – 76.97)

Study Variables	Advanced Stage Diagnosis % [b] (95%CI)			Receipt of Surgery % [b] (95%CI)		
	Non-Hispanic White (n=39,726)	Non-Hispanic Black (n=4,295)	Hispanic (n=6,256)	Non-Hispanic White (n=39,726)	Non-Hispanic Black (n=4,295)	Hispanic (n=6,256)
Contextual-level factors:						
Metro/nonmetro residence [c]						
Metro	71.50 [ref] (71.03 – 71.97)	73.09 [ref] (71.77 – 74.42)	66.49 [ref] (65.20 – 67.77)	82.98 [ref] (82.53 – 83.43)	70.87 [ref] (69.75 – 71.98)	83.90 [ref] (83.20 – 84.61)
Nonmetro	71.26 (70.07 – 72.45)	68.96 (63.99 – 73.93)	65.58 (59.53 – 71.64)	83.08 (82.25 – 83.91)	69.18 (65.34 – 73.02)	82.17 (78.22 – 86.11)
County education [d]						
Highest	72.18 [ref] (71.31 – 73.05)	71.47 [ref] (67.71 – 75.22)	66.94 [ref] (62.14 – 71.74)	83.00 [ref] (82.26 – 83.75)	69.41 [ref] (66.29 – 72.54)	84.46 [ref] (81.25 – 87.67)
Upper-middle	71.2 (70.35 – 72.05)	71.74 (69.48 – 73.99)	64.74 (61.26 – 68.22)	83.24 (82.54 – 83.95)	72.10 (70.27 – 73.93)	83.30 (81.12 – 85.47)
Lower-middle	71.32 (70.33 – 72.32)	74.80 (72.26 – 77.34)	67.20 (64.41 – 69.99)	82.88 (82.08 – 83.68)	71.03 (68.89 – 73.17)	83.23 (81.68 – 84.79)
Lowest	70.91 (69.78 – 72.04)	73.01 (69.87 – 76.15)	66.39 (64.29 – 68.49)	82.78 (81.81 – 83.76)	68.83 (66.18 – 71.47)	84.24 (83.06 – 85.42)
County employment [e]						
Highest	70.82 [ref] (69.96 – 71.69)	77.45 [ref] (73.98 – 80.92)	64.94 [ref] (60.83 – 69.04)	83.10 [ref] (82.41 – 83.80)	71.38 [ref] (68.25 – 74.50)	85.86 [ref] (83.43 – 88.29)
Upper-middle	71.76 (70.88 – 72.64)	73.52 (70.29 – 76.75)	67.91 (64.71 – 71.10)	83.17 (82.48 – 83.87)	70.71 (67.98 – 73.45)	84.68 (82.67 – 86.69)
Lower-middle	71.91 (71.04 – 72.79)	72.19* (69.63 – 74.75)	66.48 (64.48 – 68.48)	82.76 (82.00 – 83.52)	73.39 (71.37 – 75.41)	83.79 (82.59 – 85.00)
Lowest	71.49 (70.38 – 72.60)	70.93* (68.41 – 73.45)	65.88 (63.02 – 68.75)	82.93 (82.06 – 83.80)	68.19 (66.09 – 70.29)	82.41* (80.81 – 84.00)

Study Variables	Advanced Stage Diagnosis % [b] (95%CI)			Receipt of Surgery % [b] (95%CI)		
	Non-Hispanic White (n=39,726)	Non-Hispanic Black (n=4,295)	Hispanic (n=6,256)	Non-Hispanic White (n=39,726)	Non-Hispanic Black (n=4,295)	Hispanic (n=6,256)
County poverty [f]						
Highest	70.44 [ref] (69.43 – 71.45)	70.80 [ref] (66.44 – 75.16)	63.49 [ref] (59.07 – 67.91)	83.70 [ref] (82.84 – 84.56)	70.31 [ref] (66.77 – 73.85)	84.15 [ref] (81.50 – 86.81)
Upper-middle	71.23 (70.32 – 72.14)	71.45 (67.92 – 74.98)	63.65 (59.9 – 67.41)	82.94 (82.18 – 83.71)	68.59 (65.63 – 71.55)	84.38 (82.17 – 86.60)
Lower-middle	72.04* (71.13 – 72.95)	72.25 (69.94 – 74.55)	66.94 (64.78 – 69.11)	83.02 (82.29 – 83.75)	70.75 (68.85 – 72.64)	83.27 (82.03 – 84.50)
Lowest	72.53* (71.40 – 73.66)	74.48 (72.20 – 76.77)	69.00 (66.31 – 71.70)	82.11* (81.22 – 83.00)	71.81 (69.87 – 73.75)	84.14 (82.55 – 85.73)
Random effect						
County variance	0.0031	<0.0001	0.0248	0.0527*	<0.0001	<0.0001

Notes: [a] Adjusted for all the variables listed in the table, year of diagnosis and county random effects. [b] Average adjusted predicted probabilities. [c] Metro vs. nonmetro categories are based on the Rural-Urban Continuum Codes (RUCC Codes: 1-3 vs. 4-9) from the Economic Research Service, U.S. Department of Agriculture. [d] Sorted by percentage of a county population with less than 9th grade education in ascending order, and categorized into quartiles. [e] Sorted by percentage of persons aged 16 and over who are unemployed in a county in ascending order, and categorized into quartiles. [f] Sorted by percentage of persons in a county whose incomes are below the 100% federal poverty level threshold in ascending order, and categorized into quartiles.

CI, confidence interval. [ref] reference group. * $p<0.05$

Receipt of Surgery Treatment

Racial/Ethnic Disparities in Receipt of Surgery Treatment

Receipt of surgery treatment varied by race/ethnicity. On average, NHW patients had the highest probability of receiving surgery treatment (83.40%, 95%CI: 83.04% - 83.76%) followed by Hispanic patients (81.96%, 95%CI: 81.16% - 82.76%) and patients in Other racial/ethnic groups (81.94%, 95%CI: 80.92% - 82.97%). NHB patients (77.65%, 95%CI: 76.73% - 78.58%) had the lowest probability of receiving surgery (p's<0.05).

Factors Associated with Disparities in Receipt of Surgery

Age at diagnosis was positively and significantly associated with receipt of surgery, with the youngest group (18-45 years old) having the highest surgery rate (93.81, 95%CI: 93.20% - 94.41%), and the oldest group (older than 76) having the lowest surgery rate (71.86%, 95%: 71.11% - 72.62%) (p<0.05). Married patients were significantly more likely to receive surgery treatment compared with their unmarried counterparts (81.13% vs. 84.31%, p<0.05). If patients were diagnosed at advanced stage, the probability for receiving surgery treatment significantly decreased by 14.97 percentage points (94.29% vs. 79.32%, p<0.05). Being insured significantly increased the probability of receiving surgery treatment by 5.24 percentage points (84.29% vs. 80.94%, p<0.05) (Appendix A: Table 2.1). No interaction between race/ethnicity and other variables was significantly associated with receipt of surgery.

Contextual-level factors including metro/nonmetro residence and all the county-level SES indicators were not significantly associated with receipt of surgery. However, the probability of receiving surgery treatment varied significantly by county (variance: 0.0451,

p=0.0004). When comparing model adjusted for individual-level factors only (results not shown) with the full model, the county random effect (variance) decreased from 0.0526 to 0.0451.

Factors Contributing to Racial/Ethnic Disparities in Receipt of Surgery

Results based on the sub analysis regarding receipt of surgery stratified by race/ethnicity are reported in Table 3 (Odds Ratios are presented in Appendix G: Table 3.2). For patients in all three racial/ethnic groups, age at diagnosis was negatively associated with the probability of receiving surgery treatment. However, when comparing differences in average probability of surgery receipt between the youngest group (18-45 years old) and oldest group (older than 76 years), the probability decreased by 20.22 percentage points (94.28% vs. 73.40%, $p<0.05$) in NHW patients, 28.72 percentage points (85.07% vs. 56.35%, $p<0.05$) in NHB patients, and 25.00 percentage points (94.00% vs. 69.00%, $p<0.05$) in Hispanic patients. Being married was positively and significantly associated with higher probability of receiving surgery treatment for patients in all three groups ($p's<0.05$). Based on sub analysis including insurance status, the association between receipt of surgery treatment and insurance status was only found to be significant among NHW and Hispanic patients, but not among NHB patients (Appendix B: Table 3.1). Receipt of surgery was also significantly associated with stage at diagnosis for patients in all three groups. When diagnosed at advanced (vs. early) stage, the probability of receiving surgery treatment decreased by 13.98 percentage points (94.12% vs. 80.14%, $p<0.05$) for NHW patients, 29.33 percentage points (89.11% vs. 65.12%, $p<0.05$) for NHB patients, and 17.01 percentage points (96.44% vs. 79.43%, $p<0.05$) for Hispanic patients.

For patients in all racial/ethnic groups, receipt of surgery was not significantly associated with metro/nonmetro residence and county-level education. For Hispanic patients, those living in counties in the lowest quartile rank of county employment rate were significantly less likely to

receive surgery treatment compared to their counterparts in counties in the highest quartile rank of county employment rate (82.41% vs. 85.86%, $p<0.05$). However, the association between county-level employment rate and receipt of surgery was not significant for NHB and Hispanic patients. County-level poverty was significantly associated with receipt of surgery for NHW patients, and patients from the counties in the lowest quartile had significantly lower probability of receiving surgery compared with their counterparts from counties in the highest quartile (82.11% vs. 83.70%, $p<0.05$). However, this association was also not found to be significant in other two racial/ethnic groups. The average predicted probabilities of receiving surgery significantly varied across counties for NHW patients (variance: 0.0527, $p<0.0001$), but not for NHB and Hispanic patients.

Ovarian Cancer-Cause Specific Mortality

Racial/Ethnic Disparities in Ovarian Cancer-Cause Specific Mortality

Results based on Cox proportional hazards model with shared frailty are shown in Table 4. The 5-year ovarian cancer-cause specific mortality varied significantly by counties (variance: 0.0042, $p=0.0010$). When comparing model adjusted for individual-level factors only (results not shown) with the full model, county random effect (variance) decreased from 0.0055 to 0.0042. However, since the county variance was so small and not clinically meaningful, the reported Hazard Ratio was not adjusted for random effects. Adjusting for all the variables listed in Table 1 and year of diagnosis, NHB patients had a 1.24-fold increased hazards of ovarian cancer cause-specific death compared to NHW patients (95% CI: 1.18 – 1.30, $p<0.05$). While not statistically significant, Hispanic patients and patients in Other racial/ethnic groups had 2% (95%CI: 0.94 – 1.03) and 4% (95%CI: 0.90 – 1.02) decreased hazards than NHW patients, respectively.

Table 4

Adjusted Hazard Ratios for Ovarian Cancer-Cause Specific Mortality [a]

Study Variables	Ovarian Cancer-Cause Specific Mortality (N=54,580) HR (95%CI)
Race/ethnicity	
Non-Hispanic White	Ref
Non-Hispanic Black	1.24 (1.18 – 1.30)*
Hispanic	0.98 (0.94 – 1.03)
Other	0.96 (0.90 – 1.02)
Age at diagnosis	
18-45	Ref
46-55	1.33 (1.25 – 1.41)*
56-65	1.51 (1.43 – 1.60)*
66-75	1.84 (1.74 – 1.95)*
>=76	2.57 (2.42 – 2.73)*
Marital status	
Not married	Ref
Married	0.86 (0.83 – 0.88)*
Stage	
Non-advanced	Ref
Advanced	4.66 (4.43 – 4.91)*
Surgery	
No	Ref
Yes	0.32 (0.31 – 0.33)*
Grade	
Well differentiated	Ref
Moderately differentiated	1.91 (1.72 – 2.13)
Poorly differentiated	2.33 (2.10 – 2.58)
Undifferentiated	2.32 (2.09 – 2.59)
Unknown	2.15 (1.94 – 2.39)
Histology	
Serous	Ref
Mucinous	1.63 (1.52 – 1.75)*
Endometrioid	0.76 (0.70 – 0.81)*
Clear cell	1.31 (1.21 – 1.41)*
Other or unspecified	1.23 (1.19 – 1.27)*
Contextual-level factors:	
Metro/nonmetro residence [b]	
Metro	Ref
Nonmetro	1.09 (1.04 – 1.14)*
County education [c]	
Highest	Ref

Study Variables	Ovarian Cancer-Cause Specific Mortality (N=54,580) HR (95%CI)
Upper-middle	0.99 (0.94 – 1.04)
Lower-middle	0.98 (0.93 – 1.03)
Lowest	1.01 (0.95 – 1.08)
County employment [d]	
Highest	Ref
Upper-middle	0.93 (0.89 – 0.97)*
Lower-middle	0.94 (0.89 – 0.99)*
Lowest	0.96 (0.90 – 1.01)
County poverty [e]	
Highest	Ref
Upper-middle	1.06 (1.00 – 1.11)*
Lower-middle	1.07 (1.01 – 1.14)*
Lowest	1.09 (1.02 – 1.16)*
Random effect	
County variance	0.0042*

Notes: [a] Adjusted for all the variables listed in the table, year of diagnosis and county random effects. [b] Metro vs. nonmetro categories are based on the Rural-Urban Continuum Codes (RUCC Codes: 1-3 vs. 4-9) from the Economic Research Service, U.S. Department of Agriculture. [c] Sorted by percentage of a county population with less than 9th grade education in ascending order, and categorized into quartiles. [d] Sorted by percentage of persons aged 16 and over who are unemployed in a county in ascending order, and categorized into quartiles. [e] Sorted by percentage of persons in a county whose incomes are below the 100% federal poverty level threshold in ascending order, and categorized into quartiles.

HR, hazard ratio. CI, confidence interval. [ref] reference group. * $p<0.05$

Factors Associated with Disparities in Ovarian Cancer-Specific Mortality

The risk of death due to ovarian cancer within five years of diagnosis significantly increased with age at diagnosis. Patients who were diagnosed after the age of 76 years had a 2.57-fold increased hazards of death than patients diagnosed at 18-45 years old (95%CI: 2.42 – 2.73, $p<0.05$). Being married was a significant protective factor against ovarian cancer death: married patients were 14% less likely to die from ovarian cancer compared with unmarried patients (HR: 0.86, 95%CI: 0.83- 0.88, $p<0.05$). Being diagnosed with advanced stage

significantly increased the hazards of ovarian cancer death by 4.66-fold (95%CI: .4.43 – 4.91, p<0.05). If surgery treatment had been received, the risk of death due to ovarian cancer decreased by 68% (HR: 0.32, 95%CI: 0.31 – 0.33, p<0.05). No interaction other than interaction between race/ethnicity and insurance was significantly associated with ovarian cancer-cause specific mortality (Appendix C: Table 4.1).

With respect to contextual-level factors, patients living in nonmetro counties had higher risk of death due to ovarian cancer compared with their counterparts living in metro counties (HR: 1.09, 95%CI: 1.04 – 1.14, p<0.05). Ovarian cancer cause-specific mortality did not differ by county-level education. Regarding county-level employment rate, patients from counties in upper-middle (HR: 0.93, 95%CI: 0.89 – 0.97, p<0.05) and lower-middle (0.94, 95%CI: 0.89 – 0.99, p<0.05) quartiles were less likely to die from ovarian cancer compared with patients from counties in the highest quartile; however, the risk of death did not significantly differ between the lowest quartile (HR: 0.96, 95%CI: 0.90 – 1.01) and the highest quartile. Ovarian cancer cause-specific mortality also significantly varied by county-level poverty, and patients living in counties in lower rank had increased risk of death compared with their counterparts living in counties in higher rank (p <0.05).

Factors Contributing to Racial/Ethnic Disparities in Ovarian Cancer- Specific Mortality

As shown in Table 5, for patients in all three racial/ethnic groups, the hazards of dying from ovarian cancer was positively associated with increasing age. However, when comparing the hazards of death between patients diagnosed at age older than 76 and patients diagnosed between 18-45 years old, the hazards of ovarian cancer cause-specific death increased by 2.56-fold for NHW patients (95%CI: 2.38 – 2.76, p<0.05), 2.40-fold for NHB patients (95%CI: 2.01 – 2.86, p<0.05), and 2.91- fold for Hispanic patients (95%CI: 2.47 – 3.43, p<0.05). The protective

effect of being married was only significant in NHW patients (HR: 0.84, 95%CI: 0.82 – 0.87, p<0.05) and NHB patients (HR: 0.82, 95%CI: 0.74 – 0.91, p<0.05) but not in Hispanic patients (HR: 0.98, 95%CI: 0.90 – 1.07). The effect of insurance status on ovarian cancer mortality also varied by race/ethnicity. Being insured significantly decreased the risk of death due to ovarian cancer for NHW patients (HR: 0.79, 95%CI: 0.68 – 0.93, p<0.05). However, although not significant, being insured was found to be associated with increased risk of ovarian cancer death for NHB patients (HR: 1.36, 95%CI: 0.99 – 1.88, p>0.05) and for Hispanic patients (HR: 1.03, 95%CI: 0.80 – 1.34) (Appendix D: Table 5.1). Being diagnosed at advanced stage was a significant risk factor for ovarian cancer cause-specific death for patients in all three racial/ethnic groups. However, when diagnosed at advanced (vs. early) stage, the hazards of death due to ovarian cancer significantly increased by 4.65- fold in NHW patients (95%CI: 4.38 – 4.95, p<0.05), 3.78-fold in NHB patients (95%CI: 3.24 – 4.41, p<0.05), and 5.98 in Hispanic patients (95%CI: 5.05 – 7.09, p<0.05). Receipt of surgery significantly decreased risk of ovarian cancer death for patients in all three racial/ethnic groups, and the effect sizes were similar across the racial/ethnic groups.

In regard to contextual-level factors, survival difference by metro/nonmetro residence was significant for NHW patients (HR: 1.09 95%CI: 1.04 – 1.15, p<0.05), but not for NHB and Hispanic patients. County-level education was not significantly associated with ovarian cancer-cause specific mortality for patients in either of the three groups. County-level employment rate was significantly associated with ovarian cancer-cause specific mortality in NHW patients, and patients from counties in the upper-middle (HR: 0.93, 95%CI: 0.88 – 0.97, p<0.05), lower-middle (HR: 0.93, 95%CI: 0.88 – 0.98, p<0.05) and lowest quartile (HR: 0.93, 95%CI: 0.87 – 0.99, p<0.05) had significantly higher mortality compared with patients from the highest quartile

counties, respectively. However, these associations were not significant for patients from other racial/ethnic groups. Similarly, the association between county-level poverty and ovarian cancer-cause specific mortality was significant only in NHW patients, and patients from lower quartile counties had higher risk of ovarian cancer death than patients from the highest quartile counties (p's<0.05). Ovarian cancer-cause specific mortality significantly varied by county, but only for NHW patients (variance: 0.0044, p=0.0010).

Table 5

Factors Contributing to Disparities in Ovarian Cancer-Cause Specific Mortality, by Race/Ethnicity [a]

Study Variables	Ovarian Cancer-Cause Specific Mortality HR (95%CI)		
	Non–Hispanic White (n=39,726)	Non–Hispanic Black (n=4,295)	Hispanic (n=6,256)
Age at diagnosis			
18-45	Ref.	Ref.	Ref.
46-55	1.29 (1.19 – 1.39)*	1.58 (1.33 – 1.88)*	1.36 (1.17 – 1.59)*
56-65	1.51 (1.40 – 1.62)*	1.61 (1.36 – 1.91)*	1.61 (1.38 – 1.87)*
66-75	1.82 (1.69 – 1.96)*	1.90 (1.60 – 2.25)*	2.01 (1.72 – 2.34)*
>=76	2.56 (2.38 – 2.76)*	2.40 (2.01 – 2.86)*	2.91 (2.47 – 3.43)*
Marital status			
Not married	Ref.	Ref.	Ref.
Married	0.84 (0.82 – 0.87)*	0.82 (0.74 – 0.91)*	0.98 (0.90 – 1.07)
Stage			
Non-advanced	Ref.	Ref.	Ref.
Advanced	4.65 (4.38 – 4.95)*	3.78 (3.24 – 4.41)*	5.98 (5.05 – 7.09)*
Surgery			
No	Ref.	Ref.	Ref.
Yes	0.32 (0.31 – 0.34)*	0.33 (0.30 – 0.38)*	0.30 (0.27 – 0.35)*
Grade			
Well differentiated	Ref.	Ref.	Ref.
Moderately differentiated	1.84 (1.63 – 2.08)*	2.48 (1.68 – 3.67)*	1.87 (1.35 – 2.59)*
Poorly differentiated	2.22 (1.97 – 2.49)*	2.79 (1.92 – 4.07)*	2.37 (1.74 – 3.24)*

Study Variables	Ovarian Cancer-Cause Specific Mortality HR (95%CI)		
	Non–Hispanic White (n=39,726)	Non–Hispanic Black (n=4,295)	Hispanic (n=6,256)
Undifferentiated	2.21 (1.95 – 2.50)*	2.98 (2.00 – 4.44)*	2.27 (1.63 – 3.16)*
Unknown	2.10 (1.87 – 2.37)*	2.59 (1.78 – 3.78)*	1.85 (1.35 – 2.53)*
Histology			
Serous	Ref.	Ref.	Ref.
Mucinous	1.51 (1.39 – 1.65)*	2.30 (1.89 – 2.81)*	2.07 (1.70 – 2.52)*
Endometrioid	0.72 (0.66 – 0.78)*	0.86 (0.67 – 1.09)	0.97 (0.79 – 1.20)
Clear cell	1.26 (1.15 – 1.38)*	1.70 (1.25 – 2.30)*	1.77 (1.39 – 2.25)*
Other or unspecified	1.19 (1.15 – 1.24)*	1.31 (1.17 – 1.46)*	1.41 (1.27 – 1.57)*
Contextual-level factors:			
Metro/nonmetro residence [b]			
Metro	Ref.	Ref.	Ref.
Nonmetro	1.09 (1.04 – 1.15)*	1.05 (0.89 – 1.25)	1.20 (0.97 – 1.5)
County education [c]			
Highest	Ref.	Ref.	Ref.
Upper-middle	0.98 (0.93 – 1.04)	0.98 (0.83 – 1.15)	1.02 (0.82 – 1.26)
Lower-middle	0.97 (0.92 – 1.03)	0.99 (0.83 – 1.17)	1.05 (0.86 – 1.28)
Lowest	0.99 (0.93 – 1.06)	1.03 (0.85 – 1.24)	1.10 (0.88 – 1.37)
County employment [d]			
Highest	Ref.	Ref.	Ref.
Upper-middle	0.93 (0.88 – 0.97)*	0.93 (0.78 – 1.11)	0.92 (0.78 – 1.09)
Lower-middle	0.93 (0.88 – 0.98)*	1.12 (0.95 – 1.31)	0.86 (0.71 – 1.04)
Lowest	0.93 (0.87 – 0.99)*	1.13 (0.95 – 1.35)	0.84 (0.69 – 1.02)
County poverty [e]			
Highest	Ref.	Ref.	Ref.
Upper-middle	1.06 (1.00 – 1.12)	1.05 (0.87 – 1.26)	1.07 (0.90 – 1.28)
Lower-middle	1.09 (1.02 – 1.16)*	0.99 (0.82 – 1.19)	1.07 (0.88 – 1.30)
Lowest	1.14 (1.06 – 1.23)*	0.92 (0.76 – 1.12)	1.16 (0.94 – 1.44)
Random effect			
County variance	0.0044*	0.0032	<0.0001

Notes: [a] Adjusted for all the variables listed in the table, year of diagnosis and county random effects. [b] Metro vs. nonmetro categories are based on the Rural-Urban Continuum Codes (RUCC Codes: 1-3 vs. 4-9) from the Economic Research Service, U.S. Department of Agriculture. [c] Sorted by percentage of a county population with less than 9th grade education in ascending order, and categorized into quartiles. [d] Sorted by percentage of persons aged 16 and over who are unemployed in a county in ascending order, and categorized into quartiles. [e] Sorted by percentage of persons in a county whose incomes are below the 100% federal poverty level threshold in ascending order, and categorized into quartiles.

HR, hazard ratio. CI, confidence interval. Ref., reference group. * $p<0.05$

Changes in Racial Disparities over Time

Results of Joinpoint regression analysis which tested the change in racial/ethnic disparities in ovarian cancer diagnosis, surgery treatment and survival over time are presented in Figures 1-3. Adjusting for variables listed in Table 1, except for insurance status, racial/ethnic disparities in advanced stage diagnosis, receipt of surgery and ovarian cancer-cause specific mortality did not vary significantly from 2001 to 2012 (all p's >0.05).

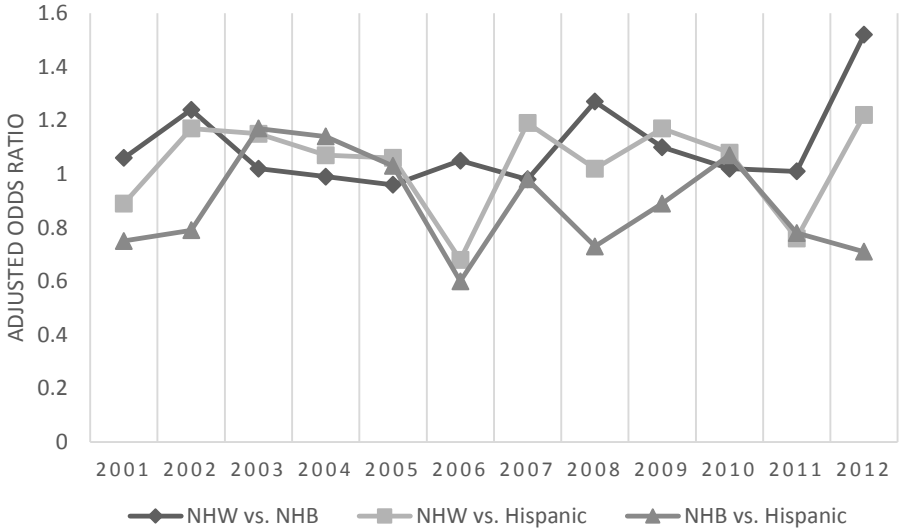

Figure 1. Racial/Ethnic Disparities in Advanced Stage Diagnosis: Trend over Years 2001-2012

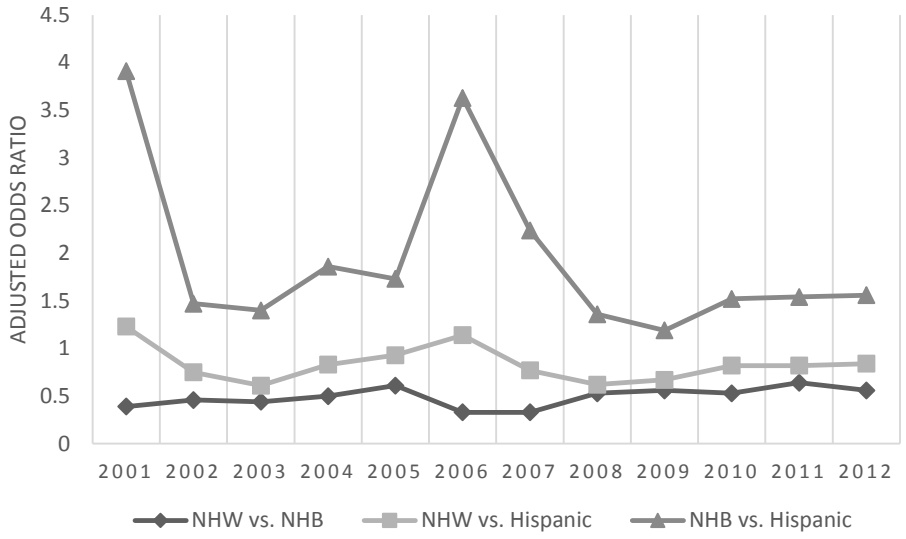

Figure 2. Racial/Ethnic Disparities in Receipt of Surgery: Trend over Years 2001-2012

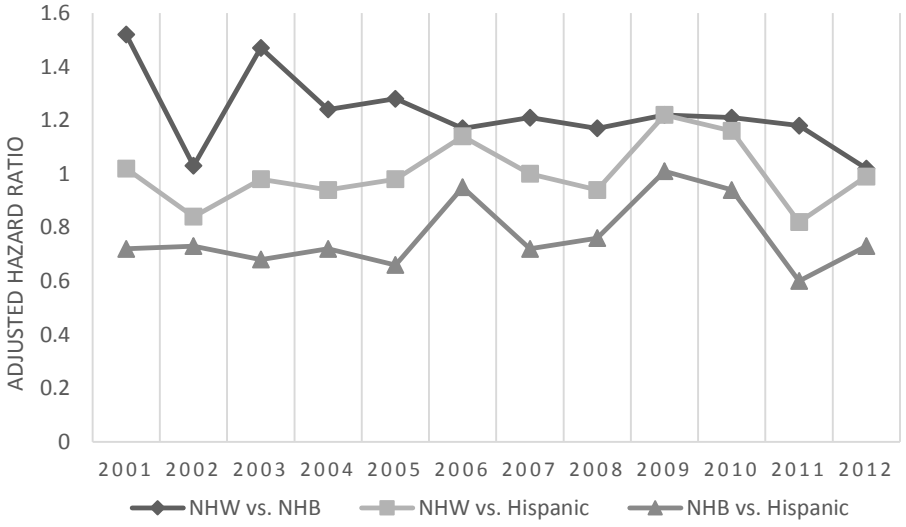

Figure 3. Racial/Ethnic Disparities in Ovarian Cancer-Cause Specific Mortality: Trend over Years 2001-2012

CHAPTER 5

DISCUSSION

This study examined racial/ethnic disparities in ovarian cancer advanced stage diagnosis, receipt of surgery treatment, and survival outcome, and assessed trend in racial/ethnic disparities over 12 years using longitudinal panel dataset. Several individual- and contextual-level factors which contribute to those racial/ethnic disparities were identified. Based on most recent national cancer registry data, this study updates the knowledge base on changes in ovarian cancer racial/ethnic disparities over time.

Racial/ethnic disparities in ovarian cancer diagnosis, treatment, and survival may be attributed to multiple factors, such as tumor biology, genetic differences, healthcare accessibility and quality, or a combination of those factors. This study focused on assessing effects of individual- and contextual-level socio demographic and economic characteristics on ovarian cancer racial/ethnic disparities, while adjusting for tumor pathological differences.

Racial/Ethnic Disparities

Compared to NHB patients, NHB patients have a significant disadvantage in ovarian cancer, specifically in advanced stage diagnosis, receipt of surgery treatment, and ovarian cause-specific mortality. This finding is consistent with many previous studies based on national- or state-level data (Chan, et al., 2008; Howell, et al., 2013; Morris, Sands, & Smith, 2010; Terplan, et al., 2012). Two studies had either contrary or insignificant findings regarding stage of diagnosis between the two racial groups; however, the results were based on unadjusted analysis (Du, et al., 2008; Kim, et al., 2010). In the current study on NHB patients living in counties with the employment rate ranked in the first quartile were less likely to be diagnosed at advanced stage.

This finding suggests that certain contextual-level characteristics, such as county-level employment rate or other related factors, may be contributing to racial/ethnic disparities in ovarian cancer diagnosis.

The study suggests no significant differences in stage of diagnosis and survival between Hispanic and NHW patients. However, Hispanic patients have a significantly lower probability of receiving surgery treatment compared with NHW patients. Definitive conclusions regarding ovarian cancer racial/ethnic disparities between Hispanic and Other racial/ethnic groups have not been established in previous studies, primarily due to the limited data on ovarian cancer cases among Hispanic women. One study based on 1996-2006 California Cancer Registry data found no significant differences on stage of diagnosis between Hispanics and NHW. This finding is consistent with my finding (Morris, et al., 2010). The current study also indicates that Hispanic patients have the youngest mean age at diagnosis (55.63 years), followed by patients from Other racial/ethnic groups (55.88 years), and NHBs (59.57 years). NHWs have the oldest mean age at diagnosis (62.55 years). Based on 2000-2004 SEER 12 data, which included 1,215 Hispanic ovarian cancer patients, Ibeanu and Diaz-Montes's study (2005) also supports my result by indicating that Hispanic are significantly more likely to be diagnosed at a younger age compared to NHWs and NHBs. Findings of Ibeanu and Diaz-Montes that Hispanics patients were significantly less likely to be diagnosed with ovarian cancer at advanced stage compared to NHW patients was based on unadjusted analysis (Ibeanu and Diaz-Montes, 2005). Adjustment for individual socio demographic characteristics, tumor pathological characteristics, metro/nonmetro residence and county SES, the current study does not find a significant difference in ovarian cancer advanced stage diagnosis between Hispanics and NHWs.

Individual-Level Factors Contributing to Racial/Ethnic Disparities

Age

Being diagnosed at a younger age has long been associated with better health outcomes for cancer patients. In the current study, younger age at diagnosis was found to be independently associated with decreased risk of advanced stage diagnosis, increased probability of receiving surgery treatment, and decreased hazards due to ovarian cancer. This age advantage remained in all racial/ethnic subpopulations. However, to what extend age at diagnosis can affect each level of the ovarian cancer continuum differs by race/ethnicity. For example, based on the stratified (by race/ethnicity) and adjusted results, when comparing the probabilities of receiving surgery treatment between women diagnosed at the age of 76 or older and those who were diagnosed between 18-45 years, the differences in surgery rates between these two age groups are 20.00, 28.72 and 25.00 percentage points for NHW, NHB, and Hispanic patients, respectively. This result indicates age at diagnosis has a stronger association with receipt of surgery for NHB patients and Hispanic patients than NHW patients. In other words, compared to NHW patients, NHB and Hispanic patients may be more likely to forgo surgery treatment due to age consideration. Similarly, differences in age at diagnosis may also contribute differently to ovarian cancer cause-specific death by racial/ethnic groups. Based on the results of Cox proportional hazard models stratified by race/ethnicity, when comparing women diagnosed at age of 76 or older to those who were diagnosed between the ages of 18-45**,** the ovarian cancer-cause specific hazard ratios were 2.56, 2.40, and 2.91 for NHWs, NHBs, and Hispanics, respectively, which indicates that being diagnosed at an older age may be a stronger risk factor for ovarian cancer-cause specific death for Hispanic patients compared to their NHW and NHB counterparts.

Marital Status

Similar to age, in this study, marital status was also found to be a significant factor for ovarian cancer early stage of diagnosis, receipt of surgery, and survival. This finding is consistent with and supported by a study based on 2004-2008 SEER data, which revealed the advantages of being married in cancer diagnosis, treatment, and survival for patients of the top 10 lethal cancers (Aizer, et al., 2013). One study has emphasized the survival advantage for married ovarian cancer patients and indicated that advantage might be attributed to psychosocial support potentially altering immune function (Mahdi, et al., 2013). Another possible explanation regarding the marriage protective effect on general health is related to greater economic resources (Trovato & Lauris, 1989), which might be related to increased healthcare accessibility and higher quality of life. The current study finds significant association between being married and decreased probability of advance stage diagnosis, as well as increased probability of receiving surgery treatment. However, because I could not control for individual-level social economic status, whether this marriage advantage can be contributed to higher SES needs further examination.

A study based on the Health Retirement Survey data suggested about variation of association between marital status and general health by race and ethnicity. Adjusted for SES and baseline health status, compared to NHW women, for NHBs being married is significantly more protective against the 2-year mortality (Beckett & Elliott, 2002). In the current study, as specific to each level of the ovarian cancer continuum, variation in significance of association between marital status and ovarian cancer diagnosis and survival is observed across racial/ethnic groups. Being married is a significant protective factor for advanced stage diagnosis only for NHW patients, but not for NHB and Hispanic groups. The protective effect on survival is only significant for NHW and NHB patients, but not for the Hispanic patients. Similarly, whether this variation can be

explained by individual- SES or difference in healthcare accessibility and quality still needs further examination. Furthermore, because the sample sizes for NHB and Hispanics are relatively much smaller compared with NHWs, the study findings need to be replicated on samples with larger representation of NHB and Hispanic patients.

Insurance Status

Due to limited information on health insurance status, all the analysis with insurance status were conducted using sub models with cases diagnosed in 2007 and later. Based on the primary model which combined all racial/ethnic groups, being insured is significantly associated with increased probability of receiving surgery, but when stratified by race/ethnicity, this association is only significant among NHW and Hispanic patients (but not in NHB patients). However, being covered by health insurance does not mean that the ovarian cancer surgery treatment procedures are covered by insurance plan; the proportion of cost being covered may vary based on the insurance types. For example, it has been reported that compared to NHWs, NHBs were more likely to be publicly insured and less likely to have commercial insurance (Bristow, et al., 2011). However, due to the small proportion of uninsured cases and lack of information on types of insurance plan, this conclusion needs to be further confirmed in samples with higher proportion of uninsured cases and with more specific information on insurance types. No significant association between insurance status and the probability of advanced stage diagnosis is observed in either the primary model or stratified models. I was not surprised to find the absence of significant association between insurance status and advanced stage diagnosis, since ovarian cancer screening tests were not generally recommended and applied to general population due to limited tests specificity and potential harms, as a result, being health insured may not be a powerful factor to promote effective ovarian cancer screening. Regarding insurance effect on survival outcome, the

results from this study indicate interaction effect of race/ethnicity and insurance status. When stratified by race/ethnicity, being insured was found to be a significant protective factor against ovarian cancer-cause specific death for NHW patients, but significant risk factor for NHB patients; and has no significant effect on survival for Hispanic patients. Similarly, one possible explanation could still be the difference in type of insurance plan. For example, one study based on clinical record suggested public insurance was associated with increased hazard of ovarian cancer mortality (Mishka Terplan, et al., 2008).

Advanced Stage Diagnosis and Receipt of Surgery

Additionally, models examining ovarian cancer-cause specific mortality were adjusted for advanced stage diagnosis and receipt of surgery. The results based on the primary model (with all racial/ethnic groups) are consistent with previous studies; there is a significant risk effect for being diagnosed at advanced stage, and a significant protective effect for receiving surgery treatment on survival outcome. The beneficial effect on ovarian cancer survival from receiving surgery treatment remained in stratified models, and the effect sizes were similar across racial/ethnic groups. However, the association between advanced stage diagnosis and ovarian cancer survival does varies across racial/ethnic groups. Based on the stratified models, adjusting for receipt of surgery and other covariates, being diagnosed at advanced stage significantly increased ovarian cancer death by 4.65-folds for NHW patients, 3.78-folds in NHB patients, and 5.98-folds in Hispanic patients. Other potentially influencing factors such as genetic, biological, comorbidity and other related factors are required to better explain variation in association between stage at diagnosis and survival by race/ethnicity.

Contextual-level Factors Contributing to Racial/ethnic Disparities

Metro/Nonmetro Residence

In this study, the metro/nonmetro residence was treated as a contextual-level factor, and a study on metro/nonmetro differences was conceptually a rural/urban (the term which was used in most other related studies) difference. This study used the terms metro/nonmetro to be consistent with the RUCC classification system. Based on the adjusted results, metro/nonmetro residence is not significantly associated with advanced stage diagnosis and receipt of surgery treatment in either the primary model or any of the race/ethnicity stratified models. Living in nonmetro counties is a significant protective factor against ovarian cancer specific death based on the primary model; however, when stratified by race/ethnicity, this association is only found in NHW patients, but not in other two groups. The finding on the nonmetro survival advantage is contrary to the investigator's initial hypothesis that ovarian cancer patients living in metro counties have lower ovarian cancer mortality. This hypothesis was based on the fact that generally, people living in metro areas tend to have better healthcare accessibility and quality. Based on the investigator's literature review, very few studies have reported on ovarian cancer disparities by rural/urban residence, especially based on the U.S. population. Only one study based on the SEER-Medicare linked database suggested ovarian cancer patients in rural areas were more likely to have surgery at a low-volume hospital than residents of urban communities. However, according to this study, hospital surgery volume was not significantly associated with ovarian cancer outcome (Schrag et al., 2006). Yet, in a study conducted in Poland, living in urban areas was associated with being exposed to increased ovarian cancer risk factors, such as lower parity, higher education level and experiencing menarche at an earlier age (Szpurek, et al., 2013). Because the sample of the current study consisted of a very small proportion of nonmetro residents (11.11%), and this proportion

was even smaller among NHB (9.39%) and Hispanic (3.96%) patients, it is possible that the study sample size for NHB and Hispanic patients may be not large enough to generate statistically significant results. The small sample for minority patients from nonmetro areas may also indicate that although more minority populations are majorly resident in rural area (The Housing Assistance Council, 2012), the SEER cancer registry data mainly included minority patients living in urban areas. In other words, cases which are diagnosed and treated in urban healthcare facilities are more likely to be included into the cancer registry records.

County-level SES (Education, Employment and Poverty)

In this study, county-level SES was operationalized with three separate variables (rather than an index): county-level education, employment, and poverty degree. The study results indicate that ovarian cancer advanced stage diagnosis, receipt of surgery, and survival do not vary significantly by county-level education.

Living in poorer counties is significantly associated with increased probability of advanced stage diagnosis. However, this association is only significant in NHWs but not in NHBs and Hispanics. Another interesting finding is that the association between county-level employment and advanced stage diagnosis varies by race/ethnicity. Living in counties with lower employment rate had a significant protective effect against advanced stage diagnosis for NHB patients; however, although not statistically significant, lower county employment rate is a risk factor for advanced stage diagnosis for NHW and Hispanic patients.

Receipt of surgery is not significantly associated with any of the county SES measurements. Regarding the ovarian cancer cause-specific mortality, county-level employment and poverty are significantly associated with ovarian cancer death for NHW patients but not for NHB and Hispanic patients. While living in poorer counties is associated with higher ovarian cancer mortality, living

in counties with lower employment is associated with lower risk ovarian cancer death.

The association between higher contextual-level SES and better health outcomes has been well established by previous studies, as people living in higher contextual-level SES usually have better access to healthcare services (CDC, 2014b; Kirby & Kaneda, 2005). On the contrary, several studies have also indicated disadvantage of living in higher contextual-level SES community (Robert, et al., 2004; Singh, et al., 2012). For instance, Robert et al found that compared to women living in lower SES communities, those living in higher SES communities had greater odds of having breast cancer (Robert, et al., 2004). Therefore, explanation of contextual-level SES effect on health outcomes should not always focus on unequal access to healthcare services. In the current study, the findings on the negative effect of living in counties with higher employment rate may be explained by differences in exposure of other ovarian cancer risk factors such as lower parity and higher education.

County Variance

Results of the multilevel analysis suggest the probability of advanced stage diagnosis does not significantly vary by county in either primary model (i.e., adjusting for all racial/ethnic groups) or models stratified by race/ethnicity. This study finds a significant but slight county variance in surgery receipt and ovarian cancer-cause specific mortality; however, the minor and significant county variance is only observed in NHW patients but not in other two racial/ethnic groups. The county random effect decreases when contextual-level factors are added to the models, which indicates that the variation of ovarian cancer outcomes at county level may be partially explained by these contextual-level factors. However, since the ovarian cancer prevalence is relative low compared to other major cancer diseases such as breast cancer and cervical cancer, the distribution

of reported cases in certain counties might be rare, especially for minority patients which are underrepresented in this study sample, therefore, a lack of statistical power due to limited minority cases may contribute to the insignificant county variance in NHB and Hispanic subpopulations.

Racial/Ethnic Disparities Change over Time

This study does not find a significant change in ovarian cancer racial/ethnic disparities from 2001 to 2012. Based on the Joinpoint trend analysis, when comparing the racial/ethnic ORs and HRs for each two of the three racial/ethnic groups over time, no significant changes are found between any of the two racial/ethnic group combinations. This result indicates that the extend of racial/ethnic disparities in ovarian cancer advanced stage diagnosis, receipt of surgery treatment, and survival has remained stable from 2001 to 2012 among NHW, NHB, and Hispanic patients. To my knowledge, changes in prevalence of ovarian cancer advanced stage diagnosis and receipt of surgery over time have not been examined by race/ethnicity. Terplan et al's study based on SEER 9 data assessed racial survival differences between NHW and NHB patients from 1973 to 2007 (M. Terplan, et al., 2012). During this study period, racial disparities in survival (adjusted for registry, tumor stage and marital status) had been widened between the two racial groups due to differences in the receipt of surgery. However, since HRs were measured by every five-year diagnosis cohort, annual change in HRs, and cases diagnosed in recent years were not actually assessed by this study. Although the current study period partially overlaps with the 1973-2007 study period, the two studies differ in measurement and assessment, thus, by including more recent data, the current study yield different results: there is no significant change in racial/ethnic disparities from 2001 to 2012. Because the data used in the current study did not contain information on chemotherapy and newly emerged treatment such as antiangiogenic therapy, future

studies should assess changes in ovarian cancer disparities related to other types of treatment.

Limitations and Strengths

This study had several limitations. First, it has been shown that the prevalence of BRCA1 and BRCA2 mutation, which was strongly associated with ovarian cancer development, can vary by racial/ethnic groups in the U.S. (John et al., 2007; National Cancer Institute, 2015b). However, family ovarian cancer history and genetic influence were not controlled for in this study due to unavailability of such data. Second, because of the incomplete treatment information, it is types of treatment other than surgery were not examined in this study. The current three main types of treatment for ovarian cancer include surgery, chemotherapy and radiotherapy. Racial disparities regarding the receipt of chemotherapy have been reported in previous studies (Du, et al., 2008). However, since SEER data do not provide information on the receipt of chemotherapy, assessing disparities in receipt of chemotherapy and its contribution to racial/ethnic disparities in ovarian cancer outcomes is not possible in this study. Based on the SEER data, only less than 2 percent ovarian cancer patients received radio therapy. Due to considerations of statistical power, this study did not assess the effect of radiation therapy on ovarian cancer outcomes. Thirdly, individual insurance status information was only available for patients diagnosed from the year of 2007 and later. As a result, this study was not able to assess the effect of insurance status for cases diagnosed earlier; thus, the insurance status was not adjusted in the trend analysis. Finally, an important limitation of this study is the limited sample size of minority patients, especially NHB patients which accounts for less than 8 percent of the total study population. When stratified by race/ethnicity, the assessment of association between certain factors and interested outcomes might be insignificant due to limited statistical power.

This study also have several strengths. First, it is based on the most updated national level cancer registry data which allowed for a large sample size for multivariate and multilevel statistical analysis, and the large sample size also increased the representativeness of the study sample. Second, the inclusion of multi-year cohorts defined by time of diagnosis enabled the analysis to control for and study on time effects on interested outcomes.

Contributions

The current study updates the knowledge about racial/ethnic disparities in ovarian cancer diagnosis, surgery treatment and survival based on most recent national-level cancer research data. Furthermore, by applying a multilevel social ecological research approach, it provides new evidence on the effect of contextual-level factors on ovarian cancer outcomes. It also provides new insights into mechanisms through which racial/ethnic disparities in ovarian cancer are developed, and updates information on the racial/ethnic disparities change over time. Finally, this study also initiates several new future research endeavors to address the aforementioned limitations and to further explore other potential individual- and contextual-level factors contributing to racial/ethnic disparities in ovarian cancer diagnosis, treatment, and survival.

Conclusions and Implication

This study confirms that racial/ethnic disparities exist at each level of the ovarian cancer continuum diagnosis, treatment, and survival, and the extent of these racial/ethnic disparities has remained stable from 2001-2012. Both individual- and contextual-level factors contribute to the ovarian cancer racial/ethnic disparities. The effect of these factors can varies by race/ethnicity, and should be examined separate.

As certain subpopulations experience excessive health burdens related to ovarian cancer, multilevel efforts are needed to improve ovarian cancer diagnosis and treatment. An efficient way to identify and target these vulnerable populations can be based on a combination of individual-level and contextual-level factors associated with ovarian cancer outcomes. Specific policy interventions should focus on subpopulations at a greater risk for ovarian cancer diagnosed at a later stage, for forgoing surgery treatment (NHB and Hispanic patients); and ovarian cancer mortality (e.g. Hispanic patients who were diagnosed at advanced stage). Potential policy recommendation may include (1) developing or modifying insurance plans to encourage ovarian cancer screening, and to improve reimbursement for potential treatments for populations at risk; (2) developing standardized protocols and procedures for ovarian cancer treatment to reduce the probability of forgoing treatment due to lack of information or healthcare resources. Future studies should focus on exploring other factors which were not assessed in this study but may potentially influence racial/ethnic disparities in ovarian cancer outcomes, such as family history, behavioral factors, individual SES, and other types of treatment.

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APPENDICES

Appendix A: Table 2.1

Models with Insurance Status: Adjusted Prevalence of Advanced Stage Diagnosis and Receipt of Surgery (N=27,539) [a]

Study Variables	Advanced Stage Diagnosis % [b] (95%CI)	Receipt of Surgery % [b] (95%CI)
Race/ethnicity		
Non-Hispanic White	68.41 (67.79 – 69.03)[ref]	83.27 (82.78 – 83.77) [ref]
Non-Hispanic Black	71.15 (69.24 – 73.06)[*]	78.27 (77.05 – 79.49)[*]
Hispanic	69.11 (67.58 – 70.64)	81.41 (80.30 – 82.52)[*]
Other	69.15 (67.39 – 70.91)	82.34 (80.96 – 83.71)
Age at diagnosis		
18-45	53.86 (52.32 – 55.41) [ref]	94.81 (94.01 – 95.60) [ref]
46-55	64.17 (63.00 – 65.34)[*]	89.21 (88.34 – 90.08)[*]
56-65	70.43 (69.42 – 71.45)[*]	85.37 (84.56 – 86.18)[*]
66-75	74.36 (73.25 – 75.48)[*]	80.85 (79.95 – 81.75)[*]
>=76	78.48 (77.32 – 79.65)[*]	70.31 (69.21 – 71.41)[*]
Marital status		
Not married	69.01 (68.27 – 69.74) [ref]	80.94 (80.35 – 81.52) [ref]
Married	68.54 (67.85 – 69.24)	84.29 (83.72 – 84.87)[*]
Insurance		
Uninsured	69.24 (66.95 – 71.52) [ref]	77.42 (75.37 – 79.47) [ref]
Insured	68.74 (68.23 – 69.25)	82.66 (82.20 – 83.12)[*]
Stage		
Non-advanced	–	93.62 (92.96 – 94.28) [ref]
Advanced	–	79.36 (78.77 – 79.95)[*]
Grade		
Well differentiated	40.87 (38.31 – 43.43) [ref]	93.80 (91.65 – 95.95) [ref]
Moderately differentiated	57.81 (56.13 – 59.49)[*]	92.87 (91.59 – 94.14)
Poorly differentiated	72.35 (71.42 – 73.29)[*]	92.12 (91.50 – 92.74)
Undifferentiated	72.04 (70.66 – 73.43)[*]	94.80 (94.03 – 95.58)
Unknown	73.59 (72.68 – 74.51)[*]	67.85 (66.80 – 68.90)[*]
Histology		
Serous	81.40 (80.68 – 82.11) [ref]	88.06 (87.47 – 88.65) [ref]
Mucinous	47.49 (44.66 – 50.32)[*]	84.72 (82.67 – 86.77)[*]
Endometrioid	42.65 (40.42 – 44.89)[*]	92.82 (90.88 – 94.76)[*]
Clear cell	38.64 (36.23 – 41.06)[*]	93.27 (91.58 – 94.96)[*]
Other or unspecified	67.17 (66.14 – 68.20)[*]	74.56 (73.73 – 75.40)[*]
Interaction: race/ethnicity * county employment		
County employment: highest		
Non-Hispanic White	67.96 (66.74 – 69.18) [ref]	–
Non-Hispanic Black	75.68 (71.47 – 79.88)[*]	–

Study Variables	Advanced Stage Diagnosis % [b] (95%CI)	Receipt of Surgery % [b] (95%CI)
Hispanic	67.77 (63.74 – 71.80)	–
Other	70.54 (67.42 – 73.65)	–
County employment: upper-middle		
Non-Hispanic White	69.14 (67.93 – 70.34) [ref]	–
Non-Hispanic Black	68.65 (64.16 – 73.13)	–
Hispanic	69.46 (66.59 – 72.33)	–
Other	68.54 (65.25 – 71.83)	–
County employment: lower-middle		
Non-Hispanic White	68.38 (67.03 – 69.73) [ref]	–
Non-Hispanic Black	69.94 (66.70 – 73.18)	–
Hispanic	67.91 (65.52 – 70.31)	–
Other	67.74 (64.73 – 70.76)	–
County employment: lowest		
Non-Hispanic White	68.15 (66.77 – 69.53) [ref]	–
Non-Hispanic Black	70.27 (67.43 – 73.10)	–
Hispanic	71.43 (68.79 – 74.07)*	–
Other	69.80 (65.26 – 74.34)	–
Contextual-level factors:		
Metro/nonmetro residence [c]		
Metro	68.84 (68.31 – 69.37) [ref]	82.52 (82.02 – 83.01) [ref]
Nonmetro	68.11 (66.45 – 69.76)	82.22 (81.10 – 83.33)
County education [d]		
Highest	68.96 (67.83 – 70.08) [ref]	83.21 (82.35 – 84.08)
Upper-middle	68.84 (67.76 – 69.91)	82.57 (81.73 – 83.42)
Lower-middle	68.74 (67.70 – 69.77)	82.12 (81.22 – 83.03)
Lowest	68.52 (67.27 – 69.77)	82.03 (80.91 – 83.14)
County employment [e]		
Highest	68.80 (67.68 – 69.92) [ref]	82.59 (81.74 – 83.45) [ref]
Upper-middle	69.09 (68.01 – 70.16)	83.04 (82.15 – 83.92)
Lower-middle	68.39 (67.28 – 69.50)	82.59 (81.49 – 83.69)
Lowest	68.92 (67.73 – 70.11)	81.78 (80.84 – 82.72)
County poverty [f]		
Highest	67.92 (66.75 – 69.10) [ref]	82.78 (81.81 – 83.75) [ref]
Upper-middle	68.23 (67.16 – 69.31)	81.96 (81.01 – 82.92)
Lower-middle	69.44 (68.34 – 70.54)	82.90 (81.96 – 83.85)
Lowest	69.53 (68.20 – 70.87)	82.23 (81.25 – 83.21)
Random effect		
County variance	<0.0001	0.0382*

Notes: [a] Adjusted for all the variables listed in the table, year of diagnosis, interactions between race/ethnicity and county employment, and county random effects. [b] Average adjusted predicted probabilities. [c] Metro vs. nonmetro

categories are based on the Rural-Urban Continuum Codes (RUCC Codes: 1-3 vs. 4-9) from the Economic Research Service, U.S. Department of Agriculture. [d] Sorted by percentage of a county population with less than 9th grade education in ascending order, and categorized into quartiles. [e] Sorted by percentage of persons aged 16 and over who are unemployed in a county in ascending order, and categorized into quartiles. [f] Sorted by percentage of persons in a county whose incomes are below the 100% federal poverty level threshold in ascending order, and categorized into quartiles.

CI, confidence interval. [ref] reference group. * $p<0.05$

Appendix B: Table 3.1

Models with Insurance Status: Factors Contributing to Disparities in Advanced Stage Diagnosis and Receipt of Surgery, by Race/Ethnicity [a]

Study Variables	Advanced Stage Diagnosis % [b] (95%CI)			Receipt of Surgery % [b] (95%CI)		
	Non–Hispanic White (n=19.328)	Non–Hispanic Black (n=2,278)	Hispanic (n=3.460)	Non–Hispanic White (n=19.328)	Non–Hispanic Black (n=2,278)	Hispanic (n=3.460)
Age at diagnosis						
18-45	54.71 [ref] (52.62 – 56.79)	56.99 [ref] (51.95 – 62.03)	51.78 [ref] (48.63 – 54.93)	95.40 [ref] (94.34 – 96.46)	87.66 [ref] (84.10 – 91.22)	94.17 [ref] (92.50 – 95.84)
46-55	64.90* (63.48 – 66.32)	67.98* (63.74 – 72.21)	63.74* (60.66 – 66.82)	91.09 * (90.09 – 92.10)	75.69* (72.23 – 79.15)	86.63* (84.50 – 88.75)
56-65	70.43* (69.25 – 71.60)	76.08* (72.62 – 79.54)	70.21* (67.09 – 73.34)	86.72* (85.87 – 87.57)	71.97* (68.97 – 74.97)	84.54* (82.45 – 86.64)
66-75	74.20* (72.93 – 75.47)	78.40* (74.71 – 82.09)	74.92* (71.31 – 78.54)	82.94* (82.05 – 83.84)	64.29* (61.02 – 67.57)	79.14* (76.55 – 81.73)
>=76	78.87* (77.57 – 80.16)	83.30* (79.38 – 87.21)	75.49* (71.23 – 79.76)	72.37* (71.32 – 73.43)	54.86* (50.76 – 58.96)	68.08* (64.38 – 71.78)
Marital status						
Not married	70.23 [ref] (69.34 –71.11)	73.30 [ref] (71.24 – 75.35)	65.51 [ref] (63.48 – 67.54)	81.48 [ref] (80.91 – 82.05)	68.65 [ref] (66.93 – 70.36)	82.34 [ref] (81.06 – 83.63)
Married	69.74 (68.94 – 70.54)	71.4 0 (68.15 – 74.64)	64.18 (62.08 – 66.28)	84.87* (84.31 – 85.42)	73.67* (71.05 – 76.28)	85.46* (84.07 – 86.86)
Insurance						
Uninsured	70.17 [ref] (67.02 –73.32)	69.26[ref] (62.77 – 75.76)	67.78 [ref] (63.3 – 72.26)	77.54 [ref] (74.94 – 80.15)	70.37 [ref] (64.66 – 76.08)	80.39 [ref] (77.03 – 83.75)
Insured	69.95 (69.36 – 70.55)	73.04 (71.24 – 74.84)	64.53 (63.00 – 66.06)	83.28* (82.89 – 83.67)	70.10 (68.64 – 71.56)	84.02* (83.06 – 84.98)

Study Variables	Advanced Stage Diagnosis % [b] (95%CI)			Receipt of Surgery % [b] (95%CI)		
Stage						
Non-advanced	–	–	–	93.44 [ref] (92.65 – 94.23)	88.88 [ref] (86.06 – 91.71)	96.23 [ref] (94.88 – 97.58)
Advanced	–	–	–	80.52 (80.01 – 81.02)*	64.78 (62.93 – 66.63)*	79.27 (77.94 – 80.61)*
Grade						
Well differentiated	42.45 [ref] (39.31 – 45.59)	39.32 [ref] (30.31 – 48.33)	36.80 [ref] (30.39 – 43.21)	93.52 [ref] (90.88 – 96.15)	90.74 [ref] (82.19 – 99.29)	98.23 [ref] (94.96 – 101.49)
Moderately differentiated	58.62* (56.64 – 60.60)	61.85* (54.97 – 68.74)	59.70* (55.13 – 64.27)	92.59 (91.08 – 94.09)	92.12 (87.03 – 97.21)	94.92 (91.93 – 97.9)
Poorly differentiated	73.21* (72.13 – 74.30)	74.58* (71.08 – 78.08)	68.52* (65.72 – 71.33)	92.42 (91.76 – 93.08)	86.82 (84.21 – 89.43)	92.25* (90.65 – 93.85)
Undifferentiated	72.69 * (71.11 – 74.27)	79.31* (73.64 – 84.98)	69.85* (65.47 – 74.23)	95.79 (94.98 – 96.60)	86.82 (82.42 – 91.23)	93.26 (91.01 – 95.51)
Unknown	75.41* (74.32 – 76.50)	77.15* (74.48 – 79.82)	68.01* (65.45 – 70.58)	68.14* (67.10 – 69.19)	52.41* (49.58 – 55.24)	71.39* (69.19 – 73.58)
Histology						
Serous	82.00 [ref] (81.19 – 82.82)	82.37 [ref] (79.81 – 84.92)	79.55 [ref] (77.35 – 81.76)	88.41 [ref] (87.83 – 89.00)	78.85 [ref] (76.49 – 81.20)	89.42 [ref] (88.03 – 90.81)
Mucinous	48.46 * (44.92 – 51.99)	56.88* (47.7 – 66.06)	43.12* (36.13 – 50.10)	86.61* (84.14 – 89.07)	68.82* (60.47 – 77.17)	83.13* (77.92 – 88.34)
Endometrioid	41.87* (39.18 – 44.56)	46.34 * (36.54 – 56.14)	40.68* (35.07 – 46.29)	93.02* (90.74 – 95.3)	83.24 (72.71 – 93.78)	94.43* (90.13 – 98.72)
Clear cell	37.54* (34.57 – 40.50)	58.20* (46.07 – 70.32)	36.09* (28.95 – 43.23)	94.62* (92.67 – 96.57)	83.44 (71.54 – 95.34)	90.81 (85.96 – 95.66)
Other or unspecified	68.15* (66.89 – 69.41)	70.21* (67.26 – 73.15)	63.17* (60.40 – 65.95)	75.21* (74.38 – 76.05)	61.98* (59.54 – 64.42)	76.20* (74.31 – 78.09)

Study Variables	Advanced Stage Diagnosis % [b] (95%CI)			Receipt of Surgery % [b] (95%CI)		
Contextual-level factors:						
Metro/nonmetro Residence [c]						
Metro	70.10 [ref] (69.47 – 70.73)	72.94 [ref] (71.11 – 74.78)	64.76 [ref] (63.28 – 66.23)	83.12 [ref] (82.70 – 83.54)	70.62 [ref] (69.13 – 72.11)	83.82 [ref] (82.88 – 84.76)
Nonmetro	69.03 (67.28 – 70.78)	70.6 0 (63.77 – 77.44)	67.63 (59.82 – 75.43)	83.19 (82.07 – 84.31)	64.71 (58.94 – 70.49)	80.64 (75.20 – 86.09)
County Education [d]						
Highest	70.45 [ref] (69.29 – 71.61)	71.21 [ref] (66.7 – 75.71)	62.72 [ref] (56.33 – 69.10)	83.60 [ref] (82.83 – 84.37)	69.54 [ref] (65.85 – 73.23)	86.94 [ref] (83.25 – 90.63)
Upper-middle	70.21 (69.03 – 71.40)	72.17 (68.69 – 75.65)	63.26 (58.68 – 67.84)	83.11 (82.33 – 83.88)	71.13 (68.37 – 73.90)	85.01 (82.24 – 87.79)
Lower-middle	69.92 (68.67 – 71.16)	73.80 (70.23 – 77.37)	63.82 (60.51 – 67.13)	82.74 (81.91 – 83.57)	71.70 (68.69 – 74.71)	83.37 (81.16 – 85.59)
Lowest	68.91 (67.35 – 70.46)	73.75 (69.18 – 78.31)	66.12 (63.55 – 68.68)	82.90 (81.89 – 83.92)	67.10 (63.28 – 70.91)	83.11 (81.44 – 84.77)
County Employment [e]						
Highest	69.32 [ref] (68.14 – 70.49)	78.36 [ref] (74.1 – 82.61)	64.56 [ref] (59.74 – 69.38)	83.34 [ref] (82.56 – 84.12)	72.28 [ref] (68.47 – 76.10)	84.85 [ref] (81.75 – 87.95)
Upper-middle	70.68 (69.50 – 71.87)	71.05* (66.22 – 75.88)	66.78 (63.17 – 70.40)	83.38 (82.58 – 84.17)	72.06 (68.25 – 75.88)	86.43 (84.10 – 88.76)
Lower-middle	70.16 (68.82 – 71.50)	71.34* (67.28 – 75.4)	62.33 (59.47 – 65.19)	83.40 (82.51 – 84.30)	71.62 (68.51 – 74.73)	83.72 (81.92 – 85.52)
Lowest	69.73 (68.35 – 71.12)	72.22* (68.82 – 75.62)	66.91 (63.64 – 70.18)	82.39 (81.49 – 83.30)	67.41 (64.51 – 70.30)	81.12 (78.91 – 83.33)

Study Variables	Advanced Stage Diagnosis % [b] (95%CI)			Receipt of Surgery % [b] (95%CI)		
County Poverty [f]						
Highest	69.04 [ref]	71.58 [ref]	64.37 [ref]	83.41 [ref]	67.83 [ref]	82.06 [ref]
	(67.75 – 70.33)	(66.13 – 77.04)	(59.65 – 69.09)	(82.55 – 84.26)	(63.25 – 72.41)	(78.63 – 85.48)
Upper-middle	69.69	70.92	62.15	82.75	67.84	82.01
	(68.51 – 70.87)	(66.02 – 75.82)	(57.88 – 66.41)	(81.96 – 83.55)	(63.83 – 71.85)	(78.91 – 85.12)
Lower-middle	70.41	73.26	66.14	83.67	71.55	84.1
	(69.07 – 71.74)	(69.53 – 77.00)	(63.54 – 68.73)	(82.80 – 84.54)	(68.6 – 74.50)	(82.52 – 85.67)
Lowest	71.03	73.42	65.20	82.67	70.60	85.22
	(69.51 – 72.54)	(70.06 – 76.79)	(60.75 – 69.65)	(81.67 – 83.67)	(67.77 – 73.43)	(82.70 – 87.73)

Notes: [a] Adjusted for all the variables listed and year of diagnosis. [b] Average adjusted predicted probabilities. [c] Metro vs. nonmetro categories are based on the Rural-Urban Continuum Codes (RUCC Codes: 1-3 vs. 4-9) from the Economic Research Service, U.S. Department of Agriculture. [d] Sorted by percentage of a county population with less than 9th grade education in ascending order, and categorized into quartiles. [e] Sorted by percentage of persons aged 16 and over who are unemployed in a county in ascending order, and categorized into quartiles. [f] Sorted by percentage of persons in a county whose incomes are below the 100% federal poverty level threshold in ascending order, and categorized into quartiles.

CI, confidence interval. [ref] reference group. * $p<0.05$

Appendix C: Table 4.1

Model with Insurance Status: Adjusted Hazard Ratios for Ovarian Cancer-Cause Specific Mortality [a]

Study Variables	Ovarian Cancer-Cause Specific Mortality (N=27,539) HR (95%CI)
Race/ethnicity	
Non-Hispanic White	Ref.
Non-Hispanic Black	0.79 (0.56 – 1.10)
Hispanic	0.80 (0.60 – 1.07)
Other	0.93 (0.61 – 1.40)
Age at diagnosis	
18-45	Ref.
46-55	1.29 (1.17 – 1.43)*
56-65	1.46 (1.33 – 1.61)*
66-75	1.78 (1.62 – 1.96)*
>=76	2.56 (2.32 – 2.82)*
Marital status	
Not married	Ref.
Married	0.86 (0.82 – 0.90)*
Insurance	
Uninsured	Ref.
Insured	0.80 (0.69 – 0.94)*
Stage	
Non-advanced	Ref.
Advanced	3.93 (3.63 – 4.26)*
Surgery	
No	Ref.
Yes	0.29 (0.27 – 0.31)*
Grade	
Well differentiated	Ref.
Moderately differentiated	2.11 (1.73 – 2.56)*
Poorly differentiated	2.75 (2.28 – 3.31)*
Undifferentiated	2.60 (2.14 – 3.15)*
Unknown	2.51 (2.08 – 3.03)*
Histology	
Serous	Ref.
Mucinous	1.77 (1.56 – 2.00)*
Endometrioid	0.75 (0.66 – 0.86)*
Clear cell	1.42 (1.26 – 1.59)*
Other or unspecified	1.35 (1.28 – 1.42)*

Study Variables	Ovarian Cancer-Cause Specific Mortality (N=27,539) HR (95%CI)
Interaction:	
Race/ethnicity * insurance	
NHW * uninsured	Ref.
NHB * insured	1.56 (1.11 – 2.20)*
Hispanic * insured	1.29 (0.96 – 1.73)
Other * insured	1.08 (0.71 – 1.65)
Contextual-level factors:	
Metro/nonmetro residence [b]	
Metro	Ref.
Nonmetro	1.13 (1.05 – 1.21)*
County education [c]	
Highest	Ref.
Upper-middle	0.96 (0.90 – 1.03)
Lower-middle	0.98 (0.91 – 1.05)
Lowest	1.00 (0.92 – 1.08)
County employment [d]	
Highest	Ref.
Upper-middle	0.93 (0.87 – 0.99)*
Lower-middle	0.96 (0.89 – 1.03)
Lowest	1.01 (0.94 – 1.09)
County poverty [e]	
Highest	Ref.
Upper-middle	1.05 (0.98 – 1.13)
Lower-middle	1.02 (0.94 – 1.10)
Lowest	1.05 (0.96 – 1.14)
Random effect	
County variance	0.0015

Notes: [a] Adjusted for all the variables listed in the table, year of diagnosis, interaction between race/ethnicity and insurance status, and county random effect. [b] Metro vs. nonmetro categories are based on the Rural-Urban Continuum Codes (RUCC Codes: 1-3 vs. 4-9) from the Economic Research Service, U.S. Department of Agriculture. [c] Sorted by percentage of a county population with less than 9th grade education in ascending order, and categorized into quartiles. [d] Sorted by percentage of persons aged 16 and over who are unemployed in a county in ascending order, and categorized into quartiles. [e] Sorted by percentage of persons in a county whose incomes are below the 100% federal poverty level threshold in ascending order, and categorized into quartiles.
HR, hazard ratio. CI, confidence interval. Ref., reference group. * $p<0.05$

Appendix D: Table 5.1

Models with Insurance Status: Factors Contributing to Disparities in Ovarian Cancer-Cause Specific Mortality, by Race/Ethnicity [a]

Study Variables	Ovarian Cancer-Cause Specific Mortality HR (95%CI)		
	Non–Hispanic White (n=19.328)	Non–Hispanic Black (n=2,278)	Hispanic (n=3,460)
Age at diagnosis			
18-45	Ref.	Ref.	Ref.
46-55	1.34 (1.17 – 1.53)*	1.18 (0.90 – 1.55)	1.30 (1.03 – 1.64)*
56-65	1.53 (1.35 – 1.74)*	1.24 (0.96 – 1.62)	1.49 (1.19 – 1.87)*
66-75	1.88 (1.66 – 2.14)*	1.31 (1.01 – 1.71)*	1.88 (1.48 – 2.39)*
>=76	2.75 (2.42 – 3.13)*	1.86 (1.42 – 2.45)*	2.55 (1.97 – 3.29)
Marital status			
Not married	Ref.	Ref.	Ref.
Married	0.84 (0.80 – 0.89)*	0.88 (0.75 – 1.02)	0.93 (0.81 – 1.07)
Insurance			
Uninsured	Ref.	Ref.	Ref.
Insured	0.79 (0.68 – 0.93)*	1.36 (0.99 – 1.86)	1.03 (0.8 – 1.34)
Stage			
Non-advanced	Ref.	Ref.	Ref.
Advanced	3.93 (3.57 – 4.33)*	2.94 (2.32 – 3.74)*	4.95 (3.88 – 6.33)*
Surgery			
No	Ref.	Ref.	Ref.
Yes	0.30 (0.28 – 0.33)*	0.29 (0.24 – 0.35)*	0.26 (0.21 – 0.31)*
Grade			
Well differentiated	Ref.	Ref.	Ref.
Moderately differentiated	2.05 (1.62 – 2.59)*	2.15 (1.17 – 3.95)*	2.04 (1.19 – 3.49)*
Poorly differentiated	2.67 (2.14 – 3.34)*	3.11 (1.79 – 5.41)*	2.82 (1.69 – 4.68)*
Undifferentiated	2.48 (1.97 – 3.12)*	3.26 (1.81 – 5.86)*	2.82 (1.66 – 4.78)*
Unknown	2.57 (2.05 – 3.22)*	2.43 (1.39 – 4.23)*	2.09 (1.25 – 3.50)*
Histology			
Serous	Ref.	Ref.	Ref.
Mucinous	1.69 (1.45 – 1.97)*	2.12 (1.53 – 2.95)*	2.31 (1.66 – 3.20)*
Endometrioid	0.75 (0.64 – 0.88)*	0.57 (0.34 – 0.96)*	1.08 (0.77 – 1.50)
Clear cell	1.31 (1.13 – 1.51)*	1.73 (1.09 – 2.75)*	2.43 (1.72 – 3.43)*
Other or unspecified	1.30 (1.22 – 1.38)*	1.43 (1.22 – 1.68 *	1.65 (1.41 – 1.93)*
Contextual-Level Factors:			

Study Variables	Ovarian Cancer-Cause Specific Mortality HR (95%CI)		
	Non–Hispanic White (n=19.328)	Non–Hispanic Black (n=2,278)	Hispanic (n=3,460)
Metro/nonmetro residence [b]			
Metro	Ref.	Ref.	Ref.
Nonmetro	1.14 (1.05 – 1.23)*	1.07 (0.82 – 1.39)	1.20 (0.87 – 1.66)
County education [c]			
Highest	Ref.	Ref.	Ref.
Upper-middle	0.95 (0.88 – 1.02)	1.02 (0.82 – 1.28)	1.10 (0.79 – 1.52)
Lower-middle	0.98 (0.91 – 1.06)	0.96 (0.75 – 1.21)	1.12 (0.83 – 1.52)
Lowest	0.95 (0.87 – 1.04)	1.18 (0.93 – 1.49)	1.17 (0.84 – 1.62)
County employment [d]			
Highest	Ref.	Ref.	Ref.
Upper-middle	0.93 (0.87 – 1.00)	0.85 (0.66 – 1.09)	0.80 (0.62 – 1.03)
Lower-middle	0.99 (0.92 – 1.07)	0.92 (0.73 – 1.15)	0.73 (0.56 – 0.96)*
Lowest	0.98 (0.91 – 1.07)	1.14 (0.91 – 1.43)	0.84 (0.65 – 1.08)
County poverty [e]			
Highest	Ref.	Ref.	Ref.
Upper-middle	1.06 (0.99 – 1.14)	0.97 (0.75 – 1.26)	0.80 (0.62 – 1.03)
Lower-middle	1.03 (0.95 – 1.12)	0.89 (0.69 – 1.15)	0.73 (0.56 – 0.96)
Lowest	1.12 (1.02 – 1.22)*	0.76 (0.59 – 0.99)*	0.84 (0.65 – 1.08)

Notes: [a] Adjusted for all the variables listed in the table and year of diagnosis. [b] Metro vs. nonmetro categories are based on the Rural-Urban Continuum Codes (RUCC Codes: 1-3 vs. 4-9) from the Economic Research Service, U.S. Department of Agriculture. [c] Sorted by percentage of a county population with less than 9th grade education in ascending order, and categorized into quartiles. [d] Sorted by percentage of persons aged 16 and over who are unemployed in a county in ascending order, and categorized into quartiles. [e] Sorted by percentage of persons in a county whose incomes are below the 100% federal poverty level threshold in ascending order, and categorized into quartiles.

HR, hazard ratio. CI, confidence interval. Ref., reference group. * $p<0.05$

Appendix E: Table 6

Racial/ethnic Disparities in Advanced Stage Diagnosis, Receipt of Surgery and Survival: Trend over time, 2001-2012

Year	Late Stage Diagnosis (OR)			Receipt of Surgery (OR)			Ovarian Cancer Mortality (HR)		
	NHW vs. NHB	NHW vs. Hispanic	NHB vs. Hispanic	NHW vs. NHB	NHW vs. Hispanic	NHB vs. Hispanic	NHW vs. NHB	NHW vs. Hispanic	NHB vs. Hispanic
2001	1.06	0.89	0.75	0.39	1.23	3.91	1.52	1.02	0.72
2002	1.24	1.17	0.79	0.46	0.75	1.47	1.03	0.84	0.73
2003	1.02	1.15	1.17	0.44	0.61	1.40	1.47	0.98	0.68
2004	0.99	1.07	1.14	0.50	0.83	1.86	1.24	0.94	0.72
2005	0.96	1.06	1.03	0.61	0.93	1.73	1.28	0.98	0.66
2006	1.05	0.68	0.60	0.33	1.14	3.63	1.17	1.14	0.95
2007	0.98	1.19	0.98	0.33	0.77	2.24	1.21	1.00	0.72
2008	1.27	1.02	0.73	0.53	0.62	1.36	1.17	0.94	0.76
2009	1.10	1.17	0.89	0.56	0.67	1.19	1.22	1.22	1.01
2010	1.02	1.08	1.07	0.53	0.82	1.52	1.21	1.16	0.94
2011	1.01	0.76	0.78	0.64	0.82	1.54	1.18	0.82	0.6
2012	1.52	1.22	0.71	0.56	0.84	1.56	1.02	0.99	0.73
AAPC*(%)	1.24	0.00	-1.28	2.95	-1.09	-3.86	-1.48	1.12	1.57
P value	0.30	1.00	0.50	0.10	0.55	0.20	0.17	0.32	0.29

OR, odds, ratio. *Average Annual Percent Change

Appendix F: Table 2.2

Adjusted Odds Ratio of Advanced Stage Diagnosis and Receipt of Surgery [a]

Study Variables	Advanced Stage Diagnosis (N=54,580) OR (95%CI)	Receipt of Surgery (N=54,580) OR (95%CI)
Race/ethnicity		
Non-Hispanic White	Ref.	Ref.
Non-Hispanic Black	1.47 (1.18 – 1.84)*	0.48 (0.43 – 0.54)*
Hispanic	0.90 (0.75 – 1.09)	0.82 (0.74 – 0.92)*
Other	1.12 (0.95 – 1.31)	0.82 (0.71 – 0.94)*
Age at diagnosis		
18-45	Ref.	Ref.
46-55	1.68 (1.57 – 1.80)*	0.41 (0.35 – 0.48)*
56-65	2.38 (2.23 – 2.55)*	0.25 (0.21 – 0.29)*
66-75	3.04 (2.83 – 3.27)*	0.16 (0.14 – 0.18)*
>=76	3.93 (3.63 – 4.25)*	0.06 (0.05 – 0.07)*
Marital status		
Not married	Ref.	Ref.
Married	0.95 (0.90 – 0.99)*	1.53 (1.43 – 1.64)*
Stage		
Non-advanced	Ref.	Ref.
Advanced	–	0.10 (0.09 – 0.11)
Grade		
Well differentiated	Ref.	Ref.
Moderately differentiated	2.28 (2.07 – 2.51)*	1.13 (0.84 – 1.51)
Poorly differentiated	4.95 (4.52 – 5.42)*	1.00 (0.77 – 1.32)
Undifferentiated	4.67 (4.20 – 5.19)*	1.56 (1.16 – 2.09)*
Unknown	4.66 (4.25 – 5.11)*	0.10 (0.07 – 0.12)*
Histology		
Serous	Ref.	Ref.
Mucinous	0.19 (0.17 – 0.21)*	0.49 (0.42 – 0.58)*
Endometrioid	0.15 (0.14 – 0.16)*	1.54 (1.21 – 1.96)*
Clear cell	0.11 (0.10 – 0.12)*	1.81 (1.42 – 2.30)*
Other or unspecified	0.45 (0.42 – 0.47)*	0.18 (0.16 – 0.19)*
Interaction: race/ethnicity*county employment		
NHW * highest	Ref.	
NHB * upper middle	0.76 (0.56 – 1.01)	–
NHB * lower middle	0.71 (0.54 – 0.93)*	–

NHB * lowest	0.71 (0.54 – 0.92)*	–
Hispanic * upper middle	1.12 (0.88 – 1.42)	–
Hispanic * lower middle	1.14 (0.92 – 1.42)	–
Hispanic * lowest	1.17 (0.93 – 1.49)	–
Other * upper middle	0.83 (0.66 – 1.04)	–
Other * lower middle	0.71 (0.58 – 0.87)*	–
Other * lowest	0.88 (0.67 – 1.17)	–
Contextual-level factors:		
Metro/nonmetro residence [b]		
Metro	Ref.	Ref.
Nonmetro	0.98 (0.90 – 1.05)	0.94 (0.83 – 1.05)
County education [c]		
Highest	Ref.	Ref.
Upper-middle	0.94 (0.87 – 1.01)	1.04 (0.91 – 1.18)
Lower-middle	0.97 (0.89 – 1.05)	0.99 (0.86 – 1.14)
Lowest	0.93 (0.84 – 1.01)	1.03 (0.89 – 1.19)
County employment [d]		
Highest	Ref.	Ref.
Upper-middle	1.06 (0.98 – 1.15)	0.99 (0.88 – 1.11)
Lower-middle	1.07 (0.99 – 1.17)	1.00 (0.88 – 1.13)
Lowest	1.02 (0.93 – 1.13)	0.89 (0.78 – 1.03)
County poverty [e]		
Highest	Ref.	Ref.
Upper-middle	1.04 (0.97 – 1.13)	0.90 (0.79 – 1.03)
Lower-middle	1.13 (1.03 – 1.24)*	0.91 (0.78 – 1.06)
Lowest	1.16 (1.05 – 1.28)*	0.89 (0.76 – 1.05)
Random effect		
County variance	0.007	0.0451*

Notes: [a] Adjusted for all the variables listed in the table, year of diagnosis, interaction between race/ethnicity and county employment, and county random effects. [b] Metro vs. nonmetro categories are based on the Rural-Urban Continuum Codes (RUCC Codes: 1-3 vs. 4-9) from the Economic Research Service, U.S. Department of Agriculture. [c] Sorted by percentage of a county population with less than 9th grade education in ascending order, and categorized into quartiles. [d] Sorted by percentage of persons aged 16 and over who are unemployed in a county in ascending order, and categorized into quartiles. [e] Sorted by percentage of persons in a county whose incomes are below the 100% federal poverty level threshold in ascending order, and categorized into quartiles.

OR, odds ratio. CI, confidence interval. Ref. reference group. * $p<0.05$

Appendix G: Table 3.2

Factors Contributing to Disparities in Advanced Stage Diagnosis and Receipt of Surgery, by Race/Ethnicity (Odds Ratio) [a]

Study Variables	Advanced Stage Diagnosis OR(95%CI)			Receipt of Surgery OR (95%CI)		
	Non–Hispanic White (n=39,726)	Non–Hispanic Black (n=4,295)	Hispanic (n=6,256)	Non–Hispanic White (n=39,726)	Non–Hispanic Black (n=4,295)	Hispanic (n=6,256)
Age at diagnosis						
18-45	Ref.	Ref.	Ref.	Ref.	Ref.	Ref
46-55	1.71 (1.56 – 1.86)*	1.67 (1.33 – 2.10)*	1.74 (1.48 – 2.06)*	0.45 (0.36 – 0.57)*	0.48 (0.33 – 0.68)*	0.27 (0.19 – 0.38)*
56-65	2.38 (2.18 – 2.59)*	2.43 (1.93 – 3.05)*	2.63 (2.19 – 3.15)*	0.25 (0.21 – 0.31)*	0.28 (0.20 – 0.39)*	0.24 (0.17 – 0.33)*
66-75	3.03 (2.77 – 3.32)*	2.88 (2.25 – 3.68)*	3.28 (2.68 – 4.02)*	0.16 (0.13 – 0.20)*	0.18 (0.13 – 0.25)*	0.14 (0.10 – 0.19)*
>=76	3.95 (3.60 – 4.34)*	4.03 (3.05 – 5.31)*	3.70 (2.92 – 4.68)*	0.06 (0.05 – 0.07)*	0.09 (0.06 – 0.13)*	0.05 (0.03 – 0.07)*
Marital status						
Not married	Ref.	Ref.	Ref.	Ref.	Ref.	Ref
Married	0.94 (0.89 – 0.99)*	0.88 (0.74 – 1.04)	0.93 (0.82 – 1.06)	1.59 (1.47 – 1.72)*	1.51 (1.22 – 1.86)*	1.31 (1.08 – 1.60)*
Stage						
Non-advanced	Ref.	Ref.	Ref.	Ref.	Ref.	Ref
Advanced	–	–	–	0.11 (0.09 – 0.12)*	0.11 (0.08 – 0.14)*	0.06 (0.04 – 0.08)*
Grade						
Well differentiated	Ref.	Ref.	Ref.	Ref.	Ref.	Ref
Moderately differentiated	2.18 (1.95 – 2.45)*	2.80 (1.95 – 4.02)*	2.74 (2.09 – 3.60)*	1.30 (0.93 – 1.81)	0.51 (0.17 – 1.53)	0.75 (0.27 – 2.10)
Poorly differentiated	4.78 (4.29 – 5.33)*	5.38 (3.83 – 7.55)*	5.06 (3.91 – 6.53)*	1.25 (0.92 – 1.69)	0.35 (0.12 – 0.99)*	0.63 (0.24 – 1.64)
Undifferentiated	4.48 (3.96 – 5.07)*	5.64 (3.72 – 8.53)*	5.17 (3.79 – 7.03)*	2.14 (1.53 – 2.99)*	0.40 (0.13 – 1.20)	0.67 (0.24 – 1.83)
Unknown	4.66 (4.17 – 5.20)*	5.42 (3.89 – 7.55)*	4.38 (3.40 – 5.64)*	0.11 (0.08 – 0.15)*	0.04 (0.01 – 0.11)*	0.06 (0.02 – 0.16)*
Histology						
Serous	Ref.	Ref.	Ref.	Ref.	Ref.	Ref
Mucinous	0.18 (0.16 – 0.20)*	0.26 (0.19 – 0.36)*	0.21 (0.17 – 0.27)*	0.49 (0.40 – 0.60)*	0.47 (0.30 – 0.75)*	0.55 (0.35 – 0.88)*
Endometrioid	0.14 (0.13 – 0.15)*	0.16 (0.12 – 0.22)*	0.17 (0.14 – 0.21)*	1.45 (1.09 – 1.92)*	1.26 (0.65 – 2.44)	2.32 (1.03 – 5.25)*
Clear cell	0.11 (0.10 – 0.12)*	0.17 (0.11 – 0.26)*	0.13 (0.10 – 0.17)*	2.05 (1.51 – 2.78)*	0.90 (0.42 – 1.95)	1.19 (0.64 – 2.21)

Study Variables	Advanced Stage Diagnosis OR(95%CI)			Receipt of Surgery OR (95%CI)		
	Non–Hispanic White (n=39,726)	Non–Hispanic Black (n=4,295)	Hispanic (n=6,256)	Non–Hispanic White (n=39,726)	Non–Hispanic Black (n=4,295)	Hispanic (n=6,256)
Other or unspecified	0.47 (0.44 – 0.50)*	0.42 (0.34 – 0.51)*	0.39 (0.34 – 0.46)*	0.17 (0.16 – 0.19)*	0.22 (0.18 – 0.27)*	0.17 (0.14 – 0.22)*
Contextual-Level Factors:						
Metro/nonmetro Residence [b]						
Metro	Ref.	Ref.	Ref.	Ref.	Ref.	Ref
Nonmetro	0.98 (0.91 – 1.07)	0.78 (0.58 – 1.06)	0.95 (0.67 – 1.35)	1.01 (0.89 – 1.16)	0.86 (0.60 – 1.23)	0.79 (0.47 – 1.34)
County Education [c]						
Highest	Ref.	Ref.	Ref.	Ref.	Ref.	Ref
Upper-middle	0.94 (0.87 – 1.01)	1.02 (0.78 – 1.33)	0.88 (0.65 – 1.21)	1.03 (0.90 – 1.19)	1.27 (0.92 – 1.76)	0.85 (0.51 – 1.41)
Lower-middle	0.95 (0.86 – 1.04)	1.23 (0.92 – 1.64)	1.02 (0.74 – 1.39)	0.98 (0.84 – 1.15)	1.15 (0.82 – 1.63)	0.84 (0.52 – 1.36)
Lowest	0.92 (0.83 – 1.02)	1.10 (0.81 – 1.48)	0.97 (0.70 – 1.35)	0.97 (0.81 – 1.16)	0.95 (0.66 – 1.37)	0.97 (0.58 – 1.62)
County Employment [d]						
Highest	Ref.	Ref.	Ref.	Ref.	Ref.	Ref
Upper-middle	1.06 (0.98 – 1.15)	0.77 (0.57 – 1.05)	1.19 (0.92 – 1.54)	1.01 (0.89 – 1.15)	0.94 (0.66 – 1.35)	0.84 (0.56 – 1.26)
Lower-middle	1.07 (0.99 – 1.17)	0.71 (0.54 – 0.95)*	1.09 (0.82 – 1.45)	0.95 (0.83 – 1.10)	1.20 (0.86 – 1.68)	0.74 (0.48 – 1.15)
Lowest	1.04 (0.95 – 1.15)	0.66 (0.49 – 0.90)*	1.06 (0.78 – 1.42)	0.98 (0.83 – 1.15)	0.76 (0.53 – 1.09)	0.62 (0.39 – 0.97)*
County Poverty [e]						
Highest	Ref.	Ref.	Ref.	Ref.	Ref.	Ref
Upper-middle	1.05 (0.97 – 1.14)	1.04 (0.76 – 1.41)	1.01 (0.77 – 1.32)	0.90 (0.77 – 1.04)	0.86 (0.59 – 1.25)	1.03 (0.69 – 1.55)
Lower-middle	1.11 (1.01 – 1.22)*	1.09 (0.80 – 1.48)	1.22 (0.90 – 1.63)	0.91 (0.77 – 1.08)	1.04 (0.72 – 1.51)	0.88 (0.57 – 1.37)
Lowest	1.14 (1.02 – 1.28)*	1.25 (0.91 – 1.72)	1.37 (0.99 – 1.91)	0.80 (0.66 – 0.97)*	1.14 (0.78 – 1.68)	1.00 (0.61 – 1.62)
Random Effect						
County Variance	0.0031	<0.0001	0.0248	0.0527*	<0.0001	<0.0001

Notes: [a] Adjusted for all the variables listed in the table, year of diagnosis and county random effects. [b] Metro vs. nonmetro categories are based on the Rural-Urban Continuum Codes (RUCC Codes: 1-3 vs. 4-9) from the Economic Research Service, U.S. Department of Agriculture. [c] Sorted by percentage of a county

population with less than 9th grade education in ascending order, and categorized into quartiles. [d] Sorted by percentage of persons aged 16 and over who are unemployed in a county in ascending order, and categorized into quartiles. [e] Sorted by percentage of persons in a county whose incomes are below the 100% federal poverty level threshold in ascending order, and categorized into quartiles.

OR, odds ratio. CI, confidence interval. Ref. reference group. * $p<0.05$