Survival Disparity in Black & White Women with Ovarian Cancer:

The Role of Mediators and Contextual Factors

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THESIS

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LIST OF ABBREVIATIONS

95% CI	95% Confidence Interval
AAIR	Age-adjusted Incidence Rate
AJCC	American Joint Committee on Cancer
APC	Annual Percent Change
BOCS	Breast-Ovarian Cancer Syndrome
BRCA1	Breast Cancer 1 Gene
BRCA2	Breast Cancer 2 Gene
CA125	Cancer Antigen 125
DNA	Deoxyribonucleic Acid
FIGO	Féderation Internationale de Gynécologie et d'Obstétrique
FSH	Follicle-stimulating Hormone
HR	Hazard Ratio
HNPCC	Hereditary Nonpolyposis Colon Cancer
HRT	Hormone Replacement Therapy
ICD	International Classification of Diseases
IP	Intraperitoneal
IR	Incidence Rate
IRR	Incidence Rate Ratio
IV	Intraveneous
LH	Luteinizing Hormone
MR	Mortality Rate

LIST OF ABBREVIATIONS (continued)

NAACCR	North American Association of Central Cancer Registries
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institutes
NCHS	National Center for Health Statistics
NDI	National Death Index
OC	Oral Contraceptives
OSE	Ovarian Surface Epithelium
RCT	Randomized Control Trial
RR	Relative Risk
SEER	Surveillance Epidemiology and End Results
SE	Standard Error
SES	Socioeconomic Status
TNM	Tumor Node Metastasis
WHO	World Health Organization

SUMMARY

Despite treatment advances in recent decades, ovarian cancer remains one of the most lethal cancers. This is due primarily to the fact that most women are diagnosed at a late stage, when treatment is far less successful. The National Cancer Institute (NCI) estimates that, of the 21,990 new cases of ovarian cancer diagnosed in 2011 in the United States, more than 15,000 women will ultimately die from their disease (www.cancer.gov, accessed November 28, 2011).

Across study populations, the incidence of ovarian cancer has been consistently higher in White women than in Black women (Goodman et al. 2003; Goodman et al. 2009). A recent analysis of SEER data shows that the mortality rate, measured by the average annual percent change (APC), for ovarian cancer has declined (Alterkruse 2010), although this improvement has been greater for White women (APC = -1.6) than for Black women (APC = - 0.4). Differences in survival between Black and White women with ovarian cancer have been shown to exist at all stages of disease, with Blacks having consistently poorer survival than Whites (Chan et al. 2008; Terplan et al. 2008; Terplan et al. 2009). Indeed, a previous analysis of a subset of our cases has demonstrated a significant survival disparity within stage (Kim et al. 2010).

The goal of this project was to develop a new understanding of the factors that contribute to the observed differences in survival between Blacks and White women diagnosed with epithelial ovarian cancer (hereinafter, "ovarian cancer")[1] in the United States.

[1] Epithelial ovarian cancer are tumors of epithelial cell origin, which is the predominant cell type (90% of ovarian cancer tumors) and are distinct from germ cell and stromal tumors both in terms of etiology and prognosis.

I. INTRODUCTION

A. Aims and Hypotheses

We hypothesize that variables traditionally treated as either confounders or effect modifiers are instead intermediate variables, and that they partly account for racial disparities in ovarian cancer survival. We further hypothesize that neighborhood context mitigates the effect of race on survival. This dissertation project will used cases of ovarian cancer from a population-based case-control study conducted in Cook County, Illinois between 1994 and 1998.[2] Although differences in both incidence and survival exist among women of other racial and ethnic groups, these differences are not as pronounced as those between Black and White women. Moreover, data from this case-control study do not contain adequate numbers of non-White or non-Black cases, so this analysis will be confined to Blacks and Whites. The specific aims are described in detail as follows.

1. Aim 1

We evaluated patient characteristics (including self-reported race), proxy measures of healthcare access, socioeconomic status, and tumor characteristics in order to determine significant predictors of late-stage diagnosis. In addition, we examined whether or not these predictors of late-stage disease differed by race. We hypothesized that there would be racial differences in early- and late-stage diagnosis, and that predictors of late-stage diagnosis would differ by race.

2. Aim 2

We began our work with area-level measures of concentrated disadvantage and affluence by estimating the effects of neighborhood context and individual-level prognostic factors on the observed

[2] Case-control study conducted in Cook County, Illinois between 1994 and 1998. F.G. Davis.

survival disparity between Black and White women with ovarian cancer. We hypothesized that neighborhood context would have a significant independent effect on the racial disparity in survival, such that greater concentrated disadvantage would mitigate the effect of race, and further, that greater concentrated affluence would reduce the risk of shorter survival in both Black and White women diagnosed with ovarian cancer.

3. **Aim 3**

We evaluated available covariates related to three domains—i.e., socioeconomic environment, hormonal and reproductive factors, and tumor characteristics—in order to determine whether they were mediators in the pathway between race and disparate survival. We hypothesized that the domains, and the individual components within them, would account for the racial disparity in five-year survival.

B. Background and Significance

1. The biology of epithelial ovarian cancer

a. Ovarian function

The ovarian follicle consists of the oocyte, which represents the "reproductive cargo" of the follicle, and the somatic cells that function as the ovarian "nurse" cells. The major stages of ovarian folliculogenesis are the formation of the primordial follicle; recruitment into the growing pool to form a primary, secondary, and tertiary follicle; and lastly, ovulation and subsequent formation of a corpus luteum (Edson et al. 2009). At birth women have approximately 400,000 follicles within each ovary. This number is reduced as women age, with none present after menopause. Follicles remain in a primary follicle stage until puberty. The first event for a maturing follicle is an increase in size of the primary oocytes. In this stage, fluid-filled spaces appear among the follicle cells, which unite to form a cavity or

Gaafian follicle. Primary oocytes undergo two nuclear divisions which produce four cells, with each division resulting in one-half of the original number of chromosomes. The first meiotic division occurs within the ovary just before ovulation, and the second division occurs immediately after the sperm enters the egg.

Secondary oocytes enter the next cycle of division very rapidly, producing one ovum and three ova, which subsequently degenerate. The ovum is released from the ovary at this secondary stage, triggering the second meiotic division in the oviduct by the entry of the sperm.

The cyclic release of pituitary gonadotropins determines ovulation. Specific gonadotropins such as luteinizing hormone (LH) and follicle-stimulating hormone (FSH) play a key role in two important ovarian carcinogenesis hypotheses described below.

b. **Symptoms and clinical detection of ovarian tumors**

The lack of clinical signs and symptoms means that most cases of ovarian cancer are diagnosed at late stages (III/IV) when the prognosis is poor. Early-stage disease has non-specific symptoms including irregular menses, abdominal or pelvic pain, dyspareunia (painful intercourse), and/or changes in bowel or bladder habits. Advanced-stage disease is more likely to have symptoms, but these too are often non-specific symptoms, including abdominal bloating/distention, early satiety, nausea, constipation, and/or dyspnea (shortness of breath). An adnexal (pelvic) mass on examination is the most common sign of ovarian cancer—particularly in postmenopausal women where the ovaries have become nonpalpable. Ascites, abdominal distention, and/or symptoms such as pelvic or abdominal pain, early satiety, and/or urinary symptoms are all key to the detection of ovarian cancer (NCCN Guidelines V2.2011).

Currently there is no population-based screening tool for ovarian cancer (MacDonald et al. 1998). The cell surface glycoprotein, CA-125, is shed from the surface of damaged cells and which can be elevated in certain malignant conditions, has been considered as a screening test and has some utility as a

tumor marker to assess response to treatment and as a marker for recurrent ovarian cancer (Verheijen et al. 1999). The combination of routine pelvic exams, transvaginal ultrasound, and CA-125 levels, while expensive and relatively invasive, has been shown to increase the sensitivity and specificity of screening for ovarian cancer (Jacobs et al. 1993; Schutter et al. 1998).

In the presence of a suspicious pelvic mass, the clinician will obtain the patient's family history to determine risk level. A complete workup consists of an abdominal/pelvic exam, gastrointestinal evaluation (where clinically indicated), ultrasound and/or abdominal/pelvic scan, chest imaging, complete blood count (CBC), CA-125 or other tumor markers (where clinically indicated), and a chemistry profile with liver function test (NCCN Guidelines V2.2011).

c. **Epithelial sub-types**

Ovarian tumors originate from one of three cell types: epithelial cells, stromal cells, and germ cells. More than 90% of ovarian tumors are epithelial, while sex cord-stromal and germ cell tumors account for 5-6% and 2-3%, respectively (Sankaranarayanan et al. 2006). There are six distinct histological sub-types of epithelial ovarian cancer based on cell morphology: serous, mucinous, endometrioid, clear cell, undifferentiated, and unclassified (Benedet 2000). Histologic sub-type is an important prognostic factor for ovarian cancer. For example, compared to serous tumors, both mucinous and clear cell tumors have been associated with decreased overall survival as well as progression-free survival, while endometrioid tumors have demonstrated significantly increased survival (Omura et al. 1991; Akahira et al. 2001; Winter et al. 2007) (TABLE I).

TABLE I

SURVIVAL TIME BY HISTOLOGICAL SUB-TYPE (Akahira et al. 2001)

Epithelial sub-types	Hazard Ratio (95% CI)
Serous (Reference)	1.0
Mucinous	2.43 (1.23-3.62)
Clear Cell	2.64 (1.44-3.84)
Endometrioid	0.90 (0.61-1.20)

Within each of these sub-types, tumors are further classified in terms of their malignant potential ("malignant" or "borderline," i.e., tumors of low malignant potential). Thus, a high-grade serous tumor is classified as a malignant tumor, while a low-grade serous tumor is classified as borderline.

There is a growing body of evidence that serous tumors, which are the most common sub-type, may actually represent two distinct histologies, with different underlying pathogeneses, molecular events, behaviors, and prognoses (Vang et al. 2009; McCluggage 2011). In spite of their initial response to chemotherapy, high-grade serous tumors commonly recur, and the survival of women with these tumors is significantly shorter than the survival of women with the less common low-grade serous tumors (Malpica et al. 2004).

d. **Genetic and molecular epidemiology**

Oncogenic transformation occurs as the result of accumulated mutational events, which are facilitated by genetic instability. There is evidence that mutations in DNA repair and replication genes are present in >58% of cancer cell lines, suggesting that the genetic instability derived from these changes is a feature of most cancers (Poulogiannis et al. 2010). The DNA repair mechanism is critical for genetic stability. The process of DNA repair induces apoptosis of damaged cells and insures that base-to-base mismatches are corrected during DNA replication.

As with other cancers, ovarian tumors develop through a process of accumulated mutations in a number of genes, including tumor-suppressor genes and proto-oncogenes. Family history is one of the strongest risk factors for disease. Women with one first-degree relative with ovarian cancer are estimated to have a 5% lifetime risk of developing the disease, while women with two first-degree relatives are estimated to have a 7% lifetime risk (Werness et al. 2001; Pharoah et al. 2002). Germ line mutations in genes associated with ovarian tumors occur in two hereditary syndromes, which together account for slightly less than 10% of all ovarian cancers (Lynch et al. 1998).

Approximately 90% of hereditary cancers are associated with the Breast-Ovarian Cancer Syndrome (BOCS), which involves mutations in the BRCA1 and BRCA2 tumor suppressor genes (Risch et al. 2001; Prat et al. 2005). The location within BRCA1/2 determines the development of either breast or ovarian cancer. Mutations in BRCA1 are more common in women with hereditary ovarian cancer than are mutations in BRCA2. Estimates of the disease penetrance associated with BRCA1 and BRCA2 mutations vary considerably. The BRCA1 mutation carries an estimated 40-60% lifetime risk of developing ovarian cancer, while BRCA2 carries an estimated risk of 10-20% (Easton et al. 1995).

Both BRCA1 and BRCA2 are large tumor suppressor genes located on chromosomes 17q21 and 12q12-13, respectively. They have a similar structure, with many coding exons and a large coding exon that occupies half of the coding region (Miki et al. 1994; Tavtigian et al. 1996; Prat et al. 2005). Both BRCA1 and BRCA2 proteins have similar multiple functions, including DNA repair, transcriptional regulation of gene expression, and cell cycle control (Scully et al. 2000). Women with BOCS carry a germ line BRCA mutation in which somatic loss of the second allele leads to BRCA inactivation and eventual development of carcinoma (Prat et al. 2005).

Lynch Syndrome, also called hereditary nonpolyposis colon cancer (HNPCC), is an autosomal dominant syndrome and is the second syndrome associated with an increased risk of ovarian cancer—accounting for approximately 10% of hereditary cancers (Risch et al. 2001; Prat et al. 2005). Ovarian cancer occurs in 5-10% of female HNPCC patients. Generally, HNPCC is caused by mutations in genes involved in DNA mismatch repair.

Microsatellites are stretches of DNA in which a short pattern of 1 to 5 nucleotides is repeated (repeat units). The HNPCC cells exhibit microsatellite instability, a genetic alteration in which a germ line microsatellite allele has gained or lost repeat units. HNPCC patients carry a mutation in one of the mismatch repair genes, primarily hMSH2 and hMLH1, although hPMS1and hPMS2 are also involved (Prat et al. 2005) (Lynch et al. 1998). Somatic loss of the second allele leads to gene inactivation and development of carcinoma (Prat et al. 2005).

While family history of specific cancers is an important risk factor for ovarian cancer, most cases are sporadic. Epithelial tissue generally requires five to six genetic events in cells undergoing malignant transformation in order for cancer to develop (Vogelstein et al. 1993). Even in women with inherited susceptibility at BRCA1/2, tumorigenesis is associated with the subsequent loss of the remaining wild-type allele (Szabo et al. 1995). Among sporadic cases, loss of heterozygosity in tumor tissue has been estimated at more than 70% (Szabo et al. 1995).

Finally, numerous somatic alterations in a number of loci other than BRCA1/2 are involved in ovarian cancer, including amplification/overexpression of oncogenes, mutations or losses in tumor suppressor genes, and replication-error-repeat phenomenon (Porter-Jordan et al. 1994; Jones et al. 1995; Liu et al. 1995; Teneriello et al. 1995; Newman et al. 1997). Both GATA4 and GATA6 are transcription factors that are expressed in a variety of tissues, including the ovaries. They are important upstream

factors during the primitive endoderm (an epithelial cell type) differentiation of pluripotent embryonic stem cells (Capo-chichi et al. 2003). Recent studies suggest that the expression of the transcription factors GATA6 and GATA4 vary by histological sub-type. For example, loss of GATA4 and GATA6 was found in 99% and 67% of serous tumors, respectively, while GATA4 and GATA6 were both expressed in 92% of mucinous tumors (Cai et al. 2009).

e. **Cellular origin of ovarian epithelial tumors**

The ovarian surface epithelium was among the least studied parts of the ovary until it became apparent that it might be the tissue of origin for epithelial ovarian tumors (Choi et al. 2007). However, debate remains concerning the cellular and molecular mechanisms by which the ovarian surface epithelium (OSE) undergoes malignant transformation and neoplastic progression.

The dominant hypothesis regarding the cellular origin of ovarian epithelial tumors is that these tumors arise from the OSE and its inclusion cysts (Auersperg et al. 2001; Tung et al. 2003). The OSE is the "modified pelvic mesothelium that covers the ovary" and can take on "phenotypic characteristics of Müllerian (usually tubal) epithelium" (Auersperg et al. 2001). The role of the OSE was questioned because of the lack of experimental models (both human and animal). However, in the 1980s information about the normal functions of the OSE and its relationship to ovarian cancer began to emerge, and studies have shown the capacity of the OSE to give rise to ovarian adenocarcinomas (Auersperg et al. 1998; Ong et al. 2000; Auersperg et al. 2001).

Rather than the surface OSE, OSE-lined clefts (invaginations) and inclusion cysts are common sites of early neoplastic progression (Deligdisch et al. 1995; Scully 1995). Inclusion cysts have been hypothesized to form from OSE fragments that are trapped in or near ruptured follicles at the time of ovulation (Radisavljevic 1977; Murdoch 1994). An alternative theory is that they arise through inflammatory

adhesions of surface OSE which becomes apposed at sites of surface invaginations (clefts), combined with localized stromal proliferation" (Scully 1995).

The OSE transports materials to and from the peritoneal cavity and takes part in cyclical ovulatory ruptures and repair. It must proliferate in order to repair defects in the surface of the ovary and has the capacity to alter its state of differentiation along pathways leading to stromal or aberrant epithelial phenotypes, depending upon whether the response to stimuli is one of repair or rupture. As a repair response, OSE cells assume phenotypic characteristics of stromal cells. Alternatively, the OSE acquires epithelial characteristics of the Müllerian duct-derived epithelia (i.e., of the oviduct, endometrium, and endocervix) when it undergoes metaplasia, benign tumor formation, and neoplastic progression (Auersperg et al. 2001). The progression to malignancy leads the OSE to lose its stromal characteristics and to acquire the characteristics of the Müllerian duct-derived epithelia, and this feature has led some to hypothesize that epithelial tumors originate outside the ovary.

Scully has noted that different histologic sub-types of epithelial ovarian cancer resemble the phenotypes of different organs of the female genital tract (TABLE II). Others have suggested that the epithelial lining of the fallopian tube may provide an alternative site of origin for high-grade serous tumors in BRCA mutation positive women" (Dubeau,1999; Crum, 2007; Lee, 2007).

TABLE II

HISTOLOGIC SUB-TYPE BY FEMALE GENITAL TRACT PHENOTYPE (Scully 1995)

Histologic type	Organ of the Female Genital Tract
Serous	Fallopian tube
Endometrioid/clear cell	Endometrium
Mucinous	Endocervix/gastrointestinal tract

In 1999, Dubeau argued that these histologic subtypes are “morphologically indistinguishable” from neoplasms arising from these same organs, which are themselves derived from Müllerian ducts, and that cells in normal ovaries do not resemble any of those epithelia, and that the ovary is not of “Müllerian origin.” Instead, Dubeau offers an alternative candidate for the cell of origin: the secondary Müllerian system. These are “small tubular structures lined by Müllerian epithelium in the paratubal and paraovarian areas” (Dubeau 1999).

Some of the problems with the OSE hypothesis have been resolved by studies that have since shown the capacity of the OSE to give rise to ovarian adenocarcinomas (Ong et al. 2000; Auersperg et al. 2001). Moreover, Dubeau’s point that ovarian carcinomas are Müllerian-like instead of mesothelioma-like is countered by the fact that that the OSE acquires epithelial characteristics of the Müllerian duct-derived epithelium when it undergoes metaplasia, benign tumor formation, and neoplastic progression (Auersperg et al. 2001).

An additional hypothesis for ovarian tumor development is called the “stem cell niche concept” in which somatic stem cells reside within a niche, where they remain quiescent until activation by an injury or other stimulation. The OSE cells have the stem cell property of self-renewal, which makes them candidates for this hypothesis (Liu et al. 1995; Choi et al. 2007).

f. **Ovarian carcinogenesis**

Three general principles underlie all cancer development and inform hypotheses related to ovarian carcinogenesis. The first principle is that cancer results from genetic errors in normal cells that have the potential to become cancer cells. The second principle is that more than one genetic error must occur for cancer to develop. The third principle is that each time DNA replicates it does so without 100% fidelity (Cohen et al. 1991). Cohen and colleagues describe a general model of

carcinogenesis in which cancer develops either through damage to the DNA of a cell or by increasing the number of cell divisions, thus increasing the opportunity for genetic error to occur during DNA replication. For genetic errors to result in carcinogenesis, they must occur in a cell with the potential for developing into cancer—generally a stem cell (Cohen et al. 1991).

Endogenous hormones contribute to the development of cancer through their role in regulating cell proliferation and apoptosis (Lukanova et al. 2005). Dysregulation of these cellular processes may enhance the survival of cells with mutations in proto-oncogenes and tumor suppressor genes (Rao et al. 1991). The avascular nature of the OSE make its cells susceptible to the effects of hormones such as gonadotropins (Lukanova et al. 2005).

There are two hypotheses, which are not mutually exclusive, related to ovarian carcinogenesis: the incessant ovulation hypothesis and the gonadotropin hypothesis. Several well-established risk and protective factors for ovarian cancer may operate through the mechanisms proposed by these hypotheses and are described below. There is also a growing body of evidence to suggest that factors causing epithelial inflammation are involved in ovarian carcinogenesis.

The differentiation of the ovarian surface epithelium contributes to the incessant ovulation hypothesis, which was first proposed by Fathalla in 1971 and subsequently supported by both epidemiological and experimental data (Godwin et al. 1992; Testa et al. 1994). This hypothesis proposes that frequent ovulation contributes to an increased risk of epithelial ovarian cancer because of the repeated rupture and repair of the OSE at the sites of ovulation, which provides an opportunity for genetic aberrations. This “repetitive wounding during the release of the ovum” and the cell proliferation that occurs after ovulation, in order to repair the OSE, results in mutations accumulating in the epithelial cells and ultimately the formation of tumors (Fathalla 1971; Lukanova et al. 2005; Smith et al. 2008).

Nulliparity, early age at menarche, and late age at natural menopause, all of which contribute to longer lifetime ovulation, are all risk factors for ovarian cancer. These factors potentially increase the lifetime number of ovulatory cycles—thus increasing the opportunity for cellular damage (Anderson et al. 2004). Oral contraceptive use and lacation both reduce the number of ovulatory cycles and have been shown to be protective against ovarian cancer (Lee 1987; Whittemore et al. 1992). The significant protective effect of long-term oral contraceptive use (≥ five years) has been shown to mute the risk associated with both BRCA1/2 mutations (Narod et al. 1998; Modugno et al. 2003).

In 1983, Cramer and Welch proposed the gonadotropin hypothesis. Data from animal models suggest that the secretion of high levels of gonadotropins, namely LH and FSH, were associated with ovarian tumors. The gonadotropin hypothesis postulates that excessive LH, FSH, and estrogen stimulation of ovarian inclusion cysts, formed through repeated invaginations (clefts) of the ovarian surface epithelium during incessant ovulations, results in increased proliferation and malignant transformation of the ovarian epithelium (Cramer et al. 1983; Akhmedkhanov et al. 2001).

The association between hormone replacement therapies (HRTs), in particular unopposed estrogen and progesterone, bolsters this hypothesis. The use of HRTs increases ovarian cancer risk through the estrogen-induced proliferation of ovarian cells (Danforth et al. 2007). Oral contraceptive use and lactation have been shown to reduce the risk of ovarian cancer in a dose-response manner (Lee 1987; Whittemore et al. 1992) by reducing the amount of FSH and suppressing the secretion of LH and FSH.

Epithelial inflammation is also involved in ovarian carcinogenesis. Several factors such as asbestos and talc exposures, endometriosis, and pelvic inflammatory disease cause epithelial inflammation. Conversely, the protective effects of tubal ligation and hysterectomy reduce exposure from local genital tract irritants and perhaps inflammation (Figure 1).

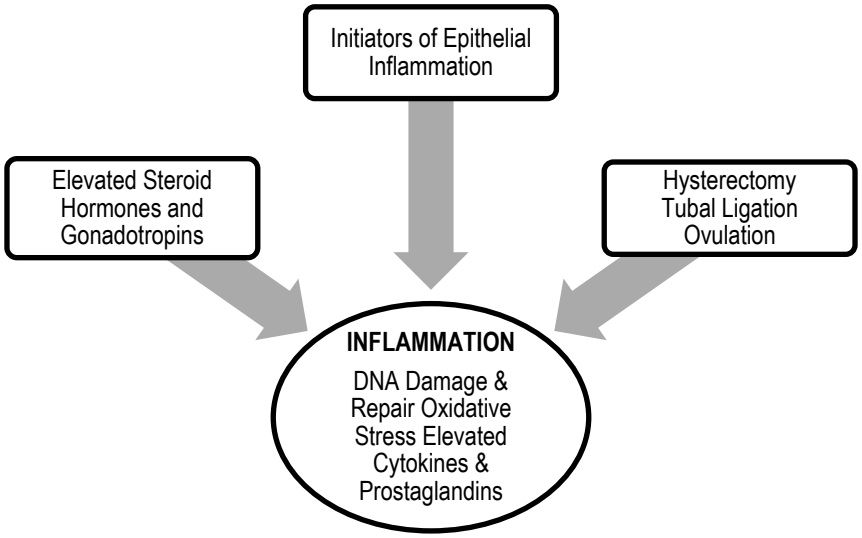

Figure 1 Inflammation as a mechanism in ovarian carcinogenesis (Adapted from Ness et al. 1999).

The theory that carcinogenesis may be mediated by oxidative damage to DNA was based on the finding that mutations in critical genes, such as the p53 tumor suppressor gene, can lead to tumors. Damage to genetic DNA may contribute to mutagenicity, and more rapidly dividing cells (a hallmark of chronic inflammation) are more likely to develop errors in DNA replication and repair (Schildkraut et al. 1997). Inflammation produces toxic oxidants that cause direct damage to DNA, proteins, and lipids and may play a direct role in carcinogenesis (Dreher et al. 1996). Finally, substances associated with inflammation, such as cytokines, growth factors, and prostaglandins may play an important role in ovarian mutagenesis (Ness et al. 1999).

g. **Racial differences in reproductive and immune system factors**

Age at menarche and natural age at menopause represent the beginning and the end of a woman's reproductive life cycle and presumably relate to the number of lifetime ovulatory cycles. Data from large cross-sectional studies have consistently demonstrated that Black females initiate puberty

earlier than White females and that Blacks have younger age at menarche than Whites (12.16 years for Blacks and 12.88 years for Whites) (Herman-Giddens et al. 1997). Blacks have also had the largest decline in mean age at menarche from 13.6 years (95% CI, 13.1-14.1) in women born prior to 1920, to 12.2 years (95% CI, 11.8-12.6) in the 1980-84 birth cohort (McDowell et al. 2007). These differences may be due to underlying biological factors such as differential gynecoid fat mass (Koprowski et al. 1999) or differential prepubertal insulin levels, which stimulate hormone production from ovarian cells (Casazza et al. 2008; Butts et al. 2009). Environmental influences, such as improved nutrition and increasing BMI (McDowell et al. 2007), as well as exposure to endocrine-disrupting chemicals, may induce these changes (Crain et al. 2008), and differences in these factors may account for the racial difference in the onset of menarche .

There is some evidence in the literature that Blacks have earlier onset of natural menopause (Mayberry et al. 1992) and correspondingly lower levels of estradiol and LH compared to Whites (Freeman et al. 2005). Inflammation plays a key role in ovarian carcinogenesis, and recent studies suggest that racial differences exist in immune system-related gene polymorphisms (Koshiol et al. 2010; Skibola et al. 2010). In addition, immune status has been associated with race, with Blacks having higher levels of immunoglobulin G levels than Whites (Tollerud et al. 1995).

2. **Descriptive statistics**

In spite of major advances in treatment for ovarian cancer, survival gains have disproportionately benefitted White women. There is strong evidence of a survival disadvantage for Black women at the national level, and there are suggestions of this in the State of Illinois.

a. **Incidence and mortality at the county, state, and national level**

Incidence and mortality rates are presented for Cook County, Illinois, where the cases in this analysis resided, as well as the State of Illinois and the United States. In some cases the time periods or the specific statistics differ, such that direct comparisons cannot be made between these three areas. However, these statistics do provide a general sense of the incidence and mortality at a more local level. At the county, state, and national levels, the incidence of ovarian cancer is higher in White women than in Black women (TABLE III). In Cook County the average percent change in the ovarian cancer mortality rate for all races combined shows improvement (-0.6, 95% CI, -0.8, -0.3). There is a similar trend at the national level, although the improvement is greater for White women (-1.6) than for Black women (-0.4). However, in Illinois the average annual percent change in the rate between 1975 and 2007 shows improvement for Whites (-0.6) but not for Blacks (0.2) (TABLE IV).

TABLE III

AGE-ADJUSTED OVARIAN CANCER INCIDENCE RATE (IR) BY RACE AND REGION

INCIDENCE STATISTICS	COOK COUNTY, IL		ILLINOIS	UNITED STATES
	Age-adjusted IR per 100,000 (95% CI)[a]		Age-adjusted IR per 100,000 (95% CI)[b]	Age-adjusted IR per 100,000 [c]
PERIOD	1993-1997	2003-2007	2003-2007	2003-2007
BLACK	11.9 (10.7,13.2)	9.8 (8.8,10.9)	9.7 (8.8,10.7)	10.2
WHITE	16.9 (16.1,17.7)	14.4 (13.6,15.1)	13.8 (13.4,14.3)	13.9

[a] Illinois State Cancer Registry.
[b] State Cancer Profile.
[c] SEER, based on cases diagnosed in 2003-2007 from 17 SEER geographic areas.

TABLE IV

OVARIAN CANCER MORTALITY RATE (MR) AND AVERAGE ANNUAL PERCENT CHANGE, BY RACE AND REGION

MORTALITY STATISTICS	COOK COUNTY, IL		ILLINOIS		UNITED STATES	
	Annual MR (over rate period) per 100,000 (95% CI)[a]	Average APC in MR (95% CI) [a]	Average APC in MR (95% CI) [a]		Age-adjusted MR[b]	Average APC in MR (95% CI) [b]
PERIOD	2003-2007	2003-2007	1975-2007		2003-2007	1998-2007
ALL RACES	8.7 (8.3,9.2)	-0.6 (-0.8, -0.3)	Black	0.2 (-0.4, 0.7)	7.2	-1.6
			White	-0.6 (-0.8, -0.4)	9.2	-0.4

[a] State Cancer Profile
[b] SEER, based on cases diagnosed in 2003-2007 from 17 SEER geographic areas.

b. **Incidence and survival patterns among Blacks and Whites in the United States**

Across study populations, the incidence of ovarian cancer has consistently been highest among White women. A recent analysis of data from the North American Association of Central Cancer Registries (NAACCR) examined ethnic and racial variations in primary carcinoma of the ovary, peritoneum, and fallopian tube (Goodman et al. 2009). In terms of age-adjusted incidence rates (per million), the highest rates for ovarian carcinoma at all stages were among Whites, and race-specific incident rate ratios were significantly lower among all other race/ethnicity groups compared with White women (Table V). These data indicate a 26.5% decrease in incidence rates between 1973 and 2005 ($P_{trend} < 0.0001$). However, the rate of decline was somewhat greater for Whites than for Blacks (-0.76% versus -0.72%, $p < 0.0001$).

TABLE V

AGE-ADJUSTED INCIDENCE RATES (AAIR) AND INCIDENCE RATE RATIOS (IRR) PER MILLION, BY SUMMARY STAGE AND RACE/ETHNICITY, 1995-2003 (Goodman et al. 2009)

RACE/ETHNICITY	AAIR (95% CI) BY SUMMARY STAGE			IRR
	Localized	Regional/distant	Unstaged	
NON-HISPANIC WHITE	22.91 (22.56-23.27)	94.94 (96.22-97.66)	7.35 (7.15-7.55)	Reference
NON-HISPANIC BLACK	10.32 (9.61-11.06)	61.85 (60.04-63.69)	6.05 (5.49-6.65)	0.62
HISPANIC	15.46 (14.63-16.31)	62.99 (60.40-65.66)	3.49 (2.89-4.18)	0.78

Despite the higher incidence of ovarian cancer among Whites, survival among Blacks is significantly poorer. The most recent SEER data show that across all age categories the five-year relative survival is substantially higher for White women than for Black women (Table VI).

TABLE VI

FIVE-YEAR RELATIVE SURVIVAL (PERCENT) CANCER OF THE OVARY (INVASIVE), BY RACE AND DIAGNOSIS YEAR [a]

	White			Black		
Year of Diagnosis	All Ages	< 65 years	65+	All Ages	< 65 years	65+
1999-2006	45.0	56.0	29.5	36.7	44.7	20.9

[a] Based on the SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta); based on follow-up of patients into 2007. Excludes borderline cases or histologies: 8442, 8451, 8462, 8472, & 8473.

In an analysis of SEER data from 1988-2001, a significantly higher proportion of Black women presented with late-stage disease (FIGO Stage III-IV) compared to Whites (74.8% versus 70.1%, $p < .0001$). Five-year survival was significantly better for Whites compared to Blacks (44.1% versus 40.7%, < .0001), in part due to the underlying difference in stage at diagnosis between the two groups (Chan et al. 2008).

This survival advantage for White women represents a reversal that appears to have taken place in the past two decades that may be associated with treatment. Platinum-based chemotherapy was shown definitively to be more effective than non-platinum containing regimens, and aggressive surgical cytoreduction was also shown to increase survival time (Omura et al. 1986; Omura 1989). A recent meta-analysis which stratified on the timeframe for patient enrollment, thus accounting for important treatment advances introduced in the 1980s, found that Blacks had better survival prior to 1985, whereas after 1985 the relative survival advantage favored Whites (Figure 2). Pooling the studies that captured patients prior to 1985 yielded a relative risk of five-year survival of 0.93 for Whites compared to Blacks. However, the pooled relative risk of five-year survival for Whites compared to Blacks after 1985 was 1.17 (95% CI 1.05-1.31). This suggests that these more recent survival differences may, at least in part, be the result of unequal application of newer and more effective treatments.

Study (Year)	Relative Risk of Five-Year Survival
Inclusion Period Before 1985	(95% CI)
Barnholtz-Sloan (1973-79)	0.95 (0.83-1.08)
Kosary (1974)	0.92 (0.87-0.97)
Smith (1979)	0.96 (0.77-1.20)
Young (1984)	0.97 (0.85-1.11)
Pooled RR (White Survival)	**0.93 (0.89-0.97)**
Inclusion Period After 1985	
Averette (1995)	1.11 (1.02-1.20)
Barnholtz-Sloan (1990-97)	1.16 (1.05-1.29)
Chan (2008)	1.08 (1.02-1.15)
O'Malley (2003)	1.07 (0.66-1.73)
Parham (1997)	1.37 (1.28-1.46)
Pooled RR (White Survival)	**1.17 (1.04-1.31)**

Figure 2 Five-year survival among women with ovarian cancer by race and year of diagnosis (Adapted from Terplan et al. 2009).

3. Factors associated with ovarian cancer incidence and survival

There are a number of well-established risk and prognostic factors associated with ovarian cancer incidence and survival, some of which are known to vary by race. These factors are described in detail as follows.

a. Risk and protective factors for ovarian cancer

Established risk factors for developing ovarian cancer include age and a family history of breast, ovarian, or colorectal cancers inherited in an autosomal dominant pattern (Permuth-Wey et al. 2009). Potential risk factors include early age at menarche and late age at menopause. These conditions both lengthen the reproductive phase and increase the number of ovulatory cycles, which increases the opportunity for cellular damage (Anderson et al. 2004). Although hormone replacement therapy (HRTs) suppresses gonadotropins, HRTs are generally associated with an increased risk of ovarian cancer specifically unopposed estrogens, which have a stimulatory effect on the OSE (Hunn et al. 2012). Additionally, dietary fat, obesity, alcohol consumption (Permuth-Wey et al. 2009), and smoking (Jordan et al. 2006) are suspected risk factors.

Oral contraceptive use, parity, lactation, tubal ligation, and hysterectomy are established protective factors against ovarian cancer (Permuth-Wey et al. 2009) due to their roles in promoting anovulation and in reducing gonadotropins (Riman et al. 1998). Oral contraceptive use is associated with a decreased risk of ovarian cancer (Narod et al. 1998), and with greater risk reduction associated with longer duration of use (Braem et al. 2010). Similarly, parity reduces ovarian cancer risk, and this reduction increases with each additional pregnancy (Adami et al. 1994). Breastfeeding has been associated with modest decreases in risk for ovarian cancer, although the trends with duration are inconsistent (Riman et al. 2004). Both tubal

ligation and hysterectomy have been associated with reductions in ovarian cancer risk—although the mechanisms here are less clear. One possible explanation is that both of these procedures lead to a reduced blood supply to the ovaries and thus reduces the local hormone level—specifically FSH and LH (Riman et al. 1998). It has also been suggested that these two surgeries reduce ovarian exposure to infectious agent that may cause inflammation (Sogaard et al. 2006).

White women are somewhat more likely to be nulliparous than Black women (Chandra et al. 2005), and are more likely to use hormone replacement therapy (Brett 2001), as well as oral contraceptives (Mosher et al. 2010). Black women have somewhat earlier age at menarche than Whites (McDowell et al. 2007) and earlier onset of natural menopause (Mayberry et al. 1992). However, there do not appear to be differences in smoking or alcohol consumption between the two groups, www.cdc.gov/brfss, accessed January, 2011. Tubal ligation and hysterectomy are somewhat more prevalent in Blacks than in Whites (Chandra et al. 2005). However, both the rate and duration of breastfeeding are higher among White women (Singh et al. 2007).

b. **Clinical prognostic factors**

Age at diagnosis, histologic subtype and pathologic grade, tumor stage at diagnosis, and residual disease after primary surgery are all well-established prognostic factors in patients with ovarian cancer (Brun et al. 2000; Clark et al. 2001). Suboptimal surgery, no chemotherapy treatment (Brun et al. 2000; Du et al. 2008), and pre-diagnosis dietary patterns of higher consumption of milk and certain meats have all been associated with poorer survival (Dolecek et al. 2010). While not directly related to survival, economic resources such as measures of income are related to the type and quality of healthcare received (Parham et al. 1997), which in turn may influence survival. Optimal surgery combined with adjuvant chemotherapy (Berkenblit et al. 2005), as well as increased pre-diagnosis consumption of

certain fruits and vegetables, are factors associated with improved survival (Nagle et al. 2003; Dolecek et al. 2010). The performance status of patients and the presence of ascites are additional prognostic factors that are considered in terms of treatment and prognosis (Clark et al. 2001).

The literature is inconsistent with respect to differences in age at diagnosis between Blacks and Whites. For example, an analysis of SEER data found that Black women were more likely than White women to be diagnosed at older ages (McGuire et al. 2002). However, other analyses have found no significant difference in age at diagnosis (Parham et al. 1997; McGuire et al. 2002), and still others have found that Blacks were younger at diagnosis than Whites (Chan et al. 2008). Similarly, there is inconsistent evidence with respect to racial differences in histologic subtype and pathologic grade (Parham et al. 1997; McGuire et al. 2002; Chan et al. 2008). Much of the literature suggests that a greater proportion of Black women present with late-stage disease at diagnosis (Parham et al. 1997; Chan et al. 2008). However, analyses of smaller datasets have not found similar differences (McGuire et al. 2002; Kim et al. 2010). Finally, there is widespread evidence that White women are more likely to be surgically staged and to receive a combination of surgery plus adjuvant chemotherapy (Parham et al. 1997; Harlan et al. 2003; Chan et al. 2008).

i. **Tumor histology and pathologic grade**

Tumor histology is an important prognostic factor for ovarian cancer. Compared to serous tumors, both mucinous and clear cell tumors have been associated with decreased overall survival as well as progression-free survival, while endometrioid tumors have demonstrated significantly increased survival (Omura et al. 1991; Akahira et al. 2001; Winter et al. 2007).

The Féderation Internationale de Gynécologie et d'Obstétrique (FIGO) recommends the use of a simplified version of the World Health Organization's (WHO) histologic typing of ovarian tumors, as follows:

serous, mucinous, endometrioid, clear cell, undifferentiated, and unclassified (Benedet 2000). Table V describes these sub-types. Significant differences in survival exist between Blacks and Whites, even within the same histologic sub-type. Recent SEER data shows that the most pronounced differences occur in Black and White women diagnosed with mucinous tumors (32.6% and 51.8%, respectively) and clear cell tumors (33.8% and 63.2%, respectively).

Five pathologic tumor grades are defined by the American Joint Committee on Cancer (AJCC). The current classification system combines these five categories into four: low-grade; high-grade; unclassified; and borderline tumors (Table VII). These pathologic grades are important in terms of clinical staging and subsequent treatment, as well as survival. The majority of tumors are categorized as high grade, and while these tumors are more chemosensitive than low-grade tumors, they are more likely to recur. Low grade tumors are slower growing but less likely to respond to chemotherapy (Ozols et al. 1980; Kosary 1994; Ozols 2003).

TABLE VII

FIGO CLASSIFICATION OF HISTOLOGIC SUB-TYPE AND GRADES FOR OVARIAN NEOPLASMS*

HISTOLOGIC TYPE	DESCRIPTION
Serous	Includes serous benign cystadenomas, serous cystadenomas with proliferating activity of the epithelial cells & nuclear abnormalities but no infiltrative destructive growth—low potential or borderline malignancy, & serous cystadenocarcinomas
Mucinous	Includes mucinous benign cystadenomas, mucinous cystadenomas with proliferating activity of the epithelial cells & nuclear abnormalities but no infiltrative destructive growth—low potential or borderline malignancy, & mucinous cystadenocarcinomas
Endometrioid	Includes endometrioid benign cysts, endometrioid tumors with proliferating activity of the epithelial cells & nuclear abnormalities but no infiltrative destructive growth—low malignant potential or borderline malignancy, & endometrioid adenocarcinomas
Clear cell	Includes benign clear cell tumors, clear cell tumors with proliferating activity of the epithelial cells and nuclear abnormalities but with no infiltrative destructive growth—low malignant potential or borderline malignancy, and clear cell cystadenocarcinomas
Undifferentiated	Includes malignant tumors of epithelial structure that is too poorly differentiated to be placed in any other sub-type group
Unclassified	Includes tumors that cannot be allotted to one of the above groups, as well as tumors with no histology
PATHOLOGIC GRADE	DESCRIPTION
Borderline	Tumors with low malignant potential
Low Grade	Well differentiated
High Grade	Moderately to poorly differentiated
Unclassified	Grade cannot be assessed

*Adapted from the National Cancer Institute—http://www.cancer.gov/cancertopics/pdq/treatment/ovarianepithelial/HealthProfessional/page2,

accessed 11/15/10, and Benedet, 2000.

ii. **Tumor stage at diagnosis**

Tumor stage at diagnosis is also an important predictor of ovarian cancer survival (Vergote et al. 1992), as is the completeness of staging (Zanetta et al. 1998). Recommended treatment is based on stage at diagnosis. For example, completely staged low-risk patients with stage IA, low-grade tumors may not need additional treatment following initial surgical staging[3], whereas high-risk patients with stage III/IV tumors have a greater risk of relapse and require adjuvant chemotherapy following debulking surgery (Vermorken et al. 2010). Table VIII presents the FIGO staging system, along with the Denoix tumor, node, metastasis (TNM) classification of malignant cancers.[4]

TABLE VIII

FIGO STAGING, TUMOR, NODE, METASTASIS CLASSIFICATION, AND DESCRIPTION OF OVARIAN NEOPLASMS

FIGO STAGING *(sub-staging)*	GROUPING	DESCRIPTOR
I	T1	Tumor limited to one or both ovaries
IA	*T1a, N0, M0*	Tumor limited to 1 ovary, capsule intact, no tumor on ovarian surface or malignant cells in ascites/peritoneal washings*
IB	*T1b, N0, M0*	Tumor limited to both ovaries, capsules intact, no tumor on ovarian surface or malignant cells in ascites/peritoneal washings*
IC	*T1c, N0, M0*	Tumor limited to 1/ both ovaries with any of the following: capsule ruptured, tumor on ovarian surface, malignant cells in ascites/peritoneal washings*
II	T2	Tumor involves one or both ovaries with pelvic extension
IIA	*T2a, N0, M0*	Extension and/or implants on the uterus and/or fallopian tubes, no malignant cells in ascites or peritoneal washings
IIB	*T2b, N0, M0*	Extension to and/or implants on other pelvic tissues. No malignant cells in ascites or peritoneal washings
IIC	*T2c, N0, M0*	Pelvic extension and/or implants (stage IIA or stage IIB) with malignant cells in ascites or peritoneal washings
III	T3 and/or N1	Tumor involves one or both ovaries with microscopically confirmed peritoneal implants outside the pelvis and/or regional lymph node metastasis
IIIA	*T3a, N0, M0*	*Microscopic peritoneal metastasis beyond pelvis (no macroscopic tumor)*
IIIB	*T3b, N0, M0*	*Macroscopic peritoneal metastasis beyond pelvis no more than 2 cm or less in greatest dimension*
IIIC	*T3c, N0, M0* *Any T,N1,M0*	*Peritoneal metastasis beyond pelvis more than 2 cm in greatest dimension and/or regional lymph node metastasis*
IV	Any T and any N,M1	Distant metastasis (excludes peritoneal metastasis); If pleural effusion is present, positive cytologic test results must exist to designate a case to stage IV; parenchymal liver metastasis equals stage IV

[3] Many clinicians would recommend enrollment in a clinical trial for patients with early-stage disease due to the lack of clinical data supporting a single standard of care for these patients.

[4] A description of the Denoix tumor, node, metastasis (TNM) classification system is included in the Appendix.

iii. **Residual disease**

The residual tumor status (in terms of both volume and number) following primary surgical cytoreduction is an important prognostic factor for advanced ovarian cancer (Ng et al. 1990; Omura et al. 1991; Hoskins et al. 1992; Hoskins et al. 1994; Chi et al. 2001). It has been demonstrated that patients with larger residual lesions experience decreased survival (Hoskins et al. 1992). Patients left with one centimeter or less of residual disease after surgery have significantly longer survival than those left with more than one centimeter of disease (Chi, Liao et al. 2001).

4. **Ovarian cancer treatment**

a. **Current standard of care**

The current standard of care for the majority of patients with ovarian cancer is initial cytoreductive surgery followed by platinum-taxane chemotherapy. There are important differences in both the delivery and type of chemotherapeutic agents used, based on the FIGO stage at diagnosis. The current National Comprehensive Cancer Network (NCCN) guidelines recommend that patients with advanced-stage disease (FIGO stage III/IV) receive radical cytoreductive surgery followed by combination chemotherapy with a taxane and a platinum compound delivered through intravenous or intraperitoneal routes. By contrast, low-risk patients with stage IA, low grade tumors may not need additional treatment following initial surgical staging. The following sections summarize these treatment components and conclude with a historical perspective to provide context for the present relevance of this analysis in view of the fact that the study population for this analysis consists of patients diagnosed between 1994 and 1998.

b. **Surgery**

Surgery plays a central role in both the diagnosis (surgical staging) and treatment (debulking) of ovarian cancer. Complete surgical staging consists of a laparotomy which includes

suctioning of ascites, or washings for cytologic assessment if no ascites, and thorough inspection and palpation of the right and left diaphragm, liver, gall bladder, stomach, omentum, spleen, kidneys and retroperitoneum. A total hysterectomy and bilateral salpingo-oophorectomy is performed. Enlarged lymph nodes are removed; patients with tumor nodules 2 cm or less in the upper abdomen undergo bilateral pelvic and para-aortic lymph node dissection to complete staging. As much gross tumor as possible is removed, termed cytoreduction or debulking (Benedet 2000). Optimal debulking is considered by the Society of Gynecologic Oncologists (Rabin et al.) to be achieved if residual cancer is less than 1 cm in maximum dimension, and operative findings at the time of tumor debulking determine the stage of disease.

Current NCCN and FIGO treatment guidelines recommend that most patients with clinical stage II-IV receive surgical debulking (i.e., cytoreductive surgery). The importance of cytoreductive surgery prior to chemotherapy is that the removal of a large volume of tumor leaves fewer cells that are potentially resistant to chemotherapy and allows for more complete tissue penetration of the cytotoxic drugs (Helm 2009). Cytoreductive surgery was introduced in the late 1980s and was a key component in the standard of care for patients diagnosed during this study period.

c. **Chemotherapy**

Several large randomized control trials (RCTs) conducted in the early 1990s defined the new standard of care in the treatment of advanced ovarian cancer. The United States Gynecologic Oncology Group protocol 111 and the European-Canadian Intergroup trial established the superiority of paclitaxel plus cisplatin over cyclophosphamide plus cisplatin in patients with late-stage disease (McGuire et al. 1996; Piccart et al. 2000). Subsequently, the German Arbeitsgemeinschaft Gynaekologische Onkologie protocol OVAR-3 and the Gynecologic Oncology Group protocol 158 demonstrated equal efficacy for the combination of carboplatin plus paclitaxel, but better tolerance over

paclitaxel plus cisplatin (du Bois et al. 2003). As a result of these trials, platinum-based agents (i.e., cisplatin or carboplatin) and taxanes (i.e., paclitaxel, docetaxel) are at now the core of primary adjuvant treatment for late-stage disease, with carboplatin plus paclitaxel favored due to its reduced toxicity as compared to cisplatin (du Bois et al. 2003; Ozols et al. 2003).

d. **Delivery of chemotherapeutic agents**

Intraperitoneal chemotherapy (IP therapy) is the administration of chemotherapeutic agents directly into the peritoneal cavity to achieve high cytotoxic drug dosage at the tumor site. The rationale behind IP therapy is that the largest proportion of ovarian cancer cases is confined to the peritoneaum (stages I through IIIC) (Runowicz 2008), and IP therapy allows for the administration of high doses of cytotoxic drugs while reducing tissue exposure outside the peritoneum. Two trials conducted in the 1990s established the safety and efficacy of IP therapy (Alberts et al. 1996; Markman et al. 2001). However, many clinicians have been reluctant to adopt IP therapy, because of the complexity of both peritoneal administration and catheter-placement techniques (Armstrong et al. 2006). In 2006, the results of the GOG-172 phase 3 trial comparing IV paclitaxel plus cisplatin with IV paclitaxel plus IP cisplatin and paclitaxel in patients with stage III ovarian cancer were published. This trial demonstrated significant improvements in both progression-free and overall survival in the IP-therapy groups as compared to the IV-therapy groups (Armstrong et al. 2006), which eventually led to more widespread acceptance of IP therapy in optimally debulked stage II and III patients. Since the early part of this decade, the National Comprehensive Cancer Network (NCCN) Guidelines have recommended consideration of IP therapy in patients with <1 cm optimally debulked stage II and stage III (i.e., Category 1) patients (NCCN Guidelines version 2010).

5. **Historical perspective on treatment of Black and White women with ovarian cancer: 1990s to the present**

National data from SEER and the Patterns of Care Studies were analyzed for 1991 and 1996. This analysis revealed important information with respect to the treatment guidelines at the time, the percentage of patients then receiving guideline therapy, and changes in those trends over time. A significantly greater percentage of patients with late-stage disease received guideline therapy than patients with either stage I or stage II disease did, and these trends remained consistent across both periods. The 1991 weighted percentage of White women who received guideline therapy was 52.1%, versus 35.8% of Black women. This gap narrowed slightly in 1996 to 59% of Whites and 46.2% of Blacks. Finally, after adjusting for factors such as year of diagnosis, age, insurance status, and geographic location, the percentages of Black and White women receiving guideline therapy both rose slightly in 1996, when 54% of White women received guideline therapy, compared to 37% of Black women (Harlan et al. 2003).

The 1994 National Institutes of Health Consensus Development Conference Statement on ovarian cancer was influential in developing guidelines for treatment during the period for which patients in this analysis were diagnosed (i.e., 1994-1998). Although the United States Food and Drug Administration approved the use of paclitaxel in 1992, it was not part of the guideline therapy requirement for late-stage disease later in the 1990s when the patients in this analysis were diagnosed. Three important clinical guidelines were reviewed in an effort to reconstruct the clinical practices that may have impacted the treatment of these Cook County patients. They include guidelines by the NCCN, the FIGO Committee on Gynecologic Oncology, Clinical Practice Guidelines, and the 1994 NIH Consensus Development Conference. As Table IX indicates, the most substantive difference between the current standard of care

and the standards in place between 1994 and 1998 was the current recommendation to use IP chemotherapy in optimally debulked patients.

TABLE IX

COMPARISON OF OVARIAN CANCER STANDARDS OF CARE FOR THE STUDY PERIOD (1994-1998) AND THE CURRENT PERIOD, BY STAGE OF DISEASE

	STANDARD OF CARE 1994-1998		CURRENT STANDARD OF CARE	
SURGERY	EARLY-STAGE	LATE-STAGE	EARLY-STAGE	LATE-STAGE
	Diagnostic laparoscopy, followed by staging & debulking by laparotomy if malignancy is detected[a, b]	Optimal debulking Interval cytoreduction where necessary[a, b,c]	Laparotomy/total abdominal hysterectomy/bilateral salpingo-oophorectomy with omprehensive staging or unilateral salpingo-oophorectomy (to preserve fertility)[d]	Optimal debulking, neoadjuvant chemotherapy followed by Interval, cytoreduction[d]
CHEMOTHERAPY	No adjuvant therapy with stage IA, grade 1 & most IB,1 tumors Adjuvant tx with all grade 3, stage IC, and clear cell[a], as well as grade 2[b,c]	IV platinum (cisplatin or carboplatin) plus paclitaxel[a, b,c]	No adjuvant therapy with stage IA, grade 1 tumors Consideration of IV carboplatin plus taxane for stage IA,IB, grade 2-3 and all stage IC[d]	IP chemotherapy in <1cm optimally debulked stage II and III patients; or IV carboplatin plus taxane[d]

[a] 1994 NIH Consensus Development Conference Statement
[d] NCCN Clinical Practice Guidelines in Oncology, Ovarian Cancer, Version 1.2011
[b] FIGO Committee on Gynecologic Oncology, Clinical Practice Guidelines
[c] NCCN Clinical Practice Guidelines in Oncology, Ovarian Cancer, Version 1.1996

6. **The impact of treatment advances on the disparity in ovarian cancer survival**

Treatment advances, particularly the use of platinum-based chemotherapy and debulking surgery, have had a significant impact on ovarian cancer survival for patients who receive them. A prospective study of more than 500 patients with ovarian cancer treated at Helsinki University Hospital between January 1, 1977 and December 31, 1990 allowed researchers to analyze trends in survival specifically related to major treatment advances during this period. Cumulative survival was calculated for three separate time periods: 1977-80; 1981-85; and 1986-90. Improvements in survival were strongly

associated with chemotherapy containing cisplatin ($p < 0.001$). After controlling for age, tumor grade, type of surgery and chemotherapy received, patients who received optimal debulking surgery and chemotherapy that did not contain cisplatin had a 2.9-fold increased risk of death (95% CI 1.2-7.0) compared to patients who received optimal debulking surgery and chemotherapy containing cisplatin (Venesmaa 1994). In the 1980s, cisplatin became the main adjuvant chemotherapy in Europe and the United States. The combination of cisplatin and cytoreductive surgery account for significant improvements in five-year survival rates ranging from 30-35% in the 1970s versus 35-42% in the 1980s (Einhorn et al. 1985; Balvert-Locht et al. 1991; Ries 1993; Hogberg et al. 2001). Since the mid-1980s, widespread adoption of this optimal treatment regimen has had a significant impact in extending ovarian cancer survival (Venesmaa 1994; Bjorge et al. 1998) however, these treatment advances have disproportionately benefitted White women.

Black women are less likely to receive standard chemotherapy (Harlan et al. 2003; Du et al. 2008), or combined surgery and chemotherapy (Cress et al. 2003). The National Cancer Database Study (NCDB),[5] conducted with more than 25,000 cases diagnosed after 1985, revealed that Black women were treated less aggressively than White women—even when they received care within the same facility (Parham et al. 1997). For example, within the same facility, 33% of Black women with early stage disease were given optimal treatment compared to 43% of White women (Figure 3).

[5] Data were from cases submitted to the NCDB for invasive epithelial ovarian cancer diagnosed between 1985-1988 and 1990-1993. African-American women were compared with non-Hispanic White women with the same disease. The groups of White women with which African-American women were compared were classified as “White-same facility” and “White-other facility”. “White-same facility” were White patients from hospitals that contributed a substantial proportion of African-American patients. “White-other facility” were White patients from hospitals that contributed few or no African-American.

	Early Stage D			Late Stage		
	African Americans	Whites Same Facility	Whites Other Facility	African Americans	Whites Same Facility	Whites Other Facility
Treated Cases	385	1703	5276	1079	3735	10885
Percent Treated Optimally	33	43	45	61	70	70
Percent Surgery Only	59	47	48	19	17	16
Percent Chemotherapy Only	3	3	2	16	10	11

Figure 3 First course treatment of malignant ovarian carcinoma cases, by stage and racial group (Adapted from Parham et al. 1997).

7. Measures of socioeconomic environment

a. Concentrated disadvantage and concentrated affluence

Area-level measures of socioeconomic status were based on two well-established measures of neighborhood structural characteristics: concentrated disadvantage and concentrated affluence (Sampson 1999; Browning 2006). In the absence of individual-level information on socioeconomic status, these area-level variables provide measures of the socioeconomic status of our study population. Moreover, these summary measures represent a more comprehensive measure of overall socioeconomic circumstances than single census-level variables, and health outcomes have been demonstrated to be negatively associated with residence in disadvantaged neighborhoods and positively associated with residence in affluent neighborhoods (Ellen 2001; Do et al. 2008).

The idea of concentrated disadvantage is rooted in the idea that structural disadvantage results in conditions that can adversely affect on individuals (Browning et al. 2002). This variable (at the census-tract level) was constructed using the following variables derived from the U.S. Census: percent below poverty; percent unemployed; percent receiving public assistance; percent in female-headed households; percent

under age 18; and percent African-American. These variables represent various aspects of structural disadvantage and were all found to be dominated by factor loadings >0.60 (Browning 2006).

Concentrated affluence is related but conceptually distinct from concentrated disadvantage. Just as poverty has become more concentrated, so has the "spatial sorting" of residents by resources such as education, occupation, and income (Sampson 1999). Rather than to consider socioeconomic distribution on a continuum from highly disadvantaged to highly affluent, Sampson and colleagues pointed out the need to separate these two effects. It is not just the absence of resources that negatively impacts an outcome, but also that concentrated socioeconomic resources may exert an independent and positive effect on an outcome. The concentrated affluence variable (also at the census- tract level) was constructed using the following Census-derived variables: percent of families with incomes above $75,000 (for the 2000 Census period) and $50,000 (for the 1990 Census period); percent of adults with a college education; and percent of the civilian labor force employed in professional or managerial occupations (Sampson 1999).

b. **Neighborhood context**

Sampson and colleagues have defined neighborhood as "ecological units nested within successively larger communities". Implicit in this definition is the concept of neighborhood differentiation which includes aspects such social inequality between neighborhoods and the idea that neighborhood characteristics can influence aspects of residents' lives (Sampson 2002).

Although individual measures of socioeconomic status and well-established prognostic factors play a role in ovarian cancer survival, they may not fully account for the differential survival observed between Black and White women. The neighborhoods in which patients reside may contribute to these differences. Indeed, residential environment has been found to contribute to poor health outcomes such as hypertension (Pickering 1999) and cardiovascular disease (Diez-Roux et al. 1997). Multivariate analysis

evaluating area socioeconomic status and cancer incidence, detection, and survival have been reported in the breast and prostate cancer literature (Klassen et al. 2004; Sanderson et al. 2006; Barrett et al. 2008; Campbell et al. 2009; Schootman et al. 2009; Pornet et al. 2010). There is some precedent in the literature for considering community as an independent predictor for ovarian cancer survival. In a multivariate analysis[6] of women in Northern California with ovarian cancer, women residing there were 2.6 times more likely to die from the disease than were women in the San Francisco area. The authors speculate that these results may be due to differences in access to cancer treatment facilities, as well as the type of facility available to rural women (O'Malley et al. 2003).

[6] Community was treated as a fixed effect in this analysis.

II. METHODS

A. Data

1. Study population

The original study population consisted of 704 cases of ovarian cancer diagnosed between June 1, 1994 and December 31, 1998 (Figure 2). Cases were residents of Cook County, Illinois, between 18-74 years of age at the time of diagnosis, and White or Black race. The diagnosis of epithelial ovarian cancer (hereafter, "ovarian cancer") was confirmed histologically after surgery through two independent pathology reviews using the International Histological Classification of Ovarian Tumors recommended by FIGO (Pecorelli et al. 1999). This analysis was restricted to women who self-reported their race as either Black or White (n=702). Following a review of histology codes, 102 tumors were determined to be either benign or stromal, or of germ-cell origin, and were subsequently excluded from the analysis because of differences in risk and prognostic factors, as well as differences in treatment for these tumors. Of the remaining 600 cases, vital status was valid for 589 women (100 Black and 489 White women). Of these women, 351 were interviewed, and they provided additional information on demographics and gynecologic history. Of this subset, 344 were verified as epithelial cases (54 Black and 290 White women).

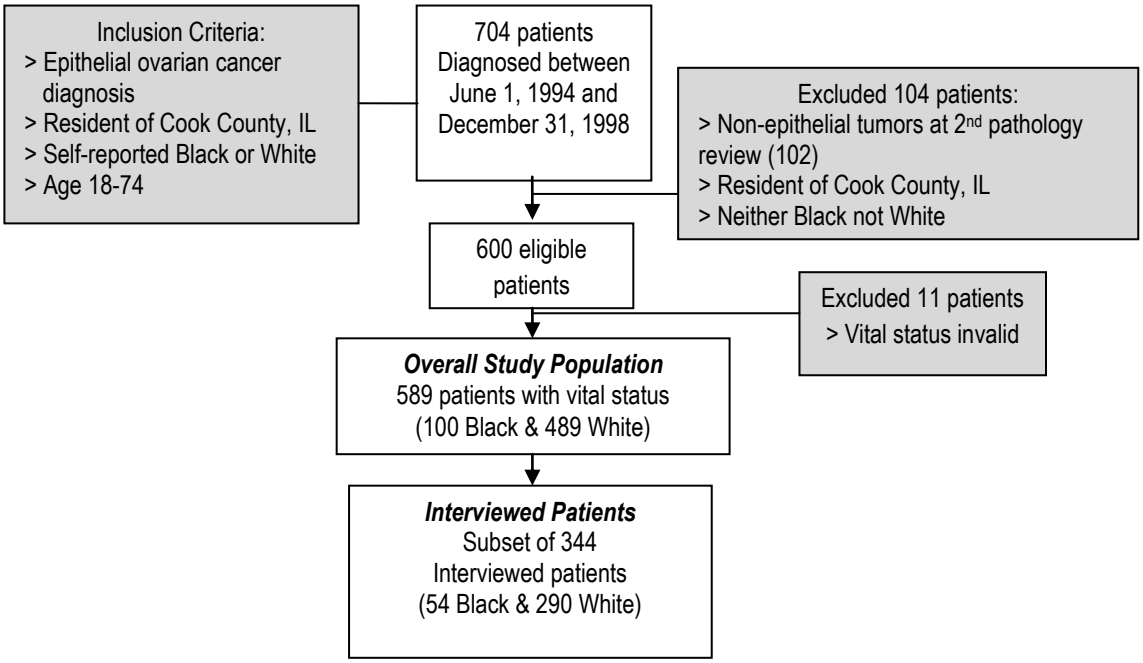

Figure 4 Description of study population.

2. **Vital status**

Case information on social security number, first and last name, and month, day, and year of birth (linkage variables) were submitted to the National Death Index (NDI) to be matched to the NDI computerized index of death information, which has been compiled from death certificates submitted by State Vital Statistics offices to the National Center for Health Statistics (NCHS). The NDI system selects potential death record matches based on the linkage variables, and then assigns a probabilistic score and a determination of final match status suggested by NCHS. The overall completeness of these linkage variables ranged from 97.6% (for social security number) to 99.8% (for birth day), to 100% (for first and last name, and for birth month and year). Vital status was ascertained through 2008. Each case's vital status (as alive or dead) was determined though a manual review of the NDI Summary file. Dates of death for all linked cases were recorded. In cases with more than one possible match, the record with the most data

items in agreement was used. There were 11 cases with invalid (i.e., negative) survival times were excluded from the survival analysis. All unlinked cases were right-censored at the last point of follow-up, which was December 31, 2008.

3. **Cause of death**

The cause of death for each linked case was classified as either ovarian cancer, other cancer, cardiovascular disease, or other disease using the underlying or selected cause code from the appropriate revision of the International Classification of Diseases (ICD). The ICD-9 codes were used for deaths occurring between 1994 and 1998, and the ICD-10 codes were used for deaths beginning in 1999. Ovarian cancer was recorded as the cause of death for 92.8% of the women in the sample. We conducted a sensitivity analysis to confirm that the observed survival disparity persisted among only those cases with a recorded death from ovarian cancer. There was minimal difference in the analysis that included all causes of death and those that included only death from ovarian cancer. Moreover, the objective of this analysis was to assess the effects of both neighborhood context and prognostic factors on the racial disparity in overall survival. Thus, the majority of results presented here include all cases of epithelial ovarian cancer, regardless of the cause of death. This objective also informed our decision to include borderline cases. While borderline tumors differ from invasive tumors in terms of both pathologic and clinical behavior, we were concerned with the overall survival experience of this population of ovarian cancer patients. Moreover, our sensitivity analysis demonstrated a minimal difference between the analyses with and without these tumors. For this reason, borderline cases were included in these results.

4. **Survival time**

Survival time was calculated by subtracting the date of diagnosis with ovarian cancer from the date of death (for matched cases) or last date of follow-up (for unmatched cases).

B. Variables

1. Independent variable

The independent variable "race" is based upon the individual patient's self-reported racial identity as either Black or White. The number of women from other race/ethnicity groups was not adequate to include them in this analysis.

2. Dependent variables

The binary dependent variable in Aim 1 was late-stage (FIGO III/IV) versus early-stage (FIGO I/II) diagnosis. Current clinical practice often excludes FIGO II from early-stage classification because of the lack of consensus regarding the treatment and prognosis of these cases (Halpern et al. 2008; Morris et al. 2010). However, at the time of their diagnoses in the mid-to late-1990s these women would have been treated as early-stage cases. The dependent variable in Aims 2 and 3 was survival time analyzed as a binary variable (i.e., greater than or equal to five years versus less than five years).

3. Census-tract poverty and education (Aim 1)

Two U.S. Census variables at the tract level were selected as proxy measures of socioeconomic status for the women in the study: the percentage living below poverty ("poverty") and the percentage of adults over 25 years old with less than a high school education ("education"). Each patient's residential address at the time of diagnosis was geocoded to the block level and then located within a census tract. Because case ascertainment occurred between 1994 and 1998, data from both the 1990 and 2000 Census periods were used to calculate poverty and education variables. Data from these two Census periods were used to create an interpolated value representing the midpoint in the ascertainment period (i.e., 1996).[7] Using established cutoff points, census tracts with low educational attainment or high poverty

[7] Details are described in the Appendices.

were defined as those in which 1/3 or more of the population had less than a high school degree or lived below poverty, respectively. In contrast, census tracts with higher educational attainment or lower poverty were defined as those in which less than 1/3 of the population had less than a high school degree or lived below poverty, respectively (Gornick et al. 2004).

As would be expected, census-tract poverty and education were highly correlated ($p < .0001$). In order to account for measures of both poverty and education in multivariate models, we created a three-level index variable which assumed that: (1) higher socioeconomic status corresponded to a lower proportion of the population living below poverty and a lower proportion of the population with less than a high school education; (2) moderate socioeconomic status corresponded to either low poverty and low education, or high poverty and high education; and (3) lower socioeconomic status corresponded to high poverty and low education (TABLE X).

TABLE X

DESCRIPTION OF SOCIOECONOMIC STATUS INDEX

LEVEL	DESCRIPTION
Higher SES (Reference)	<1/3 of the population living below poverty and <1/3 with less than a high school education
Moderate SES	Either <1/3 of the population living below poverty and ≥1/3 with less than a high school education, or ≥1/3 of the population living below poverty and <1/3 with less than a high school education
Lower SES	≥1/3 of the population living below poverty and ≥1/3 with less than a high school education

4. **Concentrated disadvantage and concentrated affluence (Aim 2 and Aim 3)**

The concentrated disadvantage variable (at the census-tract level) was constructed using the following variables derived from the U.S. Census: percent below poverty; percent unemployed; percent receiving public assistance; percent in female-headed households; percent under age 18; and percent

African-American (Browning et al. 2002). The concentrated affluence variable (also at the census- tract level) was constructed using the following Census-derived variables: percent of families with incomes above $75,000 (for the 2000 Census period) and $50,000 (for the 1990 Census period); percent of adults with a college education; and percent of the civilian labor force employed in professional or managerial occupations (Sampson 1999). Each patient's residential address at the time of diagnosis was geocoded to the block level and then located within a census tract (Appendix A).

Because case ascertainment occurred between 1994 and 1998, data from both the 1990 and 2000 Census periods were used to create interpolated values representing the midpoint in the ascertainment period (i.e., 1996). We created an interpolated value that represented this midpoint period for each of the nine derived variables (specified above). In creating these interpolated values, the following formula was used: [1990 Census Period data * 0.4] + [2000 Census Period data * 0.6].

Each of the interpolated values for a derived variable was standardized using *proc standard*. The six derived variables used in the concentrated disadvantage variable were summed and then standardized in order to create the final summary variable. This process was repeated using the three derived variables used in the concentrated affluence summary variable. Higher scores for each of these measures represent greater concentrated disadvantage or greater concentrated affluence, as the case may be. Both variables were modeled in their continuous forms. Three-level categorical variables were based on tertiles and used in cross-tabulations with race and with the dependent variable five-year survival.

5. **Covariates Aim 1**

Pathologic grade was analyzed as a four-level categorical variable in both the tabular and regression analysis (borderline, low-grade, high-grade, and unclassified). Histologic sub-type was analyzed as a six-level categorical variable in tabular analysis (mucinous, clear cell, endometrioid, serous,

undifferentiated, and unclassified). In regression models, serous tumors were compared against the reference category, which combined the other five sub-types due to unstable cell sizes. The following characteristics were evaluated in univariate and multivariate analysis: estimated recent body mass index (normal and overweight, obese); smoking history (never, ever); education (high school or more, less than high school); marital status (married at time of diagnosis, not married at time of diagnosis); age at menarche (>13 years, 12-13, <12); estimated length of ovulatory period in tertiles (≤28 years, 29-35, ≥36); nulliparity (parous, nulliparous); and history of hormone replacement therapy (Shi et al.), oral contraceptive (OC) use, family history of breast/ovarian cancer, hysterectomy, or tubal ligation (yes, no). Age at diagnosis (≤40 years, 41-50, 51-65, >65, and continuously) was included as an adjustment variable in all models.

6. **Covariates Aim 2**

Stage at diagnosis was analyzed as a four-level categorical variable (i.e., FIGO I, II, III, IV). The original pathology report assigned tumor grade according to the five histopathologic grades defined by the American Joint Committee on Cancer (AJCC) system. In keeping with the current classification system, these five categories were combined into four: low-grade (G1: well differentiated); high-grade (G2-G4: moderately to poorly differentiated); unclassified (GX: grade cannot be assessed); and borderline tumors (GB). The FIGO version of the World Health Organization's histologic typology of ovarian tumors was used to classify the six categories of epithelial tumors: serous, which is the most common sub-type; mucinous; clear cell; endometrioid; undifferentiated; and unclassified. Epithelial tumors were considered unclassified if they could not be assigned to one of the first five groups or if they had no histology. Histologic sub-type was modeled as a dichotomous variable, with serous tumors designated as the reference level. Although current clinical practice considers residual lesions of one centimeter or less

following surgery to be an indicator of optimal debulking (and of a better prognosis), the original pathology review categorized residual lesions as two centimeters or less versus more than two centimeters. In addition, age at diagnosis (≤45 years, 46-60, ≥61, and continuously) was included as an adjustment variable in all models.

7. **Covariates Aim 3**

As in Aim 2, stage at diagnosis was analyzed both as a four-level categorical variable and as a binary variable: late-stage diagnosis (FIGO III/IV) versus early-stage diagnosis (FIGO I/II). The five histopathologic grades were combined into four: low-grade (G1: well differentiated); high-grade (G2-G4: moderately to poorly differentiated); unclassified (GX: grade cannot be assessed); and borderline tumors (GB). The FIGO version of the World Health Organization's histologic typology of ovarian tumors was used to classify the six categories of epithelial tumors: serous, which is the most common sub-type; mucinous; clear cell; endometrioid; undifferentiated; and unclassified. Epithelial tumors were considered unclassified if they could not be assigned to one of the first five groups or if they had no histology. Histologic sub-type was modeled as a nominal variable, with serous tumors designated as the reference level. Although current clinical practice considers residual lesions of one centimeter or less following surgery to be an indicator of optimal debulking (and of a better prognosis), the original pathology review categorized residual lesions as two centimeters or less versus more than two centimeters. In addition, the following characteristics were evaluated in all analyses: age at diagnosis (≤45 years, 46-60, ≥61, and continuously); concentrated disadvantage (in tertiles, and continuously); educational attainment (high school or more, less than high school, and continuously); marital status (married at time of diagnosis, not married at time of diagnosis); history of oral contraceptive (OC) use (yes/no); and history of hormone replacement therapy (Shi et al.) (yes/no). The last two of these variables were available only for the

interviewed patients, so models using the variables were restricted to this subset. Age at diagnosis was included as an adjustment variable in all models.

C. **Statistical Analysis by Aim**

1. **Aim 1: Predictors of late-stage diagnosis**

Differences in the distribution of covariates by stage at diagnosis and by race were tested using the Chi-square test for categorical variables and the *t*-test for continuous variables. Generalized linear regression (assuming a binomial distribution) was used to model the risk of being diagnosed with late-stage ovarian cancer compared with early-stage disease, as well as in the stratified analysis.

Multivariate models were fit using a forward-selection process in order to develop a final model predicting late-stage diagnosis in this population of Black and White women with ovarian cancer. Because of the small sample size, variables that were significantly ($p < 0.20$) associated with late-stage diagnosis in age-adjusted models were considered in the multivariate analysis. Model fit was assessed using the likelihood ratio test for nested models. Age at diagnosis was included in all models and only variables that were statistically significant at $p < 0.05$ were included in subsequent models. Analysis was performed using SAS, Version 9.2, Cary, North Carolina.

2. **Aim 2: The Role of neighborhood context in the racial disparity in five-year survival**

Differences in the distribution of covariates by survival time and by race were tested using Chi-square statistics for categorical variables and t-test statistics for continuous variables. The cumulative probability of survival was obtained using product-limit estimates. Log-rank test statistics were used to test the equivalence of the curves. Cox proportional hazard models were used to estimate hazard ratios (HR) and 95% confidence intervals (95%CI). Pearson correlation coefficients were used to evaluate the correlation between all of the prognostic factors. Highly correlated variables (i.e., >0.5) were not included in

the same regression model. Generalized linear regression, assuming a binomial distribution, was used to estimate the effect of neighborhood context and prognostic factors on the survival disparity. Nested models were compared in order to estimate the extent to which the estimate of the racial disparity on five-year survival changed when variables related to neighborhood context and when prognostic factors were taken into account.

3. **Aim 3: The role of mediators in the racial disparity in five-year survival**

Differences in the distribution of covariates by survival time and by race were tested using Chi-square statistics for categorical variables and t-test statistics for continuous variables. The cumulative probability of survival was obtained using product-limit estimates. Log-rank test statistics were used to test the equivalence of the curves. Cox proportional hazard models were used to estimate hazard ratios (HR) and 95% confidence intervals (95%CI). Logistic regression was used as an initial approach to assessing mediation. Variables that were significantly ($p < 0.20$) associated with the dependent variable in univariate analyses were considered potential mediators. We set a more liberal cutoff value for statistical significance in order to explore these variables as potential mediators more fully.

Mediation analysis was conducted using the method of Karlson, Holm, and Breen (Karlson 2011), which addresses the "scale identification issue" that occurs when estimating direct and indirect effects when mediators or outcome variables are categorical. In logistic regression, the inclusion of a potential mediator will alter the coefficient of the independent variable, and the outcome variable can be affected by a change in the model variance or scale due to the inclusion of the mediator, or by the effect of the mediator in the relation between the independent and dependent variable, or both. The KHB method partitions the scale issue out of the estimation of the direct and indirect effects. Analyses were conducted using the user-written KHB command in STATA (Appendix B). Based on nested models, a summary was

produced in order to report the proportion mediated by each hypothesized mediator and the domains of interest, as well as significance tests for these effects using the joint Wald test for binary variables.

One concern that arises in the analysis of survival disparities is that differences in co-morbidities may actually drive the observed disparity. In an effort to address this issue, we conducted sensitivity analyses to determine whether the findings persisted among all women whose cause of death was recorded as ovarian cancer. Survival analysis, univariate, and logistic regression analyses were performed using SAS, Version 9.2, Cary, North Carolina, and mediation analysis was performed using STATA, Version 12, College Station, Texas.

III. PREDICTORS OF LATE-STAGE DIAGNOSIS

A. Introduction

The FIGO staging system classifies ovarian neoplasms into four major groups (i.e., stages I-IV). Stage III and IV tumors are considered late-stage, involving regional (i.e., stage III) or distant metastasis (i.e., stage IV), and stage I/II tumors are generally considered early-stage. Tumor stage at diagnosis is both an important predictor of ovarian cancer survival (Vergote et al. 1992) and a key factor in determining treatment (Zanetta et al. 1998). Because there is no screening mechanism for ovarian cancer, and early-stage disease has several non-specific symptoms, including irregular menses, abdominal or pelvic pain, dyspareunia (i.e., painful intercourse), and changes in bowel or bladder habits, the vast majority of women are diagnosed at late-stages. Indeed, it has been estimated that 75% of all women with ovarian cancer are diagnosed with late-stage disease (Cannistra 2004; Jemal et al. 2004). Women diagnosed in later stages have significantly shorter survival times than those diagnosed with early-stage disease. Late-stage tumors are generally more aggressive and have a high rate of recurrence due to their resistance to platinum-based chemotherapies (Vermorken et al. 2010), and they are also associated with greater residual disease following cytoreductive surgery (Chi et al. 2001; Burges et al. 2011).

We evaluated patient characteristics (including self-reported race), proxy measures of healthcare access, socioeconomic status, and tumor characteristics in order to determine significant predictors of late-stage diagnosis. In addition, we examined whether or not these predictors of late-stage disease differed by race. In spite of major advances in treatment for ovarian cancer, survival gains have disproportionately benefitted White women (Chan et al. 2008). However, the literature is inconsistent with respect to

racial differences in the four FIGO stages at diagnosis (Parham et al. 1997; McGuire et al. 2002; Kim et al. 2010). Exploring whether there are underlying differences in predictors of late-stage diagnosis may shed some light on these contradictory findings.

Fundamentally, stage at diagnosis is affected by access to healthcare and tumor characteristics. Frequent and consistent healthcare may enable early-stage detection of ovarian cancer through a constellation of non-specific symptoms. In contrast, diminished access to care may result in lost opportunities to diagnose and treat the disease at an early stage. In our society, socioeconomic status largely determines one's access to healthcare (Kirby et al. 2005). While it has long been recognized that tumors diagnosed at late stages are typically more aggressive, less is known about the potential racial differences in factors that may influence late-stage diagnoses. We hypothesize that factors related to healthcare access, socioeconomic status, and risk factors for ovarian cancer will be found to be significant predictors of late-stage diagnosis, and that predictors of late-stage diagnosis will differ by race.

B. **Results**

Table XI presents characteristics of the study population. The majority of women were White (84%). Slightly more than half of the women in the study population were diagnosed with late-stage disease, were 51 years or older at the time of their diagnosis, or had a family history of breast/ovarian cancer. Forty-three percent of the women reported a history of HRT use, and 53% reported using oral contraceptives. The majority of women had neither a hysterectomy nor tubal ligation (87% and 92%, respectively). Most women had at least a high school education (87%) and resided in census tracts with low poverty (85%) and high education (76%). In terms of tumor characteristics, 20% of tumors were borderline, 62% were high-grade, and 54% of tumors were of the more aggressive histologic sub-types, serous and undifferentiated.

TABLE XI

CHARACTERISTICS OF THE STUDY POPULATION

CHARACTERISTIC	N (%)
Stage at Diagnosis	
Early-stage (FIGO I/II)	169 (49)
Late-stage (FIGO III/IV)	175 (51)
Race	
Black	54 (16)
White	290 (84)
Age at Diagnosis	
≤40 years	52 (15)
41-50 years	115 (34)
51-65 years	104 (30)
>65 years	73 (21)
Recent BMI	
Normal/overweight	282 (82)
Obese	62 (18)
Smoking	
Never	143 (42)
Ever	201 (58)
Age at Menarche	
>13 years	185 (54)
12-13 years	85 (Nervi et al.)
<12 years	74 (21)
Length of Ovulatory Period	
≤28 years	86 (Nervi et al.)
29-35 years	86 (Nervi et al.)
≥36 years	172 (50)
Nulliparity	
Parous	260 (76)
Nulliparous	84 (24)
Family History of Breast/Ovarian Cancer	
No	150 (44)
Yes	194 (56)
Hormone Replacement Therapy (missing=3)	
Yes	148 (43)
No	193 (57)
Hysterectomy	
Yes	43 (13)
No	301 (87)
Tubal Ligation (missing=1)	
Yes	28 (8)
No	315 (92)
Oral Contraceptive Use	
Yes	183 (53)
No	161 (47)
Education	
High school or more	299 (87)
Less than high school	45 (13)
Marital Status	
Married at time of diagnosis	195 (57)
Not married at time of diagnosis	149 (43)

(Continued)

TABLE XI

(CONTINUED)

CHARACTERISTIC	N (%)
Census Tract Poverty	
Low poverty [a]	292 (85)
High poverty [b]	52 (15)
Census Tract Education	
High education [c]	262 (76)
Low education [d]	82 (24)
Socioeconomic Status Index	
Higher SES [e]	251 (73)
Moderate SES [f]	41 (12)
Lower SES [g]	52 (15)
Pathologic Grade	
Borderline	68 (20)
Low-grade 1	41 (12)
High-grade 2-4	212 (62)
Unclassified	23 (6)
Histologic Sub-Type	
Mucinous	61 (18)
Clear cell	22 (6)
Endometrioid	54 (16)
Serous	170 (49)
Undifferentiated	17 (Nervi et al.)
Unclassified	20 (6)

[a.] Low poverty: <1/3 of the population living below poverty.
[b.] High poverty: ≥1/3 of the population living below poverty.
[c.] High education: <1/3 of the population with <high school education.
[d.] Low education: ≥1/3 of the population with <high school education.
[e.] Higher SES: low poverty and high education.
[f.] Moderate SES: either low poverty and high education, or high poverty and low education.
[g.] Lower SES: high poverty and low education.

Differences in the distribution of potential predictors of late-stage diagnosis are presented in Table XII. Age at diagnosis ($p = 0.0002$), length of ovulatory period ($p = 0.0004$), family history of breast/ovarian cancer ($p = 0.007$), oral contraceptive use ($p = 0.009$), census tract poverty ($p = 0.05$), index of socioeconomic status ($p = 0.02$), pathologic grade ($p < .0001$), and histologic sub-type ($p < .0001$) were all associated with late-stage diagnosis. There was some suggestion that HRT use ($p = 0.19$), marital status ($p = 0.12$), and census-tract education ($p = 0.11$) may also be associated with late-stage diagnosis.

TABLE XII

PERCENT DISTRIBUTION AND ASSOCIATION OF POTENTIAL PREDICTORS OF LATE-STAGE DIAGNOSIS, BY LATE AND EARLY STAGES

CHARACTERISTIC	LATE-STAGE DIAGNOSIS n=175 (%)	EARLY STAGE DIAGNOSIS n=169 (%)	P-VALUE
Patient Characteristics			
Race			0.65
White	50	50	
Black	54	46	
Age at Diagnosis			0.0002
≤ 40 years	25	75	
41-50 years	50	50	
51-65 years	55	45	
> 65 years	64	36	
Recent BMI			0.32
Normal/overweight	52	48	
Obese	45	55	
Smoking			0.87
Never	50	50	
Ever	51	49	
Age at Menarche			0.95
Older age at onset (>13 years)	51	49	
12-13 years	49	51	
<12 years	51	49	
Length of Ovulatory Period			0.0004
≤28 years	36	64	
29-35 years	45	55	
≥36 years	61	39	
Nulliparity			0.66
Parous	52	48	
Nulliparous	49	51	
Family History of Breast/Ovarian Cancer			0.007
No	43	57	
Yes	57	43	
Proxy Measures of Access to Healthcare			
Hormone Replacement Therapy (missing=3)			0.19
Yes	47	53	
No	54	46	
Hysterectomy			0.54
Yes	47	53	
No	52	48	
Tubal Ligation (missing=1)			0.75
Yes	55	45	
No	51	49	
Oral Contraceptive Use			0.009
Yes	44	56	
No	58	42	

(Continued)

TABLE XII

(CONTINUED)

CHARACTERISTIC	LATE-STAGE DIAGNOSIS n=175 (%)	EARLY STAGE DIAGNOSIS n=169 (%)	P-VALUE
Socioeconomic Status			
Education			0.32
High school or more	50	50	
Less than high school	58	42	
Marital Status			0.12
Married at time of diagnosis	47	53	
Not married at time of diagnosis	56	44	
Census-Tract Poverty			0.05
Low poverty [a]	49	51	
High poverty [b]	63	37	
Census-Tract Education			0.11
High education [c]	48	52	
Low education [d]	59	41	
Socioeconomic Status Index			0.02
Higher SES [e.]	49	51	
Moderate SES [f.]	44	56	
Lower SES [g.]	71	29	
Tumor Characteristics			
Pathologic Grade			<.0001
Borderline	10	90	
Low -grade 1	29	71	
High-grade 2-4	67	33	
Unclassified	65	35	
Histologic Sub-Type			<.0001
Mucinous	10	90	
Clear cell	36	64	
Endometrioid	44	56	
Serous	67	33	
Undifferentiated	71	29	
Unclassified	50	50	

[a.] Low poverty: <1/3 of the population living below poverty.
[b.] High poverty: ≥1/3 of the population living below poverty.
[c.] High education: <1/3 of the population with <high school education.
[d.] Low education: ≥1/3 of the population with <high school education.
[e.] Higher SES: low poverty and high education.
[f.] Moderate SES: either low poverty and high education, or high poverty and low education.
[g.] Lower SES: high poverty and low education.

Age-adjusted relative risks and the results of stratified analysis are presented in Table XIII. Women with a family history of breast or ovarian cancer were more likely to be diagnosed with late-stage ovarian cancer than those without the same family history (RR = 1.23, 95%CI 1.0-1.53). All measures related to socioeconomic status were associated with late-stage diagnosis ($p < 0.20$). Women who were unmarried at the time of their diagnosis were more likely to be diagnosed at later stages, compared to married women (RR = 1.16, 95%CI 0.95-1.41). Women who resided in census tracts with high poverty and in census tracts with low education were significantly more likely to be diagnosed with late-stage disease, compared to those who lived in low-poverty and high-education tracts, respectively (RR = 1.24, 95%CI 1.00-1.54 and RR = 1.17, 95%CI 0.96-1.44, respectively). As would be expected, tumor characteristics were strongly associated with late-stage diagnosis in both Black and White women. Compared to low-grade tumors, both high-grade and unclassified tumors were more likely to be diagnosed at late-stages. Compared to all other histologic sub-types combined, serous tumors were significantly more likely to be diagnosed at later stages (RR = 1.85, 95%CI 1.47-2.34). There was some suggestion that proxy measures of healthcare access may increase the risk of a late-stage diagnosis, although these elevated estimates did not reach statistical significance. Women who had no history of oral contraceptive use or hormone replacement therapy were more likely to be diagnosed at later stages (RR = 1.06, 95%CI 0.82-1.36 and RR = 1.09, 95%CI 0.89-1.35, respectively). Although race was not found to be an independent predictor of late-stage diagnosis in this sample ($p = 0.65$), stratified analysis was conducted in order to determine whether there were differences in predictors of late-stage diagnosis by race (TABLE XIII).

There were no statistically significant racial differences in predictors of late-stage diagnosis observed in the stratified analysis. Nevertheless, some patterns suggest certain potential differences in predictors of late-stage diagnosis by race. Black women who did not use oral contraceptives, which is a

proxy measure of healthcare access, were more likely to be to be diagnosed with late-stage disease than Black women who reported using oral contraceptives (RR = 1.69-0.93-3.08). However, this was not true for Whites (RR = 0.92, 95%CI 0.69-1.23). Marital status at the time of diagnosis was associated with late-stage diagnosis in Blacks, but not in Whites (RR = 2.22, 95%CI 1.05-4.71 and RR = 1.04, 95%CI 0.84-1.30, respectively).

TABLE XIII

RELATIVE RISKS (RR) AND 95% CONFIDENCE INTERVALS (CI) FOR POTENTIAL PREDICTORS OF LATE-STAGE DIAGNOSIS, OVERALL AND STRATIFIED BY RACE

VARIABLE	OVERALL Adjusted [a] RR (95%CI)	BLACK (n=54) Adjusted [a] RR (95%CI)	WHITE (n=290) Adjusted [a] RR (95%CI)
Patient Characteristics			
Length of Ovulatory Period			
≤28 years (Reference)	1.0	1.0	1.0
29-35 years	1.12 (0.76-1.65) [ns]	1.02 (0.36-2.84) [ns]	1.16 (0.76-1.76) [ns]
≥36 years	1.27 (0.80-2.01) [ns]	1.79 (0.54-5.96) [ns]	1.18 (0.71-1.95) [ns]
Family History of Cancer			
No (Reference)	1.0	1.0	1.0
Yes	1.23 (1.0-1.53) ‡	1.35 (0.84-2.19) [ns]	1.21 (0.94-1.55) ‡
Proxy Measures of Access to Healthcare			
Oral Contraceptive Use			
Yes (Reference)	1.0	1.0	1.0
No	1.06 (0.82-1.36) [ns]	1.69 (0.93-3.08) ‡	0.92 (0.69-1.23) [ns]
Hormone Replacement Therapy (missing=3)			
Yes (Reference)	1.0	1.0	1.0
No	1.09 (0.89-1.35) [ns]	0.84 (0.48-1.47) [ns]	1.14 (0.91-1.42) [ns]
Socioeconomic Status			
Marital Status			
Married at time of diagnosis (Reference)	1.0	1.0	1.0
Not married at time of diagnosis	1.16 (0.95-1.41) ‡	2.22 (1.05-4.71) *	1.04 (0.84-1.30) [ns]
Census-Tract Poverty			
Low poverty [b] (Reference)	1.0	1.0	1.0
High poverty [c]	1.24 (1.00-1.54) *	0.92 (0.57-1.49) [ns]	1.34 (1.10-1.62) *
Census-Tract Education			
High education [d](Reference)	1.0	1.0	1.0
Low education [e]	1.17 (0.96-1.44) ‡	0.95 (0.59-1.54) [ns]	1.27 (1.01-1.58) *
Socioeconomic Status Index			
Higher SES [f]	1.0	1.0	1.0
Moderate SES [g]	0.90 (0.66-1.24) [ns]	0.48 (0.21-1.07) ‡	1.02 (0.82-1.27) [ns]
Lower SES [h]	1.35 (1.10-1.67) *	0.81 (0.47-1.41) ‡	1.33 (1.11-1.60) *
Tumor Characteristics			
Pathologic Grade			
Low-grade 1 (Reference)	1.0	1.0	1.0
Borderline	0.36 (0.16-0.85) *	-	0.44 (0.18-1.07) ‡
High-grade 2-4	2.18 (1.34-3.55) *	1.85 (0.72-4.74) ‡	2.31 (1.31-4.08) *
Unclassified	2.11 (1.20-3.70) *	1.91 (0.70-5.24) ‡	2.11 (1.08-4.14) *
Histologic Sub-Type			
Combined types	1.0	1.0	1.0
Serous	1.85 (1.47-2.34) *	1.89 (1.05-3.41) *	1.85 (1.43-2.39) *

* p-value is <0.05; ‡ p-value is<0.20; [ns] p-value is not statistically significant.

[a] Minimally adjusted for age at diagnosis.

[b] Low poverty: <1/3 of the population living below poverty.

[c] High poverty: ≥1/3 of the population living below poverty.

[d] High education: <1/3 of the population with <high school education.

[e] Low education: ≥1/3 of the population with <high school education.

[f] Higher SES: low poverty and high education. [g] Moderate SES: either low poverty and high education, or high poverty and low education.

[h] Lower SES: high poverty and low education.

Multivariate models were fit in order to develop a final model predicting late-stage diagnosis in the study population of Black and White women with ovarian cancer (Table XIV). In order to address the problem of multicollinearity with respect to the census-tract variables, we estimated three series of models, with each series including only one of these variables. The first series of models included census-tract poverty. The second series included census-tract education. The third series included the socioeconomic status index variable, in order to account for measures of poverty and education in these multivariate models. Due to the small sample size, pathologic grade and socioeconomic status index were collapsed into dichotomous variables in order to obtain model convergence. Nevertheless, most models with census-tract education failed to converge. The final age-adjusted model included census-tract poverty, pathologic grade, and histologic sub-type. The relative risks and confidence intervals for this age-adjusted model are presented in Table XV.

TABLE XIV

RESULTS OF MULTIVARIATE MODELS [a.]

SERIES	VARIABLES	MODEL #1 β (SE)	MODEL #2 β (SE)	MODEL #3 β (SE)	MODEL #4 β (SE)	MODEL #5 [b] β (SE)
Series 1 Census-Tract Poverty	Age at diagnosis (Continuous)	0.02 (0.004)*	0.02 (0.004)*	0.02 (0.004)*	0.006 (0.004)^{ns}	-0.003 (0.004)^{ns}
	Family history of breast/ovarian cancer (Yes)	-	0.25 (0.11)*	0.24 (0.11)*	0.13 (0.10) ^{ns}	-
	Marital status (No)	-	-	0.12 (0.10)^{ns}	-	-
	Census poverty (Low)	0.21 (0.11)*	0.28 (0.11)*	0.26 (0.11)*	0.18 (0.09)^{ns}	0.06 (0.07)^{ns}
	Pathologic grade (High-grade)	-	-	-	1.25 (0.22)*	1.37 (0.21)*
	Histologic sub-type (Serous)	-	-	-	-	0.70 (0.11)*
	-2LNL	456.222 (341)	450.599 (340)	449.203	393.396	343.102
	(df)			(339)	(339)	(339)
Series 2 Census-Tract Education	Age at diagnosis (Continuous)	0.02 (0.004)*				
	Family history of breast/ovarian cancer (Yes)	-				
	Marital status (No)	-				
	Census Education (Low)	0.16 (0.11)^{ns}		Models failed to converge		
	Pathologic grade (High-grade)	-				
	Histologic sub-type (Serous)	-				
	-2LNL	457.065				
	(df)	(341)				
Series 3 SES Index	Age at diagnosis (Continuous)	0.02 (0.004)*	0.02 (0.004)*	0.02 (0.004)*	0.006 (0.004)^{ns}	0.002 (0.003)^{ns}
	Family history of breast/ovarian cancer (Yes)	-	0.23 (0.10)*	0.22 (0.11)*	0.10 (0.09) ^{ns}	0.12 (0.17)^{ns}
	Marital status (No)	-	-	0.13 (0.09)^{ns}	-	-
	SES Index (Lower)	0.30 (0.11)*	0.35 (0.10)*	0.34 (0.10)*	0.25 (0.09)*	0.12 (0.17)^{ns}
	SES Index (Mixed)	-0.10 (0.16)^{ns}	-0.07(0.16)^{ns}	-0.08(0.16)^{ns}	-0.05(0.15)^{ns}	-
	Pathologic grade (High-grade)	-	-	-	1.24 (0.22)*	0.64 (0.12)*
	Histologic sub-type (Serous)	-	-	-	-	0.39 (0.08)*
	-2LNL	452.429	447.324	445.318	390.245	370.973
	(df)	(340)	(339)	(338)	(338)	(339)

[a.] Neither the log-transformed nor the quadratic form of age at diagnosis improved the model fit appreciably.
[b.] Final multivariate model.

TABLE XV

FINAL MODEL PREDICTING LATE-STAGE DIAGNOSIS FOR OVARIAN CANCER, ADJUSTING FOR AGE AT DIAGNOSIS

MODEL VARIABLES	PARAMETER ESTIMATE (SE)	RR (95% CI)
Census-Tract Poverty		
Low poverty [a] (Reference)	-	1.0
High poverty [b]	0.06 (0.070)	1.06 (0.93-1.22)
Pathologic Grade		
Borderline & Low-grade 1 (Reference)	-	1.0
High-grade 2-4 & Unclassified	1.37 (0.21)	3.94 (2.59-5.99)
Histologic Sub-Type		
Combined types	-	1.0
Serous	0.70 (0.11)	2.01 (1.63-2.48)

[a.] Low poverty: <1/3 of the population living below poverty.
[b.] High poverty: ≥1/3 of the population living below poverty.

C. Discussion

Older age at diagnosis, longer length of ovulatory period, positive family history of breast or ovarian cancer, hormone replacement therapy and oral contraceptive use (as proxy measures of healthcare access), lower socioeconomic status (estimated by census-tract poverty and education), and tumor characteristics were all found to be independent predictors of late-stage diagnosis in the univariate analysis. However, after controlling for age at diagnosis, only lower socioeconomic status and tumor characteristics remained significant predictors of late-stage diagnosis.

In our analysis, socioeconomic status was associated with late-stage diagnosis. This association was strongest for women residing in high-poverty census tracts, as well as those at the lowest level of the socioeconomic status index. Having fewer economic resources has consistently been associated with late-stage diagnosis for a number of cancers (Clegg et al. 2009). Lower socioeconomic status increases the likelihood of late-stage diagnosis through differential access to care, as well as through lower educational attainment. Differential utilization of preventive care has been associated with late-stage diagnosis for a variety of cancers, including breast, prostate, colon, and uterine cancer (Gornick et al. 2004). There is a well-established correlation between educational attainment and overall health as well as health-seeking behavior, such that a greater proportion of individuals with lower educational attainment receive late-stage diagnoses, particularly for cancers with screening mechanisms (Lleres 2005; Gornick 2008).

Despite the fact that proxy measures of healthcare access were not significantly associated with late-stage diagnosis in our analysis, access to healthcare is an important contributing factor for late-stage diagnosis for a number of cancers (Potosky et al. 1998; Hegarty et al. 2000; Halpern et al. 2008). Diagnosis of early-stage ovarian cancer is not typical, and it is most often found in association with non-cancer-related illnesses and during routine pelvic exams conducted in women with a family history of

breast/ovarian cancer. These situations pre suppose a higher level of routine care. Thus, it is reasonable to infer that better access to, and greater utilization of, healthcare would increase the likelihood of detecting early-stage ovarian cancer. More direct measures of access to healthcare, such as employment and insurance status should be investigated with respect to late-stage diagnosis of ovarian cancer.

The observed relationship between tumor characteristics and late-stage diagnosis, specifically high-grade and serous tumors, is not unexpected. While distinct from staging, pathologic grade is also a measure of tumor status because more advanced-stage tumors are less differentiated. Serous tumors, along with undifferentiated tumors, represent the more aggressive histologic sub-types (Benedet 2000; Benedet et al. 2000).

Race was not an independent predictor of late-stage diagnosis, so it was not included in subsequent multivariate models. However, the stratified analysis suggested some potential differences in predictors of late-stage diagnosis. There were racial differences in the magnitude of the risk estimates for marital status, as well as for two proxy measures of healthcare access—use of hormone replacement therapy and oral contraceptives. And while caution should be used not to over-interpret these differences given the overlap in the confidence intervals, these measures suggest that there may be racial differences in predictors of late-stage diagnosis that should be explored further.

D. **Strengths and Limitations**

While the relatively small number of Black women in our sample mirrors the lower incidence of ovarian cancer in Blacks, it does limit our power to detect statistically significant differences. It has been suggested that histologic sub-type may play a role in the racial disparity in ovarian cancer survival (Burges et al. 2011). However, the relatively small number of non-serous tumors did not allow us to explore this fully with respect to late-stage diagnosis. The lack of information on factors, other than census-tract poverty

and education, that may influence late-stage diagnosis through access to healthcare, such as employment and insurance status is also an important limitation. Nevertheless, there are also several noteworthy strengths. Epithelial ovarian cancer diagnosis was verified through two independent pathology reviews. Moreover, this population-based study represented 83% of hospitals in Cook County, Illinois, which reflects a wide variety of institutions and contributes to the heterogeneity of the study.

E. **Conclusion**

Currently, there is no population-based screening tool for ovarian cancer (MacDonald et al. 1998). The cell-surface glycoprotein CA-125 is shed from the surface of damaged cells and can be elevated as a result of certain malignant conditions. Accordingly, it has been considered as a screening test and has some utility as a tumor marker to assess response to treatment and as a marker for recurrent ovarian cancer (Verheijen et al. 1999). The combination of routine pelvic exams, transvaginal ultrasound, and CA-125 levels has been shown to increase the sensitivity and specificity of screening for ovarian cancer (Jacobs et al. 1993; Schutter et al. 1998). However, these procedures are expensive, invasive, and unlikely to be available to women with limited economic and medical resources. In the absence of a viable screening mechanism, a better understanding of the risk factors for late-stage diagnosis is necessary. Our findings suggest that late-stage diagnosis may be influenced by, not only tumor characteristics, but also access to healthcare and socioeconomic status. Our analysis suggests that race is not an independent predictor of late-stage diagnosis. Nevertheless, there is a clear survival disadvantage for Black women diagnosed with ovarian cancer, and additional work is needed in order to understand the contributors to this disparity.

IV. THE ROLE OF NEIGHBORHOOD CONTEXT IN THE RACIAL DISPARITY IN FIVE-YEAR SURVIVAL

A. Introduction

There are several well-established prognostic factors that play a critical role in ovarian cancer survival, yet they may not fully account for the differential survival observed between Black and White women. The neighborhoods in which women reside may also contribute to these differences. In the second aim of this dissertation project, we demonstrated that area-level measures of socioeconomic status are associated with five-year survival following a diagnosis with ovarian cancer. Greater concentrated disadvantage and lower concentrated affluence, measured at the census-tract level, were both determined to be associated with shorter survival time. In addition, we demonstrated that area-level measures of socioeconomic status are important mediators of the racial disparity in five-year survival, following a diagnosis with ovarian cancer. Here, using cases of ovarian cancer diagnosed in Cook County, Illinois between 1994 and 1998[8], we will extend our work with these two area-level measures by estimating the effects of neighborhood context and individual-level prognostic factors on the observed survival disparity between Black and White women with ovarian cancer. We hypothesize that neighborhood context has a significant independent effect on the racial disparity in survival, such that greater concentrated disadvantage mitigates the effect of race, and further, that greater concentrated affluence reduces the risk of shorter survival in both Black and White women diagnosed with ovarian cancer.

In their seminal book, Massey and Denton documented the trend toward spatial concentrations of poverty and affluence in the United States that began in the 1970s. The increase in poverty and affluence, and the increased geographic concentrations of both these conditions, has led simultaneously to the emergence of an urban underclass in areas of concentrated poverty, and to increased inequality resulting

[8] Median follow-up time was 12.75 years.

from greater concentrations of affluence (Massey 1993). It is possible that the observed survival disadvantage in Black women derives, at least in part, from the increased inequality between the neighborhoods in which Black and White women, respectively, reside. Specifically, it is possible that neighborhood context plays a role in the differential survival between Blacks and Whites with ovarian cancer, such that the neighborhood where a patient resides impacts her survival independent of her own individual tumor characteristics.

Figure 5 depicts a conceptual model for the effects of neighborhood context and prognostic factors on the survival disparity in Black and White women with ovarian cancer. Neighborhood context is represented by two well-established measures of neighborhood structural characteristics: concentrated disadvantage and concentrated affluence (Sampson 1999; Browning 2006). Neighborhood factors—such as neighborhood institutions and resources, social stressors, and neighborhood social networks (Ellen 2001)—provide a contextual basis that may positively or negatively influence survival. For example, high-quality healthcare providers may be more likely to be located in affluent neighborhoods. Conversely, living in neighborhoods of concentrated disadvantage may increase barriers to receiving healthcare, such as relative lack of safety and transportation (Barrett et al. 2008), which can lead to delays in diagnosis and difficulty complying with the challenging treatment regimen for ovarian cancer.

Prognostic factors are represented by four measures related to tumor characteristics: stage at diagnosis; pathologic grade; histologic sub-type; and residual lesion status. Stage and pathologic grade reflect the status of the tumor at the time of diagnosis, and they are important determinants of treatment as well as predictors of ovarian cancer survival (Vergote et al. 1992). Histologic sub-type and residual lesion status characterize tumor aggressiveness. More aggressive tumors, because they develop faster, tend to be more advanced at diagnosis but are also less responsive to chemotherapeutic treatment and less likely

to be completely removed through cytoreductive surgery (Omura et al. 1991; Akahira et al. 2001; Winter et al. 2007).

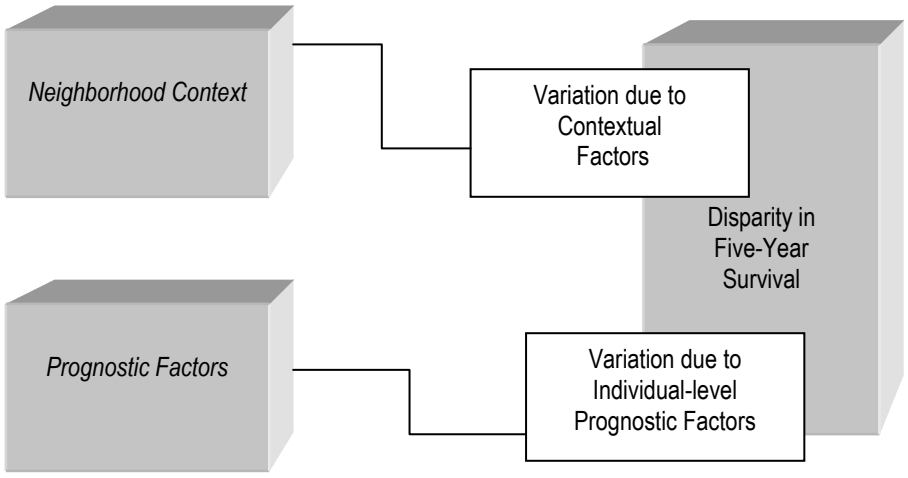

Figure 5 Conceptual model for the effect of neighborhood context and prognostic factors on the racial disparity in five-year survival.

B. **Results**

By the end of the follow-up period, 88% of Black women versus 73% of White women in our overall study population of 589 cases had died ($p = 0.001$). The mean length of survival after diagnosis for White women was 78.7 months, whereas for Black women it was 17.3 months shorter, at 61.4 months ($p = 0.007$). 50% of Black women had died at 38 months after diagnosis (95%CI 31.9-52.6), compared to 64 months after diagnosis for 50% of White women (95%CI 52.8-77.2). Figure 6 depicts the cumulative probability of overall survival (i.e., death from all causes), by race, as well as that of ovarian cancer-specific survival (i.e., ovarian), by race. Overall survival for Black and White women in the study begins to diverge at year one following diagnosis, and the hazard of death for Black women in this sample was 1.5 (95%CI 1.2-1.8). The ovarian cancer-specific survival curves begin to diverge slightly later—however, a significant

survival disparity persists there as well. Overall, 63% of Black women in our sample survived for less than five years following diagnosis, compared to 48% of White women (p = 0.007).

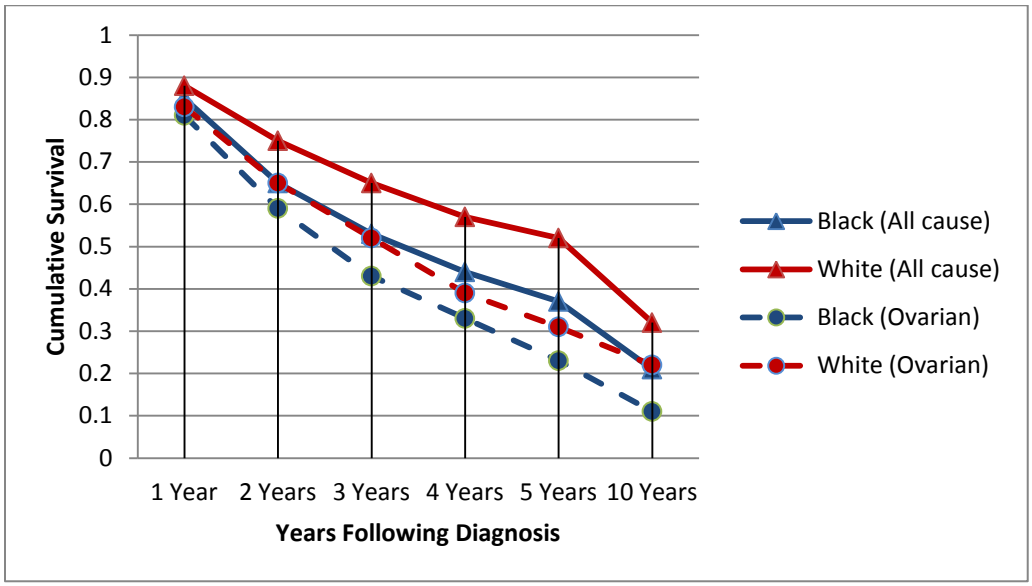

Figure 6 Cumulative probability of overall survival (all causes of death) and ovarian cancer survival (ovarian cancer death), by race.

Black and White women differed significantly in both measures related to neighborhood context, with more Black women residing in census tracts with greater concentrated disadvantage and lesser concentrated affluence (p < .0001 for both covariates). There were some racial differences in pathologic grade. Compared to White women, a smaller proportion of Black women were diagnosed with borderline tumors, while a larger proportion had unclassified tumors. (p = 0.03). A greater proportion of Black women had more aggressive histologic sub-types (p = 0.11) and larger residual lesions following surgery (p = 0.20), compared to White women. There were no appreciable differences between Black and White women in terms of age or stage at diagnosis (TABLE XVI).

TABLE XVI

PERCENT DISTRIBUTION AND ASSOCIATION OF CONCENTRATED DISADVANTAGE, AFFLUENCE, AND TUMOR CHARACTERISTICS, BY RACE

CHARACTERISTIC	Blacks n=100 (%)	Whites n=489 (%)	P-VALUE
Age at Diagnosis			0.63
≤45 years	28	26	
46-60 years	34	39	
61+ years	38	35	
Five-Year Survival			0.007
≥Five-years	37	51	
<Five-years	63	48	
Concentrated Disadvantage			<.0001
Low (1st tertile)	4	31	
Medium (2nd tertile)	12	57	
High (3rd tertile)	84	12	
Concentrated Affluence			<.0001
High (3rd tertile)	24	55	
Medium (2nd tertile)	28	24	
Low (1st tertile)	48	21	
FIGO Stage at Diagnosis			0.63
I	32	39	
II	10	8	
III	47	43	
IV	11	10	
Pathologic Grade			0.03
Borderline	15	20	
Low-grade 1	11	11	
High-grade 2-4	60	63	
Unclassified	14	6	
Histologic Sub-Type			0.11
Mucinous	11	18	
Clear cell	7	6	
Endometrioid	9	15	
Serous	53	48	
Undifferentiated	12	16	
Unclassified	8	5	
Residual Lesion Status (missing=27)			0.20
<2 centimeters	52	59	
≥2 centimeters	48	41	

Women living less than five years after diagnosis ("shorter survival") were an average of 5.6 years older at diagnosis than women living five years or more after diagnosis ("longer survival") ($p < .0001$). Differences in the distribution of variables relating to neighborhood context and prognostic factors were compared by shorter and longer survival time (TABLE XVII). Shorter survival was associated with greater

concentrated disadvantage (p = 0.006), later-stage diagnoses, high-grade tumors, more aggressive histologic sub-types, and larger residual lesions following surgery (p < .0001 for all covariates).

TABLE XVII

PERCENT DISTRIBUTION AND ASSOCIATION OF NEIGHBORHOOD CONTEXT AND PROGNOSTIC FACTORS, BY SHORTER SURVIVAL TIME (<FIVE YEARS AFTER DIAGNOSIS)

VARIABLE	SURVIVAL <5 YEARS n=298 (%)	P-VALUE
Age at Diagnosis		<.0001
≤45 years	34	
46-60 years	52	
61+ years	63	
Concentrated Disadvantage (missing=8)		0.006
Low (1st tertile)	47	
Medium (2nd tertile)	47	
High (3rd tertile)	62	
Concentrated Affluence (missing=8)		0.12
High (3rd tertile)	47	
Medium (2nd tertile)	52	
Low (1st tertile)	57	
FIGO Stage at Diagnosis		<.0001
I	21	
II	59	
III	67	
IV	82	
Pathologic Grade		<.0001
Borderline	17	
Low-grade 1	32	
High-grade 2-4	61	
Unclassified	76	
Histologic Sub-Type		<.0001
Mucinous	45	
Clear cell	46	
Endometrioid	31	
Serous	54	
Undifferentiated	73	
Unclassified	65	
Residual Lesion Status (missing=27)		<.0001
<2 centimeters	34	
≥2 centimeters	76	

Only stage at diagnosis and residual lesion status were highly correlated (0.76, $p < .0001$). This suggests some overlap in the measures. In order to avoid the problem of multicollinearity, residual lesion status was dropped from regression models evaluating the group of prognostic factors (TABLE XVIII).

TABLE XVIII

CORRELATION MATRIX FOR VARIABLES REPRESENTING PROGNOSTIC FACTORS

Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0

	Stage	Grade	Histologic Sub-Type	Residual Lesion Status
Stage	1.0 -	0.19626 <.0001	-0.02913 0.4764	0.76386 <.0001
Grade	0.19626 <.0001	1.0 -	0.01211 0.7671	0.11694 0.0051
Histologic Sub-Type	-0.02913 0.4764	-0.01211 0.7671	1.0 -	-0.08504 0.0422
Residual Lesion Status	0.76386 <.0001	0.11694 0.0051	-0.08504 0.0422	1.0 -

The independent effect of neighborhood context (i.e., concentrated disadvantage and concentrated affluence) and individual-level prognostic factors (i.e., stage at diagnosis, pathologic grade, histologic sub-type) on the racial disparity in overall five-year survival were evaluated in a series of nested log-linear risk models. The first model controls for age at diagnosis and provides a baseline estimate of the racial disparity in five-year survival. The next two models add the group of prognostic factors (model 2) and concentrated disadvantage (model 3) in order to determine the separate effects of these factors on the regression coefficient for race. The fourth model includes both the prognostic factors and concentrated disadvantage. The fifth and sixth models evaluate the effect of concentrated affluence, with and without the prognostic factors, on the racial disparity in overall survival, (TABLE XIX). As expected, there was an

appreciable difference in the risk estimate for race once the prognostic factors were incorporated into the model. The relative risk of shorter survival for Blacks compared to Whites was reduced from 1.27 (95% CI 1.08-1.49) in the age-adjusted model to 1.18 (95%CI 1.03-1.35) in the model controlling for age and the prognostic factors. Consistent with our hypothesis, once concentrated disadvantage was included in the model, the effect of race on shorter survival was no longer statistically significant (RR = 1.19, 95%CI 0.92-1.53). When the prognostic factors were included as well, the effect was further mitigated (RR = 1.12, 95%CI 0.91-1.37).

To some extent, the inclusion of concentrated affluence in the model reduced the risk of shorter survival for Black women. The relative risk was reduced from 1.27 (95%CI 1.08-1.49) in the age-adjusted model to 1.24 (95% CI 1.04-1.48) in the age adjusted model that also accounted for concentrated affluence (model 1 versus model 5). However, the inclusion of the prognostic factors in the age-adjusted model resulted in a more meaningful reduction in the risk estimate (RR = 1.16, 95%CI 1.01-1.33).

Neighborhood context—specifically, concentrated disadvantage—appears to have a threshold effect on survival. In order to tease out this potential effect, we estimated additional models using two categorical versions of these variables (tertiles and quintiles), as well as a quadratic transformation (TABLE XX). These results confirmed that the effect of concentrated disadvantage on shorter survival operates primarily through the highest levels of disadvantage. For example, women living in neighborhoods with the highest tertile of concentrated disadvantage have a non-statistically significant greater risk of shorter survival, compared to women residing in neighborhoods in the lowest tertile (RR = 1.05, 95%CI 0.85-1.29). There was no increased risk in women living in neighborhoods with moderate levels of concentrated disadvantage (RR = 0.97, 95%CI 0.82-1.16). While many of the estimates relative to concentrated disadvantage were not statistically significant, this is likely due to the small sample size and the relatively

large number of variables in the multivariate models. In the simplest models, concentrated disadvantage was independently associated with shorter survival ($p = 0.0006$). Moreover, in all of the models with concentrated disadvantage, the inclusion of this variable eliminated the effect of race on shorter survival.

TABLE XIX

RELATIVE RISKS (RR) AND 95% CONFIDENCE INTERVALS (CI) TO EVALUATE THE EFFECT OF NEIGHBORHOOD CONTEXT ON THE RACIAL DISPARITY IN OVERALL SURVIVAL

	BASELINE AGE-ADJUSTED	PROGNOSTIC FACTORS	CONCENTRATED DISADVANTAGE		CONCENTRATED AFFLUENCE	
VARIABLE	Model #1	Model #2	Model # 3	Model # 4	Model #5	MODEL # 6
Race						
White (reference)	1.0	1.0	1.0	1.0	1.0	1.0
Black	1.27 (1.08-1.49) *	1.18 (1.03-1.35) *	1.19 (0.92-1.53) ns	1.12 (0.91-1.37) ns	1.24 (1.04-1.48) *	1.16 (1.01-1.33) *
ge at Diagnosis (Years)	1.02 (1.00-1.02) *	1.01 (1.0-1.02) *	1.01 (1.0-1.02) *	1.01 (1.0-1.01) *	1.01 (1.0-1.02) *	1.02 (1.00-1.02) *
Stage at Diagnosis	-		-		-	
Stage I (reference)		1.0		1.0		1.0
Stage II		2.58 (1.83-3.65) *		2.55 (1.81-3.60) *		2.54 (1.80-3.59) *
Stage III		2.40 (1.77-3.25) *		2.34 (1.72-3.18) *		2.35 (1.73-3.18) *
Stage IV		2.73 (2.00-3.73) *		2.67 (1.96-3.65) *		2.68 (1.97-3.66) *
Pathologic Grade	-		-		-	
Low Grade (reference)		1.0		1.0		1.0
High Grade		1.76 (1.29-2.39) *		1.75 (1.29-2.38) *		1.75 (1.29-2.38) *
Histologic Sub-Type	-		-		-	
Serous (reference)		1.0		1.0		1.0
All Other Types Combined		0.99 (0.87-1.14) ns		0.99 (0.86-1.14) ns		0.99 (0.87-1.14) ns
Concentrated Disadvantage (SD)	-	-	1.02 (0.98-1.03) ns	1.02 (0.99-1.03) ns	-	-
Concentrated Affluence (SD)	-	-	-	-	0.99 (0.96-1.02) ns	0.99 (0.97-1.02) ns
-2 LL	783.110	612.172	771.535	605.171	771.725	605.185
(DF)	(586)	(550)	(577)	(541)	(577)	(541)

*p < 0.05, ns=not statistically significant

TABLE XX

RELATIVE RISKS (RR) AND 95% CONFIDENCE INTERVALS (CI) TO EVALUATE THE THRESHHOLD EFFECT OF CONCENTRATED DISADVANTAGE ON THE RACIAL DISPARITY IN SHORTER SURVIVAL (ALL CAUSES OF DEATH)

VARIABLE	CONTINUOUS	TERTILES	QUINTILES	QUADRATIC
Race				
White (reference)	1.0	1.0	1.0	1.0
Black	1.12 (0.91-1.37) ^{ns}	1.13 (0.95-1.34) ^{ns}	1.11 (0.92-1.34) ^{ns}	1.17 (0.97-1.35) ^{ns}
Age at Diagnosis	1.01 (1.00-1.01) ^{ns}	1.02 (1.00-1.02) ^{ns}	1.01 (1.00-1.01) ^{ns}	1.01 (1.00-1.01) ^{ns}
Stage at Diagnosis				
Stage I (reference)	1.0	1.0	1.0	1.0
Stage II	2.55 (1.81-3.60) *	2.59 (1.83-3.67) *	2.59 (1.82-3.67) *	2.54 (1.80-3.59) *
Stage III	2.34 (1.72-3.18) *	2.34 (1.76-3.25) *	2.39 (1.76-3.25) *	2.36 (1.74-3.20) *
Stage IV	2.67 (1.96-3.65) *	2.72 (1.99-3.71) *	2.71 (1.98-3.70) *	2.69 (1.97-3.67) *
Pathologic Grade				
Low Grade (reference)	1.0	1.0	1.0	1.0
High Grade	1.75 (1.29-2.38) *	1.76 (1.30-2.40) *	1.76 (1.30-2.40) *	1.75 (1.28-2.37) *
Histologic Sub-type				
Serous (reference)	1.0	1.0	1.0	1.0
All Other Types Combined	0.99 (0.86-1.14) ^{ns}	0.99 (0.86-1.14) ^{ns}	0.99 (0.86-1.14) ^{ns}	0.99 (0.87-1.14) ^{ns}
Concentrated Disadvantage (SD)	1.02 (0.99-1.03) ^{ns}	-	-	-
Concentrated Disadvantage (SD)	-		-	-
Low (1st tertile) (reference)		1.0		
Medium (2nd tertile)		0.98 (0.82-1.16) ^{ns}		
High (3rd tertile)		1.05 (0.85-1.29) ^{ns}		
Concentrated Disadvantage (SD)	-	-		-
1st quintile (reference)			1.0	
2nd quintile			0.97 (0.76-1.20) ^{ns}	
3rd quintile			1.00 (0.78-1.26) ^{ns}	
4th quintile			0.98 (0.76-1.23) ^{ns}	
5th quintile			1.06 (0.84-1.34) ^{ns}	
Concentrated Disadvantage (SD)	-	-	-	
Quadratic				1.01 (0.99-1.01) ^{ns}
-2 LL (DF)	605.171 (541)	781.962 (584)	611.348 (546)	605.635 (541)

*p < 0.05, ^{ns}=not statistically significant

The second series of models, which restricted the analysis to ovarian cancer deaths, produced similar results (TABLE XXI). The inclusion of concentrated disadvantage eliminated the effect of race on shorter survival, whereas the inclusion of concentrated affluence had a negligible effect on the risk of shorter survival in Black women.

TABLE XXI

RELATIVE RISKS (RR) AND 95% CONFIDENCE INTERVALS (CI) TO EVALUATE THE EFFECT OF NEIGHBORHOOD CONTEXT ON THE RACIAL DISPARITY IN SHORTER SURVIVAL (OVARIAN CANCER DEATH) [a]

VARIABLE	BASELINE AGE-ADJUSTED MODEL	PROGNOSTIC FACTORS	PROGNOSTIC FACTORS AND CONCENTRATED DISADVANTAGE	PROGNOSTIC FACTORS AND CONCENTRATED AFFLUENCE
Race				
White (reference)	1.0	1.0	1.0	1.0
Black	1.27 (1.07-1.51) *	1.17 (1.02-1.35) *	1.11 (0.91-1.36) ns	1.16 (1.00-1.34) *
Stage at Diagnosis	-			
Stage I (reference)		1.0	1.0	1.0
Stage II		2.74 (1.89-4.00) *	2.71 (1.87-3.94) *	2.70 (1.86-3.92) *
Stage III		2.58 (1.85-3.59) *	2.51 (1.80-3.50) *	2.52 (1.81-3.51) *
Stage IV		2.94 (2.10-4.12) *	2.88 (2.06-4.02) *	2.89 (2.07-4.03) *
Pathologic Grade	-			
Low Grade (reference)		1.0	1.0	1.0
High Grade		1.93 (1.38-2.72) *	1.93 (1.37-2.70) *	1.93 (1.37-2.70) *
Histologic Sub-type	-			
Serous (reference)		1.0	1.0	1.0
All Other Types Combined		0.98 (0.86-1.13) ns	0.98 (0.85-1.13) ns	0.98 (0.86-1.13) ns
Concentrated Disadvantage (SD)	-	-	1.02 (0.98-1.03) ns	-
Concentrated Affluence (SD)	-	-	-	0.99 (0.96-1.02) ns

[a.] All models adjusted for age at diagnosis
* $p < 0.05$, ns=not statistically significant

C. **Discussion**

Our results suggest that neighborhood context—specifically, concentrated disadvantage—has an independent effect on the racial disparity in five-year survival after diagnosis with ovarian cancer above and beyond the effects of prognostic factors. Importantly, when concentrated disadvantage was accounted for, the effect of race on shorter survival was no longer statistically significant.

In addition, we observed an apparent threshold effect with respect to concentrated disadvantage. Women residing in the most disadvantaged census tracts had an increased risk of shorter survival,

compared to women residing in the least disadvantaged census tracts. However, there were no increased risks for women residing in only moderately disadvantaged census tracts.

The hypothesis that greater concentrated affluence reduces the risk of shorter survival was not supported in our analysis. After accounting for prognostic factors, the inclusion of concentrated affluence reduced the relative risk of shorter survival in Black women from 1.18 to 1.16 (model 2 versus model 6, TABLE XIX).

Our analysis suggests, first, that neighborhood context plays a significant role in influencing survival for Black women and, second, that increasing socioeconomic status yields diminishing returns in terms of reducing the risk of shorter survival in women diagnosed with ovarian cancer. Because of the lethal nature of ovarian cancer, treatment fails at a certain point regardless of one's own socioeconomic circumstances (i.e., the additional healthcare that may correspond to living in a more affluent neighborhood will cease to make a difference above a certain level of relative affluence).

Conversely, there are several ways in which living in neighborhoods with higher levels of concentrated disadvantage may contribute to worse survival for Black women. Massey and Denton describe the damaging social consequences that follow from residential segregation and economic deprivation. These include social and economic isolation, as well as a structural environment of physical decay, crime, and social disorder (Massey 1993). Neighborhood-based social networks may increase or decrease awareness of health issues and available providers, which may lead to earlier or later diagnosis, respectively. The quality of these social networks is likely to impact the degree of social support that residents receive (Ellen 2001). The presence of strong social relationships may improve an individual's health-seeking behavior (Gehlert et al. 2008). Conversely, socially isolated women may be more likely to ignore the non-specific symptoms of early-stage disease, enabling tumors to progress undetected.

In addition, residents of disadvantaged neighborhoods are likely to have fewer economic resources. The economic deprivation that accompanies living in a disadvantaged neighborhood may limit access to, and the availability of, high-quality healthcare (Berk et al. 1995; Andersen 2001; Kirby et al. 2005). Social stressors such as high crime increase stress. The fear and stress associated with living in an area of high crime or unemployment, or both, may make one's health a low priority. The treatment regimen for ovarian cancer is grueling and complicated, and living in communities with high crime and structural inadequacies (e.g., limited transportation options) may make compliance particularly challenging. In short, living in a neighborhood of increased concentrated disadvantage adds an "additional layer of vulnerability" over and above one's own socioeconomic circumstances (Browning 2006).

The limited role that living in a neighborhood with higher concentrated affluence appears to play in affecting survival suggests that, as with any social good, there is diminishing marginal utility with respect to the derived benefits, and this is the case as a result of the lethal nature of ovarian cancer. Early detection and optimal treatment have been shown to prolong survival. Ultimately, however, treatment fails regardless of the level of care that living in a neighborhood with higher relative wealth may purchase.

D. **Strengths and Limitations**

To our knowledge, this is the first analysis to explore the effect of neighborhood context on the racial disparity in survival for women diagnosed with ovarian cancer. A few prior analyses have assessed the role of socioeconomic status in accounting for disparities in ovarian cancer survival between Black and White women. Du and colleagues found that rates of receiving optimal treatment for ovarian cancer were significantly lower in women residing in areas in the lowest quartile of socioeconomic status (Du et al. 2011). Higher residential-area income has also been associated with early stage detection of ovarian cancer, as well as with optimal treatment (Parham et al. 1997). In addition, Terplan and colleagues

evaluated type of insurance as a marker of socioeconomic status and found that public insurance was associated with not only recurrence of, but also increased hazard of death from, ovarian cancer (Terplan et al. 2008).

Diagnoses with epithelial ovarian cancer were verified through a second pathology review following the initial post-surgical review. Of the 71 hospitals in Cook County, Illinois 59 (83%) participated in the original case-control study. This reflects a wide variety of institutions and contributes to the heterogeneity of our study population. Vital status was ascertained through 2008, providing 10-14 years of follow-up, which is substantially longer than single-institution studies of ovarian cancer survival and most population-based analyses. The most significant advances in terms of treatment were in place at the time that our cases were diagnosed and treated (i.e., between 1994 and 1998), so the findings of this analysis remain relevant.

We have used area-level variables (i.e., concentrated disadvantage and affluence) to describe the socioeconomic status of the neighborhoods in which our study population resided at the time of their diagnoses. Although these summary measures represent a more comprehensive measure of overall socioeconomic circumstances than do single census-level variables, we concede that the heterogeneity of the residents within each neighborhood may not be fully accounted for by these measures.

E. **Conclusion**

The prognostic factors evaluated in this analysis are important in terms of both planning treatment and predicting survival of women diagnosed with ovarian cancer. In recent decades, treatment advances have significantly lengthened survival for these women. Yet Black women have both an overall and an ovarian cancer-specific survival disadvantage as compared to White women, and the causes of this relative disadvantage are not well understood.

This analysis aims to advance our understanding of the role that neighborhood context plays in the survival disparity between Black and White women diagnosed with ovarian cancer. Although we have shown that individual-level prognostic factors somewhat diminish this disparity, we have also—and more importantly—shown that neighborhood disadvantage eliminates this disparity, such that race is no longer statistically significant. We considered the role of neighborhood context in the racial disparity in ovarian cancer survival because there are specific characteristics of neighborhoods that have the potential to influence their residents' lives. Limited educational and employment opportunities arising from residential segregation (Williams et al. 2001), as well as weakened infrastructure and social support systems (Sampson 2002), are all aspects of disadvantaged neighborhoods that have the potential to adversely impact individual residents' emotional well-being, sense of community, health outcomes, and—potentially—survival following a cancer diagnosis.

This analysis assumes that concentrated disadvantage and affluence at the census-tract level reflect the socioeconomic status of the residents within these areas. Moreover, we make the additional assumption that the derived variables that make up each measure (e.g., the percentage of the population below poverty or unemployed) reflect neighborhood characteristics that may relate to racial differences in survival. Ultimately, however, these measures of neighborhood context provide only preliminary evidence of the effect of concentrated disadvantage on the racial disparity in survival. Additional questions arise: What particular features of neighborhood disadvantage contribute most to the racial disparity in ovarian cancer survival? How can the apparent effects on survival of social and economic isolation, as well as neighborhood stressors, be measured more directly? Given the absence of a viable screening mechanism for ovarian cancer and the favorable prognosis for early-stage cancers, what public health interventions

might equalize diagnostic and treatment factors for ovarian cancer, particularly in disadvantaged women? Additional studies that seek answers to these questions are warranted.

V. THE ROLE OF MEDIATORS IN THE RACIAL DISPARITY IN FIVE-YEAR SURVIVAL

A. Introduction

Mediation analysis offers a means for investigating the underlying relationship between an independent variable and a dependent variable through an intermediate variable, or mediator (MacKinnon 2008). This method is well-suited to disparities research, because it allows us to quantify the extent to which race may affect an outcome indirectly through a mediator. For our purposes, this method allows us to estimate the relative contributions of various factors in explaining the racial disparity in survival.

Strictly speaking, race defined as either Black or White is not fully analogous to a traditional dichotomous exposure (Kaufman et al. 1999), because the socioeconomic environment associated with being either Black or White also plays a contributing role in health outcomes (Cooper et al. 1997; Krieger et al. 2000). One challenge is to disentangle the effect of race from the effect of socioeconomic environment—of which socioeconomic status is a key component. Mediation analysis allows us to decompose the effect of race on survival into its direct effect and its mediated (i.e., indirect) effect through factors relating to socioeconomic environment.

Figure 7 depicts a conceptual model for hypothesized mediators in the relation between the independent variable race and the dependent variable survival. The clear boxes represent the three domains of the analysis. Survival is fundamentally dependent upon the status of the tumor at the time of diagnosis, tumor aggressiveness, the tumor's response to treatment, and the type of treatment received (Merrill et al. 2010). This conceptual model centers on the mediating role of tumor status and tumor aggressiveness in the relation between race and survival, and on the upstream factors that affect these tumor characteristics.

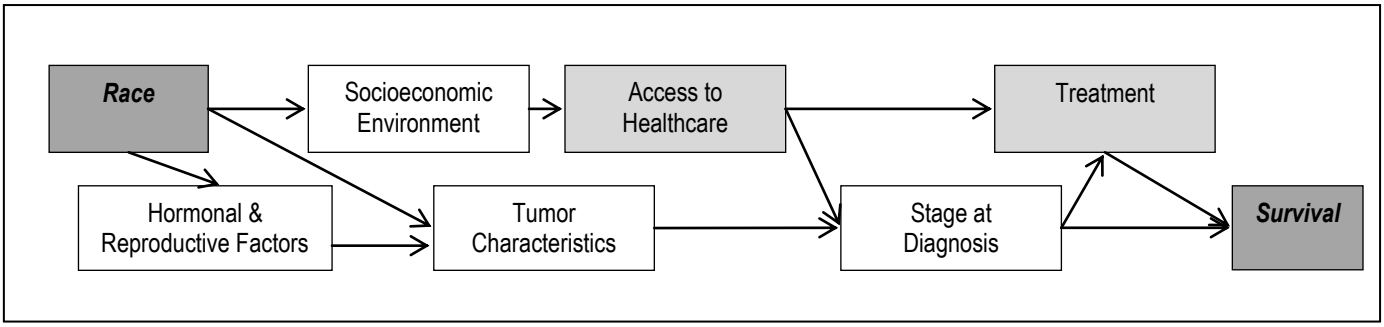

Figure 7 Conceptual model for hypothesized mediators in the relation between race and survival in Black and White women with ovarian cancer.

The experience of being Black or White in our society impacts aspects of one's socioeconomic environment such that, compared to Whites, Blacks are more often disadvantaged in terms of income, formal education, and available resources (Baquet et al. 2000; Cross et al. 2002). Economic disadvantage or, conversely, affluence largely determines one's access to healthcare (Kirby et al. 2005). Frequent and consistent healthcare may enable early stage detection of ovarian cancer through a constellation of non-specific symptoms. In contrast, diminished access to care may result in lost opportunities to diagnose and treat the disease at an early-stage. Hormonal and reproductive factors associated with longer lifetime ovulation and higher levels of gonadotropins may play a role in the survival disparity through differences in tumor characteristics. Tumor aggressiveness is associated with histologic sub-type and residual lesion status, and both are important predictors of survival. Aggressive tumors are more advanced at diagnosis and are less responsive to both surgical and chemotherapeutic treatment, which makes them more likely to recur and metastasize (Cannistra 2004; Mantia-Smaldone et al. 2011). Racial differences in tumor

aggressiveness may contribute to the survival disparity through influencing either the stage at diagnosis or the tumor's response to treatment.

Socioeconomic environment, as shown in the conceptual model, has three components: socioeconomic status, measured by two area-level variables of concentrated disadvantage and affluence; individual educational attainment, measured by years of education; and social relationships, measured by marital status. Socioeconomic environment has the potential to impact survival through differential access to healthcare. Residing in a disadvantaged neighborhood may limit an individual's access to healthcare (Gornick 2008), which in turn may increase the likelihood of advanced disease (Clegg et al. 2009). There is a well-established correlation between educational attainment and overall health (Lleres 2005), such that individuals with lower educational attainment may be less likely to access available healthcare or to comply with difficult treatments (Goldman 2001). The presence of strong social relationships may improve an individual's health-seeking behavior (Gehlert et al. 2008). Conversely, socially isolated women may be more likely to ignore the non-specific symptoms of early-stage disease, thus enabling tumors to progress undetected. Length of ovulatory period and hormone replacement therapy are risk factors associated with longer lifetime ovulation and higher gonadotropin levels (Riman et al. 2004), respectively, and may themselves have an effect on tumor progression and therefore survival.

Ovarian tumor characteristics can be categorized in terms of tumor status at the time of diagnosis and tumor aggressiveness. The stage and the pathologic grade of tumors at diagnosis will be treated as potential mediators to evaluate tumor status. Stage at diagnosis is an important predictor of ovarian cancer survival (Vergote et al. 1992). Women diagnosed with late-stage disease have significantly shorter survival times than those diagnosed with early-stage disease. While distinct from stage at diagnosis, pathologic grade is also a measure of tumor status, because moderately to poorly differentiated tumors signal more

aggressive disease, whereas well-differentiated tumors indicate less aggressive disease. Tumor aggressiveness is also determined by the epithelial histologic sub-type and residual lesion status, and both are important prognostic factors for survival. More aggressive sub-types are less responsive to platinum-based chemotherapy and less likely to be completely removed through cytoreductive surgery (Omura et al. 1991; Akahira et al. 2001; Winter et al. 2007). There are five distinct histologic sub-types of epithelial ovarian cancer based on cell morphology: mucinous; clear cell; endometrioid; serous; undifferentiated; and an unclassified category (Benedet 2000; Benedet et al. 2000). Serous tumors are more common and, along with undifferentiated tumors, represent the more aggressive histologic sub-types. The residual tumor status (in terms of size and number) following primary surgical cytoreduction is an important prognostic factor for ovarian cancer due to the fact that more aggressive tumors are less able to be optimally removed (Omura et al. 1989; Ng et al. 1990; Hoskins et al. 1992; Hoskins et al. 1994; Chi et al. 2001).

We evaluated available covariates related to three domains—i.e., socioeconomic environment, hormonal factors and reproductive factors, and tumor characteristics—in order to determine whether they are mediators in the pathway between race and disparate survival. We hypothesized that factors related to these three domains contribute to the racial disparity in five-yeat survival.

B. **Results**

Black and White women differed significantly in all measures related to socioeconomic environment, with more Black women residing in census tracts with greater concentrated disadvantage and lesser concentrated affluence ($p < .0001$ for both covariates). Compared to White women, a greater proportion of Black women had lower educational attainment ($p < .0001$), were not married at the time of their diagnoses ($p < .0001$), had more aggressive histologic sub-types ($p = 0.11$) and larger residual lesions following surgery ($p = 0.20$). Although there were no statistically significant differences in the length of

ovulatory period between Black and White women, a slightly greater proportion of Black women ovulated for 31 or more years compared to Whites (74% versus 69%, respectively). A smaller proportion of Black women used hormone replacement therapy ($p = 0.03$) and were diagnosed with borderline tumors ($p = 0.03$) (TABLE XXII).

TABLE XXII

PERCENT DISTRIBUTION AND ASSOCIATION OF COMPONENTS OF DOMAINS, BY RACE

CHARACTERISTIC	Blacks n=100 (%)	Whites n=489 (%)	P-VALUE
Age at Diagnosis			0.63
≤45 years	28	26	
46-60 years	34	39	
61+ years	38	35	
Socioeconomic Environment			
Concentrated Disadvantage			<.0001
Low (1st tertile)	4	31	
Medium (2nd tertile)	12	57	
High (3rd tertile))	84	12	
Concentrated Affluence			<.0001
High (3rd tertile)	24	55	
Medium (2nd tertile)	28	24	
Low (1st tertile)	48	21	
Educational Attainment			<.0001
High school or more	69	90	
Less than high school	31	10	
Marital Status			<.0001
Married at time of diagnosis	30	62	
Not married at time of diagnosis	70	38	
Hormonal and Reproductive Factors			
Length of Ovulation			0.69
0-10 years	4	2	
11-20 years	4	9	
21-30 years	18	20	
31-40 years	31	28	
41+ years	43	41	
Hormone Replacement Therapy (missing=3)			0.03
No	70	54	
Yes	30	46	
Tumor Status			
FIGO Stage at Diagnosis			0.63
I	32	39	
II	10	8	
III	47	43	
IV	11	10	
Pathologic Grade			0.03
Borderline	15	20	
Low-grade 1	11	11	
High-grade 2-4	60	63	
Unclassified	14	6	
Tumor Aggressiveness			
Histologic Sub-Type			0.11
Mucinous	11	18	
Clear cell	7	6	
Endometrioid	9	15	
Serous	53	48	
Undifferentiated	12	16	
Unclassified	8	5	
Residual Lesion Status (missing=27)			0.20
<2 centimeters	52	59	
≥2 centimeters	48	41	

Women living less than five years after diagnosis (“ shorter survival”) were an average of 5.6 years older at diagnosis than women living five years or more after diagnosis (“longer survival”) ($p < .0001$). Differences in the distribution of factors within each of the three domains (i.e., socioeconomic environment, access to healthcare, and tumor characteristics) were compared by shorter and longer survival time (TABLE XXIII). Shorter survival was associated with greater concentrated disadvantage ($p = 0.006$), length of ovulation ($p = 0.004$), hormone replacement therapy ($p = 0.02$), later-stage diagnoses, high-grade tumors, more aggressive histologic sub-types, and larger residual lesions following surgery ($p < .0001$ for all covariates). Neither educational attainment nor marital status was associated with shorter survival time. At $p = 0.12$, there was some suggestion that lower concentrated affluence may be associated with shorter survival (TABLE XXIII). Concentrated disadvantage, concentrated affluence, pathologic grade, and all measures related to hormonal and reproductive factors and tumor aggressiveness were considered for further evaluation as potential mediators.

TABLE XXIII

PERCENT DISTRIBUTION AND ASSOCIATION OF COMPONENTS OF DOMAINS OF INTEREST, BY SHORTER SURVIVAL TIME (<FIVE YEARS AFTER DIAGNOSIS)

DOMAIN	COMPONENT	SURVIVAL <5 YEARS n=298 (%)	P-VALUE
	Race		0.007
	White	48	
	Black	63	
	Age at Diagnosis		<.0001
	≤45 years	34	
	46-60 years	52	
	61+ years	63	
Socioeconomic Environment	Concentrated Disadvantage (missing=8)		0.006
	Low (1st tertile)	47	
	Medium (2nd tertile)	47	
	High (3rd tertile))	62	
	Concentrated Affluence (missing=8)		0.12
	High (3rd tertile)	47	
	Medium (2nd tertile)	52	
	Low (1st tertile)	57	
	Educational Attainment		0.72
	High school or more	44	
	Less than high school	47	
	Marital Status		0.36
	Married at time of diagnosis	42	
	Not married at time of diagnosis	47	
Hormonal and Reproductive Factors	Length of Ovulation		0.004
	0-10 years	13	
	11-20 years	14	
	21-30 years	45	
	31-40 years	50	
	41+ years	48	
	Hormone Replacement Therapy (missing=3)		0.02
	No	50	
	Yes	37	
Tumor Characteristics	FIGO Stage at Diagnosis		<.0001
	I	21	
	II	59	
	III	67	
	IV	82	
	Pathologic Grade		<.0001
	Borderline	17	
	Low-grade 1	32	
	High-grade 2-4	61	
	Unclassified	76	
	Histologic Sub-Type		<.0001
	Mucinous	45	
	Clear cell	46	
	Endometrioid	31	
	Serous	54	
	Undifferentiated	73	
	Unclassified	65	
	Residual Lesion Status (missing=27)		<.0001
	<2 centimeters	34	
	≥2 centimeters	76	

As an initial exploration of mediation, age-adjusted models were run for five hypothesized mediators available for the overall study population (TABLE XXIV) and two hypothesized mediators available only for the interviewed patients (TABLE XXV). Odds ratios were compared against the base model, and concentrated disadvantage, concentrated affluence, histologic sub-type, and hormone replacement therapy altered this measure somewhat.

TABLE XXIV

MODELS EVALUATING THE INCLUSION OF HYPOTHESIZED MEDIATORS ON RACE

COVARIATES	MODEL OR (95%CI)					
	Base Model	I	II	III	IV	V
Race						
White (reference)	1.0	1.0	1.0	1.0	1.0	1.0
Black	**1.8 (1.2-2.9)**	1.4 (0.8-2.7)	1.7 (1.2-2.8)	1.8 (1.1-2.9)	1.7 (1.0-2.6)	1.8 (1.1-3.1)
Age at Diagnosis (Years)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)
Concentrated Disadvantage (SD)	-	1.02 (0.9-1.0)	-	-	-	-
Concentrated Affluence (SD)	-	-	0.99 (0.96-1.02)	-	-	-
Pathologic Grade						
Borderline (reference)				1.0		
Low-grade 1	-	-	-	2.3 (1.1-4.7)	-	-
High-grade 2-4				7.0 (4.0-12.0)		
Unclassified				12.4 (5.1-29.8)		
Histologic Sub-Type						
Mucinous					0.4 (0.3-0.7)	
Clear cell	-				0.7 (0.4-1.4)	
Endometrioid		-	-	-	0.7 (0.4-1.1)	-
Serous (reference)					1.0	
Undifferentiated					2.7 (1.4-5.5)	
Unclassified					1.6 (0.7-3.5)	
Residual Lesion Status						
<2 centimeters (reference)	-	-	-	-	-	1.0
≥2 centimeters						5.9 (4.0-8.6)

TABLE XXV

MODELS EVALUATING THE INCLUSION OF HYPOTHESIZED MEDIATORS ON RACE

COVARIATES	Model OR (95% CI)		
	Base Model	VI	VII
Race			
White (reference)	1.0	1.0	1.0
Black	**1.8 (1.0-3.3)**	1.8 (0.9-3.2)	1.6 (0.9-3.0)
Age at Diagnosis (Years)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)
Length of Ovulation (Years)	-	1.0 (0.9-1.0)	-
Hormone Replacement Therapy (missing=3)			
No (reference)	-	-	1.0
Yes			0.6 (0.4-0.9)

In order to estimate the proportion of the effect of race on five-year survival that was mediated, a single-mediator model was run for each of the seven hypothesized mediators. Age at diagnosis was included as a control variable in all models. Table XXVI presents the proportion mediated by each hypothesized mediator and by each domain, as well as the p-value for the difference between the full model (including the mediator) and the reduced model (absent the mediator). Concentrated disadvantage and concentrated affluence accounted for approximately 41% and 10%, respectively, of the estimated five-year survival disparity. However, neither one of these estimates of proportion mediated reached statistical significance ($p < 0.20$). Nearly 14% ($p = 0.15$) of the estimated disparity in five-year survival was attributed to hormone replacement therapy. Length of ovulation accounted for less than 1% ($p = 0.80$) of the survival disparity. Tumor characteristics appeared to mediate the disparity in five-year survival. Pathologic grade and histologic sub-type accounted for approximately 30% ($p = 0.01$) and 11% ($p = 0.09$) of the estimated disparity in five-year survival, while residual lesion status accounted for 17% ($p = 0.22$) of the estimated disparity in five-year survival.

Socioeconomic environment accounted for 35% of the estimated disparity in five-year survival, though this estimate of the proportion mediated was not statistically significant (p = 0.39). Hormonal and reproductive factors accounted for 15% of the survival disparity (p = 0.13). Tumor characteristics accounted for nearly 37% (p = 0.03) of the disparity in five-year survival. The results were similar in the analysis restricted to ovarian cancer deaths (TABLE XXVII).

TABLE XXVI

ESTIMATES OF THE PROPORTION MEDIATED AND TESTS OF SIGNIFICANCE, IN THE RELATION BETWEEN RACE AND SURVIVAL IN OVARIAN CANCER PATIENTS, BY HYPOTHESIZED MEDIATOR AND DOMAIN (ALL CAUSES OF DEATH)

DOMAIN	HYPOTHESIZED MEDIATOR	PROPORTION MEDIATED BY THE INDIVIDUAL MEDIATOR (%)	PROPORTION MEDIATED BY THE DOMAIN (%)
Socioeconomic Environment	Concentrated Disadvantage	41 [ns]	35
	Concentrated Affluence	10 [ns]	
Hormonal and Reproductive Factors [a]	Length of Ovulation	0.5 [ns]	15 ‡
	Hormone Replacement Therapy	14 ‡	
Tumor Characteristics	Pathologic Grade	30 *	37
	Histologic Sub-type	11 ‡	
	Residual Lesion Status	17 ‡	

* p-value is <0.05; ‡ p-value is<0.20; [ns] p-value is not statistically significant.

[a.] These hormonal and reproductive factors were available only in the subset of 344 interviewed patients.

TABLE XXVII

ESTIMATES OF THE PROPORTION MEDIATED AND TESTS OF SIGNIFICANCE, IN THE RELATION BETWEEN RACE AND SURVIVAL IN OVARIAN CANCER PATIENTS, BY HYPOTHESIZED MEDIATOR AND DOMAIN (OVARIAN CANCER DEATH)

DOMAIN	HYPOTHESIZED MEDIATOR	PROPORTION MEDIATED BY THE INDIVIDUAL MEDIATOR (%)	PROPORTION MEDIATED BY THE DOMAIN (%)
Socioeconomic Environment	Concentrated Disadvantage	43 [ns]	35 [ns]
	Concentrated Affluence	11 [ns]	
Hormonal and Reproductive Factors [a]	Length of Ovulation	0.5 [ns]	16 ‡
	Hormone Replacement Therapy	14 ‡	
Tumor Characteristics	Pathologic Grade	28 *	36 *
	Histologic Sub-type	10 ‡	
	Residual Lesion Status	16 ‡	

* p-value is <0.05; ‡ p-value is<0.20; [ns] p-value is not statistically significant.

[a.] These hormonal and reproductive factors were available only in the subset of 344 interviewed patients.

C. Discussion

The literature on the racial disparity in survival following a diagnosis with ovarian cancer is consistent, and our analysis has demonstrated a significant survival disadvantage for Black women diagnosed with the disease in Cook County, Illinois, which includes the city of Chicago. Although Chicago is the fifth most racially segregated city in the United States (Logan 2011), it also has more than a dozen accredited cancer care centers (AHA Annual Survey Database, Fiscal Year 2010). Despite the availability of high-quality cancer care in Cook County, however, the mean length of survival for Black women in our sample was nearly 18 months shorter than that for White women. Moreover, 63% of Black women survived less than five years following diagnosis, compared to 48% of White women. Our analysis explored the role of mediators related to tumor characteristics, socioeconomic environment, and hormonal and reproductive factors in accounting for the survival disadvantage for Black women diagnosed with ovarian cancer.

One explanation for the survival disadvantage for Black women in our study is that a greater proportion of them had more aggressive tumors, as measured by histologic sub-type. More than one-third (37%) of the racial disparity in five-year survival following ovarian cancer diagnosis was explained by tumor characteristics, and this mediated effect was statistically significant. Nearly two-thirds (65%) of Black women in the study were diagnosed with either serous or undifferentiated tumors, which are most often found in stage III/IV (Kaku et al. 2003), compared to 54% of White women who were diagnosed with these more aggressive sub-types. It may also be possible that a greater proportion of Black women than White women actually have a more aggressive serous sub-type of ovarian cancer. Rather than being considered low-grade and high-grade variants of the same sub-type, serous sub-types are now thought to represent two distinct histologic sub-types, with different underlying pathogeneses, molecular events, behaviors, and prognoses (Vang et al. 2009; McCluggage 2011). In spite of their initial response to chemotherapy, high-

grade serous tumors commonly recur, and the survival of women with these tumors is significantly shorter than the survival of women with the less common low-grade serous tumors (Malpica et al. 2004). Although at the time the women in our sample were diagnosed, the serous sub-type was not further classified into high-grade and low-grade serous sub-types, it is possible that among the patients in our sample with serous tumors, there may be racial differences in the distribution of high-grade and low-grade serous tumors. While differences in tumor characteristics may explain some of the disparity in survival, socioeconomic factors were found to be nearly as important, and when combined with access to healthcare, these two factors seem to be even more important in explaining this disparity.

Socioeconomic environment may also influence survival indirectly through differential access to healthcare. Women living in disadvantaged neighborhoods may be more likely to have lower income and less education and to be uninsured—all of which are associated with diminished access to healthcare (Berk et al. 1995; Andersen 2001; Kirby et al. 2005). Kirby and colleagues found that, even after controlling for individual-level factors, residence in a disadvantaged neighborhood reduced the likelihood of having a consistent healthcare provider and of obtaining preventive services, and increased the likelihood of having "unmet medical needs" (Kirby et al. 2005). In the present study, socioeconomic environment, measured by a combination of individual and area-level characteristics could account for about one third of the disparity in five-year survival, although these measures did not reach statistical significance. Women living in disadvantaged neighborhoods may have fewer educational and economic resources with which to seek care for non-specific early-stage symptoms, or they may be less able to comply with the difficult treatment regimen for ovarian cancer. Conversely, women living in more affluent neighborhoods are likely to have better overall health and more overall resources, which may better enable them to seek care and to complete challenging treatments. Finally, hormonal and reproductive factors, particularly HRTs, may also

explain a portion of this disparity. Although HRTs increase the risk of developing ovarian cancer, they have been associated with modest increases in survival (Nagle et al. 2008), and this may be due to their role in decreasing gonadotropin levels (Hunn et al. 2012).

D. **Strengths and Limitations**

Individual census-tract measures such as poverty and education have often been used in the absence of individual-level data on these socioeconomic factors, and they are useful when the research question directly involves those specific factors. However, research that attempts to understand how the more expansive socioeconomic environment impacts an outcome requires a more comprehensive measure. Concentrated disadvantage and concentrated affluence represent two comprehensive measures of socioeconomic environment and are based on the concept of ecological differentiation. Sampson and colleagues describe ecological differentiation as the uneven distribution of physical and human capital across neighborhoods that are largely segregated along racial and ethnic lines. One aspect of this differentiation is the economic stratification that characterizes neighborhood concentrations of disadvantage or affluence (Sampson 1999; Sampson 2002). In essence, neighborhoods that lack economic resources become deficient in other areas such as education and employment. In contrast, neighborhoods with greater physical capital, such as good housing stock or schools, tend to draw residents with greater economic means, higher educational attainment, and greater overall resources.

Socioeconomic environment, as measured by concentrated disadvantage and affluence, has been used to explore a wide variety of outcomes, including overall health (Ellen 2001; Ross et al. 2001; Browning et al. 2002), violent crime (Sampson et al. 1997), and verbal ability in childhood (Sampson et al. 2008). Furthermore, area-level measures of poverty and education have been demonstrated to be useful markers of “social influence” on outcomes for cancers such as breast, prostate, and colon (Ward et al. 2004;

Eschbach et al. 2005; Byers et al. 2008). There is evidence in the literature on breast, prostate, and colon cancer that Blacks residing in neighborhoods with high poverty and low education experience poorer survival (Greenwald et al. 1996; Byers et al. 2008; Sprague et al. 2011) and are treated less aggressively (Schwartz et al. 2003; Byers et al. 2008).

To our knowledge, this analysis is the first to use mediation analysis, as well as to consider the roles of concentrated disadvantage and affluence, in explaining the racial disparity in survival with ovarian cancer. Some studies have used single or composite Census measures to assess the role of socioeconomic status in accounting for ovarian cancer survival disparities between Black and White women. Using an index composed of census-tract education, poverty, and income, Du and colleagues found that rates of receiving optimal treatment for ovarian cancer were significantly lower in women in the lowest quartile of socioeconomic status (Du et al. 2011). Higher residential-area income has also been associated with early-stage detection of ovarian cancer, as well as with receipt of optimal treatment (Parham et al. 1997). Finally, Terplan and colleagues evaluated type of insurance as a marker of socioeconomic status and found that public insurance was associated with not only recurrence of, but also an increased hazard of death from, ovarian cancer (Terplan et al. 2008).

Epithelial ovarian cancer diagnosis was verified through two independent pathology reviews. This population-based study, 59 of the 71 hospitals (83%) in Cook County, Illinois participated in the original case-control study. This reflects a wide variety of institutions and contributes to the heterogeneity of our population. Vital status was ascertained through 2008, providing 10 to 14 years of follow-up, which is significantly more than single-institution ovarian cancer survival studies and most population-based analyses. The most significant advances in terms of treatment were in place at the time our cases were

diagnosed and treated (between 1994 and 1998), so the findings of this analysis remain relevant in the present day.

Given our findings with respect to socioeconomic environment, access to healthcare may well be an important mediator of the racial disparity in survival, and our inability to evaluate this is an important limitation. Direct measures of healthcare access (i.e., insurance status) and utilization of preventive care are needed in order to assess these measures as potential mediators of disparate survival.

The absence of information on chemotherapy, surgery, and type of provider is a significant limitation of the available data. Black women are less likely to receive standard chemotherapy (Harlan et al. 2003; Du et al. 2008), and they are less likely to receive combined surgery and chemotherapy (Cress et al. 2003). The National Cancer Data Base Study (NCDB), conducted with more than 25,000 cases diagnosed after 1985, revealed that Black women with ovarian cancer were treated less aggressively than White women—even when they received care within the same facility (Parham et al. 1997). It is possible that a portion of the disparity in five-year survival could be explained through racial differences in treatment delivered and in response to treatment. Future research should attempt to confirm these hypotheses with individual-level patient data.

E. **Conclusion**

Treatment advances in the last two decades, particularly the combination of platinum-based chemotherapy and cytoreductive surgery, have provided a significant improvement in survival for ovarian cancer patients who receive them (Einhorn et al. 1985; Balvert-Locht et al. 1991; Ries 1993; Venesmaa 1994; Bjorge et al. 1998; Hogberg et al. 2001). Yet despite these important advances, Black women with ovarian cancer experience a significant survival disadvantage. A better understanding of the specific factors leading to this disparity is needed in order to reduce it. We have demonstrated that differences in

pathologic grade and histologic sub-type are statistically significant mediators in the relation between race and disparate survival. Lacking individual treatment data, we are unable to clarify if the mediated effect is due to these tumor characteristics or due to differential treatment within similar classes of tumors. We have also demonstrated that the combined effect of factors that lie upstream in the pathway from these tumor characteristics, specifically, socioeconomic environment and hormonal and reproductive factors explain a large proportion of this disparity, although it requires further exposition.

VI. CONCLUSION

The significant survival disparity between Black and White women with ovarian cancer, as well as the lethal nature of the disease, inspired this dissertation. The goal of this project was to reach a better understanding of the factors that contribute to this survival disadvantage in Black women.

The vast majority of women with ovarian cancer are diagnosed with late-stage disease. Late-stage tumors are generally more aggressive and chemo-resistant, and thus tend to lead to shorter survival time, than early-stage tumors. The original case-control study produced a rich collection of variables related to patient and tumor characteristics. This project used those variables to conduct a comprehensive analysis of predictors of late-stage diagnosis. The dissertation also considered whether there are racial differences in predictors of late-stage diagnosis in order to determine whether stage at diagnosis contributes to the survival disparity and to address contradictory findings in the literature with respect to racial differences in stage at diagnosis (Aim 1). Without conceding the important role that individual-level socioeconomic status plays in disparate survival, the dissertation assessed whether neighborhood context, specifically disadvantage and affluence, influences the survival disparity above and beyond individual-level prognostic factors (Aim 2). This project sought to confirm whether the disparity in overall survival persisted when the outcome was restricted to ovarian cancer-specific survival (Aim 2). Recognizing that the racial disparity in survival may be due to factors that lie upstream from more proximal factors such as tumor characteristics, the type of treatment received, and the tumor's response to treatment, this dissertation investigated the underlying relationship between race and survival through a group of factors conceptualized as mediators in the relation between these two variables (Aim 3).

The first aim of this project demonstrated that age at diagnosis, census-tract poverty, an index of socioeconomic status represented by census-tract poverty and education, pathologic grade, and histologic

sub-type were all significant predictors of late-stage diagnosis. Given the absence of a population-based screening mechanism, understanding the predictors of late-stage diagnosis is an important endeavor. Lower socioeconomic status, measured at the census-tract level, may contribute to late-stage diagnosis through diminished access to care. This finding suggests that socioeconomic status plays a role in disparate survival. We found that race is not an independent predictor of late-stage diagnosis. This finding is consistent with studies that have found that there are no racial differences in stage at diagnosis, and it also suggests that factors other than racial differences in stage at diagnosis may account for the racial disparity in survival.

This dissertation's second aim estimated the effects of neighborhood context and individual-level prognostic factors on racial disparities in ovarian cancer survival. We found that when concentrated disadvantage was accounted for, the effect of race on shorter survival was no longer statistically significant. These findings support the hypothesis that the factors downstream from race have a significant effect on survival and, further, that where a women resides at the time of her diagnosis impacts her survival above and beyond her own individual circumstances.

On average, the survival time for the Black women in our sample was more than 17 months shorter than the survival time for the White women, and this finding is consistent with numerous studies that have demonstrated a significant overall survival disadvantage for Black women using all causes of death. This disparity may be partly due to racial disparities in serous co-morbidities (McBean et al. 2004; Kurian et al. 2007; Peek 2012; Stone 2012) that contribute to shorter overall survival time—even in women diagnosed with ovarian cancer. However, a relatively small number of studies that have used ovarian cancer-specific cause of death have failed to find a survival disparity and concluded that no such disparity exists. A closer look at these studies reveals that they are single institution studies with a relatively homogenous group of

patients who may have received similar treatment (Table XXVIII). We demonstrated that a significant survival disparity persisted in our sample, even when the analysis was restricted to ovarian cancer deaths. This finding strongly suggests that a survival disadvantage exists for Black women diagnosed with ovarian cancer—even in light of any racial differences in co-morbidities.

The third aim of this dissertation assessed the relative contributions of hypothesized mediators related to socioeconomic environment, hormonal and reproductive factors, and tumor characteristics. More than one-third of the racial disparity in five-year survival was explained by tumor characteristics. One possible explanation involves a component of this domain, histologic sub-type, and more specifically serous tumors. It is possible that Black women are more likely than White women to have a more aggressive serous sub-type. In fact, in an analysis restricted to women diagnosed with serous tumors, we found a statistically significant increased hazard of death for Black women. Socioeconomic environment, measured by area-level characteristics of concentrated disadvantage and affluence, accounted for about one-third of the racial disparity in ovarian cancer survival, although these measures did not reach statistical significance. Nevertheless, this suggested that socioeconomic status influences disparate survival, and this influence may be indirect, through differential access to healthcare. It is also possible that socioeconomic status plays a more direct role on survival through other, unmeasured factors. Possibilities include psychosocial stress, immune response, or other environmental factors. The literature on racial disparities in survival has focused on the association of prognostic factors, patient characteristics, and even some measures of socioeconomic status, such as poverty and education. However, there appear to be no published reports assessing the relative contribution of these factors as mediators of disparate survival. Our findings suggest that race is not truly an independent predictor of shorter survival. Rather, it

contributes to shorter survival through tumor characteristics, and quite possibly socioeconomic environment, and access to healthcare.

TABLE XXVIII

SELECTED SURVIVAL STUDIES

TYPE OF STUDY	STUDY POPULATION (FOLLOW-UP TIME)	SURVIVAL STATISTICS
Population-based		
(Chan et al. 2008)	SEER (12 registries) 7% Black, 93% White (8 years)	5-year survival (%) Blacks (29) & Whites (37)*
(Barnholtz-Sloan et al. 2002)	SEER (9 registries) 6% Black, 94% White (10 years)	Median survival (months) Blacks & White (32)*
(Parham et al. 1997)	National Cancer Data Base 7% Black, 93% White (12 years)	5-year survival (%) Blacks (30) & Whites (41)*
Single Institution		
(Morgan et al. 1996)	9% Black, 91% White (5 years)	No significant difference in ovarian cancer survival
(Terplan et al. 2008)	22% Black, 78% White (3 years)	No significant difference in ovarian cancer survival
Multiple Institutions		
(Albain et al. 2009)	1,429 Black and White women (10 years)	Significant survival disparity in late-stages HR Blacks = 1.6 (95%CI 1.2-2.2)
(McGuire et al. 2002)	SEER subset (San Francisco-Oakland Bay, Kaiser Permanente Members) 6% Black, 94% White (10 years)	Death rate ratio Blacks = 1.2 (95%CI 1.1-1.4)

* $p < 0.05$

This dissertation examined whether there were underlying differences in predictors of late-stage diagnosis in order, possibly, to shed light on the contradictory findings with respect to stage at diagnosis. Observed disparities in survival may be due partly to racial differences in certain mediators that lie along the pathway between race and this outcome. Identifying and quantifying the relative contributions of these mediators provides important insights into these disparities. In addition, contextual factors related to socioeconomic status may also play a role in the differential survival between Blacks and Whites with ovarian cancer, such that where a patient resides impacts her survival regardless of her individual circumstances.

Our finding with respect to the effect of concentrated disadvantage on the racial disparity in survival raises an important question. This variable was associated with shorter survival in univariate analysis ($p = 0.006$), and its inclusion mitigated the effect of race on survival. However, the association between concentrated disadvantage and shorter survival lost statistical significance when other factors were controlled for in multivariate models. While there was an elevated relative risk of shorter survival for women living in neighborhoods with the highest levels of concentrated disadvantage, the risk estimates do not suggest a strong effect. Why does concentrated disadvantage appear to play such an important role in the racial disparity in survival but is not strong enough or direct enough to have an independent effect on shorter survival?

The analytical methods used in this project, as well as the use of two highly-regarded area-level measures of neighborhood structural characteristics, represent a novel approach to examining the racial disparity in ovarian cancer survival. Mediation analysis allowed us to quantify the extent to which factors that lie downstream from race explain the disparity in ovarian cancer survival. The role of neighborhood context has been evaluated for a number of cancers that have disparities in incidence and/or survival. To our knowledge, this dissertation is the first analysis to consider the possible affect of contextual factor (i.e., neighborhood context) on disparate survival in women diagnosed with ovarian cancer. This dissertation evaluated the effects of socioeconomic environment on disparate survival, both as a mediator and as a contextual factor, using measures of concentrated disadvantage and concentrated affluence. These are comprehensive measures of overall socioeconomic status that were better suited to the research question of this project than single census-level variables.

The original case-control study produced a rich dataset, with detailed information on both patient and tumor characteristics. Epithelial ovarian cancer diagnosis was verified through two independent

pathology reviews. This population-based study, 59 of the 71 hospitals (83%) in Cook County, Illinois participated in the original case-control study. This reflects a wide variety of institutions and contributes to the heterogeneity of our population. Vital status was ascertained through 2008, providing 10 to 14 years of follow-up, which is significantly more than single-institution ovarian cancer survival studies and most population-based analyses. The most significant advances in terms of treatment were in place at the time our cases were diagnosed and treated (between 1994 and 1998), so the findings of this analysis remain relevant in the present day.

The adequacy of surgical staging and cytoreduction impacts the choice of chemotherapeutic regimen. In turn, the type of treatment received and the tumor's response to treatment are important determinants of ovarian cancer survival. The absence of information on these factors is an important limitation of this study. Compared to White women, a greater proportion of Black women in this study had tumors that were unclassified in terms of histologic sub-type and pathologic grade. This may be due in part to less complete surgical staging in Black women, and thus may have had negative consequences in terms of subsequent treatment. It may also be the case that the Black women in our sample received less optimal treatment than the White women, either in terms of cytoreductive surgery or chemotherapeutic regimen, possibly due to differences in healthcare providers or co-morbidities that prevented certain therapies (e.g., intraperitoneal delivery of chemotherapeutic agents). Racial differences in terms of response to treatment (i.e., initial response to chemotherapeutic agents, duration of treatment-free interval, and rate of recurrence) may also have contributed to the observed survival disparity.

This study has provided insights into the racial disparity in survival between Black and White women with ovarian cancer. However, at least four important areas should be pursued further. First, direct measures of healthcare access and utilization are needed in order to assess these potential mediators of

disparate survival. Second, this dissertation has provided preliminary evidence of the effect of concentrated disadvantage on the racial disparity in survival. However, future studies to determine which particular features of neighborhood disadvantage contribute most to the racial disparity are warranted. Third, the roles of treatment received and response to treatment in disparate survival should be explored. Research has shown that Black women are less likely to receive the optimal treatment associated with longer survival. Differences in treatment response may also contribute to disparate survival, such that Black women may develop recurrence more quickly. These are also important areas for future research. Fourth, racial differences in serous sub-type tumors should be explored as a possible contributing factor in the racial disparity in ovarian cancer survival. Histologic sub-type was a significant mediator in the relation between race and disparate survival, and, a greater proportion of Black women, compared to White women in our sample, were diagnosed with serous tumors. Although it was not possible to confirm whether or not more Black women in our study had the more aggressive serous sub-type, these women did have a statistically significant increased hazard of death within this histologic sub-type. It may be that Black women are more likely to have the more aggressive serous sub-type, which responds differently to chemotherapeutic agents and confers a much worse prognosis than the less aggressive sub-type. Further investigation into this is warranted.

The findings of this dissertation project suggest several reasons for the disparity in ovarian cancer survival. Further investigation into racial differences in tumor characteristics—in particular the serous sub-types—as well as the specific way in which socioeconomic environment contributes to disparate survival will provide the necessary evidence to support advances in both treatment and policy.

APPENDICES

APPENDIX A

FIGO Staging, Tumor, Node, Metastasis Classification, and Description of Ovarian Neoplasms

FIGO STAGING *(sub-staging)*	GROUPING	DESCRIPTOR
I	**T1**	**Tumor limited to one or both ovaries**
IA	*T1a, N0, M0*	Tumor limited to 1 ovary, capsule intact, no tumor on ovarian surface or malignant cells in ascites/peritoneal washings*
IB	*T1b, N0, M0*	Tumor limited to both ovaries, capsules intact, no tumor on ovarian surface or malignant cells in ascites/peritoneal washings*
IC	*T1c, N0, M0*	Tumor limited to 1/ both ovaries with any of the following: capsule ruptured, tumor on ovarian surface, malignant cells in ascites/peritoneal washings*
II	**T2**	**Tumor involves one or both ovaries with pelvic extension**
IIA	*T2a, N0, M0*	Extension and/or implants on the uterus and/or fallopian tubes, no malignant cells in ascites or peritoneal washings
IIB	*T2b, N0, M0*	Extension to and/or implants on other pelvic tissues. No malignant cells in ascites or peritoneal washings
IIC	*T2c, N0, M0*	Pelvic extension and/or implants (stage IIA or stage IIB) with malignant cells in ascites or peritoneal washings
III	**T3 and/or N1**	**Tumor involves one or both ovaries with microscopically confirmed peritoneal implants outside the pelvis and/or regional lymph node metastasis**
IIIA		*Microscopic peritoneal metastasis beyond pelvis (no macroscopic tumor)*
IIIB	*T3a, N0, M0*	*Macroscopic peritoneal metastasis beyond pelvis no more than 2 cm or less in greatest dimension*
IIIC	*T3b, N0, M0* *T3c, N0, M0* *Any T,N1,M0*	*Peritoneal metastasis beyond pelvis more than 2 cm in greatest dimension and/or regional lymph node metastasis*
IV	**Any T and any N,M1**	**Distant metastasis (excludes peritoneal metastasis) If pleural effusion is present, positive cytologic test results must exist to designate a case to stage IV; parenchymal liver metastasis equals stage IV**

APPENDIX B

Interpolated Values for Census Tract Education and Poverty Variables

Treatment of 1990 Census Data:
1) The proportion of the population in a given Census tract over 25 years, with less than a HS education, was calculated using the following formula: [P0570001 + P0570002] / [P05700001 to P0570007]

Where,
P0570001 = Persons 25 years and over: less than 9th grade
P0570002 = Persons 25 years and over: 9th grade to 12th grade; no diploma
P0570004 = Persons 25 years and over: Some college; no degree
P0570005 = Persons 25 years and over: Associate degree
P0570006 = Persons 25 years and over: Bachelor's degree
P0570007 = Persons 25 years and over: Graduate or professional degree

2) The proportion of the population in a given Census tract below poverty was calculated using the following formula: [P117013 +P117024] / [P117001 to P117024]

Where,
P1170001 = Persons for whom poverty status is determined: Income in 1989 above poverty level; Under 5 years
P1170002 = Persons for whom poverty status is determined: Income in 1989 above poverty level; 5 years
P1170003 = Persons for whom poverty status is determined: Income in 1989 above poverty level; 6 to 11 years
P1170004 = Persons for whom poverty status is determined: Income in 1989 above poverty level; 12 to 17 years
P1170005 = Persons for whom poverty status is determined: Income in 1989 above poverty level; 18 to 24 years
P1170006 = Persons for whom poverty status is determined: Income in 1989 above poverty level; 25 to 34 years
P1170007 = Persons for whom poverty status is determined: Income in 1989 above poverty level; 35 to 44 years
P1170008 = Persons for whom poverty status is determined: Income in 1989 above poverty level; 45 to 54 years
P1170009 = Persons for whom poverty status is determined: Income in 1989 above poverty level; 55 to 59 years
P1170010 = Persons for whom poverty status is determined: Income in 1989 above poverty level; 60 to 64 years
P1170011 = Persons for whom poverty status is determined: Income in 1989 above poverty level; 65 to 74 years
P1170012 = Persons for whom poverty status is determined: Income in 1989 above poverty level; 75 years and over
P1170013 = Persons for whom poverty status is determined: Income in 1989 below poverty level; Under 5 years
P1170014 = Persons for whom poverty status is determined: Income in 1989 below poverty level; 5 years
P1170015 = Persons for whom poverty status is determined: Income in 1989 below poverty level; 6 to 11 years
P1170016 = Persons for whom poverty status is determined: Income in 1989 below poverty level; 12 to 17 years
P1170017 = Persons for whom poverty status is determined: Income in 1989 below poverty level; 18 to 24 years
P1170018 = Persons for whom poverty status is determined: Income in 1989 below poverty level; 25 to 34 years
P1170019 = Persons for whom poverty status is determined: Income in 1989 below poverty level; 35 to 44 years
P1170020 = Persons for whom poverty status is determined: Income in 1989 below poverty level; 45 to 54 years
P1170021 = Persons for whom poverty status is determined: Income in 1989 below poverty level; 55 to 59 years
P1170022 = Persons for whom poverty status is determined: Income in 1989 below poverty level; 60 to 64 years
P1170023 = Persons for whom poverty status is determined: Income in 1989 below poverty level; 65 to 74 years
P1170024 = Persons for whom poverty status is determined: Income in 1989 below poverty level; 75 years and over

Treatment of 2000 Census Data:
1) The proportion of the population in a given Census tract over 25 years, with less than a HS education, was calculated using the following formula: [(P037003 to P037010) + (P037020 to P037027)] / [P037001]

Where,
P037001 = Population 25 years and over: Total
P037003 = Population 25 years and over: Male; No schooling completed
P037004 = Population 25 years and over: Male; Educational attainment; Nursery to 4th grade
P037005 = Population 25 years and over: Male; Educational attainment; 5th and 6th grade
P037006 = Population 25 years and over: Male; Educational attainment; 7th and 8th grade
P037007 = Population 25 years and over: Male; Educational attainment; 9th grade
P037008 = Population 25 years and over: Male; Educational attainment; 10th grade
P037009 = Population 25 years and over: Male; Educational attainment; 11th grade
P037010 = Population 25 years and over: Male; Educational attainment; 12th grade; no diploma
P037020 = Population 25 years and over: Female; Educational attainment; No schooling completed
P037021 = Population 25 years and over: Female; Educational attainment; Nursery to 4th grade

APPENDIX B (continued)

P037022 = Population 25 years and over: Female; Educational attainment; 5th and 6th grade
P037023 = Population 25 years and over: Female; Educational attainment; 7th and 8th grade
P037024 = Population 25 years and over: Female; Educational attainment; 9th grade
P037025 = Population 25 years and over: Female; Educational attainment; 10th grade
P037026 = Population 25 years and over: Female; Educational attainment; 11th grade
P037027 = Population 25 years and over: Female; Educational attainment; 12th grade; no diploma

2) The proportion of the population in a given Census tract below poverty was calculated using the following formula: [P087002] / [P087001]
Where,
P087001 = Population for whom poverty status is determined: Total
P087002 = Population for whom poverty status is determined: Income in 1999 below poverty level

3) Interpolation Values for the midpoint

The midpoint of the case ascertainment interval is 1996. The interpolated value for each of the Census tracts this period was created using the following formula:

[1990 data * 0.4] + [2000 data *0.6]

This sum yields the interpolated value of the educational level and the poverty rate for each census tract in 1996.

Appendix C

Creation of the Concentrated Disadvantage and Affluence Variables

1) The concentrated disadvantage variable was created in the following manner: Interpolated values for each of the six census variables were calculated using derived variables from the 1990 and 2000 U.S. Census data:
% Below Poverty = [povrat9 * 0.4] + [povrat0 * 0.6]
% African-American = [SHRBLK9 * 0.4] + [SHRBLK0 * 0.6]
% Female-headed household = [FFH9 * 0.4] + [FFH0 * 0.6]
% unemployed = [UNEMPRT9 * 0.4] + [UNEMPRT0 * 0.6]
% Receiving public assistance = [WELFARE9 * 0.4] + [WELFARE0 * 0.6]
% Less than 18 years = [CHILD09 * 0.4] + [CHILD0 * 0.6]

These new variables were standardized, summed, and then standardized again using *proc standard*.

2) The concentrated affluence variable was created in the following manner: First, derived variables were created for each of the three variables used on the concentrated affluence variable:

% Persons 25+ who have a bachelor's degree or more (1990): SAS variable edu1990 = educ169 / educpp9
% Persons 25+ who have a bachelor's degree or more (2000): SAS variable edu2000 = educ160 / educpp0

% Labor force in professional/managerial professions (1990): SAS variable occ90=[occ19+occ29]/indemp9
% Labor force in professional/managerial professions (2000): SAS variable occ00=[occ10+occ20]/indemp0

% Families with income >$50k (1990): SAS variable inc90 = [falt609a+falt759a+faltmx9] / favinc9d
% Families with income >$75k (2000): SAS variable inc00 = [fay0100+fay01250+fay01500+fay02000 +fay0m200] / favinc0d

Next, interpolated values for each of these variables were obtained in the following manner:
% Persons 25+ who have a bachelor's degree or more = [edu1990 * 0.4] + [edu2000 * 0.6]
% Labor force in professional / managerial professions = [occ90 * 0.4] + [occ00 * 0.6]
% Families with income >$65,000 = [inc90 * 0.4] + [inc00 * 0.6]

These new variables were standardized, summed, and then standardized again using *proc standard*.

APPENDIX D

Analytic approach for decomposing direct and indirect effects of race on survival using the KHB method in STATA (Karlson 2011)

The KHB method decomposes the independent variable in models containing single or multiple mediators, as well as control variables. The KHB command in STATA produces an estimate of the effect of the independent variable on the dependent variable accounting for the mediator(s) and any adjustment variables (Full Model), an estimate excluding the mediator (Reduced Model), a z-statistic and p-value for the difference between these nested models.

The option “summary” produces the ratios of direct and indirect effects, the percentage by which the indirect effect accounts for the total effect of independent variable on the dependent variable (Proportion Mediated), and the rescale factor, which quantifies the size of the change in the scale parameter due to the inclusion of the mediator.

In multiple mediator models, the option “disentangle” produces the percentage contribution of each mediator to the indirect effect of the independent variable.

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Survival Disparity in Black & White Women with Ovarian Cancer: The Role of Mediators and Contextual Factors

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Ovarian cancer remains one of the most lethal of all cancers. While the incidence of ovarian cancer is higher among White women, survival is significantly poorer among Black women. Yet the reasons for this disparity are not well-understood. This project evaluated predictors of late-stage diagnosis to determine if there were significant racial differences in these predictors that might explain the disparity in survival. In addition, this project examined whether factors related to socioeconomic environment, tumor characteristics, and risk factors associated with longer lifetime ovulation and higher gonadotropin levels are mediators of the racial disparity in ovarian cancer survival. Data were obtained from women diagnosed with ovarian cancer in Cook County, Illinois. Socioeconomic environment was assessed using two well-established measures: concentrated disadvantage and concentrated affluence. Tumor characteristics included tumor grade, histologic sub-type, and residual lesion status. Hormonal and reproductive risk factors included length of ovulatory period and HRT history.The proportion of the survival disparity explained by these factors was estimated by rescaling coefficients from logistic regression using the method of Karlson, Holm, and Breen (2010).

Age at diagnosis, poverty, an index of socioeconomic status, pathologic grade, and histologic sub-type were all significant predictors of late-stage diagnosis. However, race was not a significant predictor of late-stage diagnosis, which suggests that other factors may account for the racial disparity in survival.

More Black women than White women survived less than five years following their diagnoses (63% vs. 48%, respectively, p = 0.004). Tumor characteristics explained 37% percent of the racial disparity in five-year survival (p = 0.03). Socioeconomic environment accounted for 35% of the racial disparity in survival
(p = 0.39). Risk factors that may be associated with more aggressive tumors accounted for 15% of the disparity in survival (p = 0.13). Together, these factors explained 65% of the survival disparity (p = 0.20).

Differences in tumor grade and histology were shown to be important mediators in the relation between race and disparate ovarian cancer survival. Socioeconomic environment and factors associated with longer lifetime ovulation and higher levels of gonadotropins may also explain a portion of this disparity.