OVARIAN CANCER EPIDEMIOLOGY: RISK, DIAGNOSIS, AND PROGNOSIS

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ABSTRACT

There are approximately 22,200 new cases of ovarian cancer (OC) within the US each year. The overall 5-year survival rate for OC is 44%, due to late diagnosis among the majority of patients. OC is a complex, heterogeneous, and multifactorial disease.

The relationship between OC and fertility drug use is complicated due to the link between infertility and other established reproductive risk factors. We found that fertility drug use does not significantly impact OC risk among the majority of women when accounting for confounding factors. However, we observed increased OC risk among women who despite fertility drug use remained nulligravid.

Improved understanding of symptom presentation among OC patients could lead to earlier detection. However, the identification of OC-related symptoms is difficult due to their non-specific nature. Our second project identified 3 subgroups of OC patients that were defined according to the total number of symptoms experienced prior to diagnosis. Interestingly, the number of symptoms experienced did not differ significantly between early and late stage cases.

Conditional disease-free survival (DFS) accounts for elapsed time after remission thereby providing more relevant prognostic information than traditional DFS estimates. Results from our third project demonstrate that DFS estimates improve dramatically over time and that conditional DFS provides more relevant and accurate information to patients who have already survived a

period of remission. Characteristics that are predictive of DFS at time of remission, such as stage and age, lose significance as the period of remission increases.

The research presented in this dissertation is of public health significance because it contributes to what is known about the risk, diagnosis, and prognosis of OC. Enhanced knowledge of OC risk factors may improve the identification of women at increased risk of OC and contribute to our understanding of OC etiology. The characterization of symptom presentation among OC patients prior to diagnosis may assist the development of a screening tool that is able to identify women with earlier stage disease. Furthermore, more accurate methods to estimate the risk of recurrence among OC survivors has the potential to facilitate personalized follow-up care that is cost effective and improves cancer outcomes.

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PREFACE

I would like to take this opportunity to acknowledge the individuals who have contributed to this research and have supported me throughout my dissertation work. Foremost, I would like to thank my dissertation chair, Dr. Brenda Diergaarde, for her guidance and insight during this process. In addition to offering her invaluable input on this project, Dr. Diergaarde was always available to help me with any questions or problems that arose. Her support has been instrumental in the successful completion of this research and I am fortunate to have her as a mentor. I would also like to express my gratitude to the other members of my dissertation committee, Dr. Joel L. Weissfeld, Dr. Robert P. Edwards, Dr. Marnie Bertolet, and Dr. Janet M. Catov, whose input and contributions were always insightful and appreciated. I am especially grateful to Dr. Edwards for his generosity of time and expertise, which was crucial for the clinical aspects of this research. I would also like to specifically thank Dr. Bertolet for her patience during our many meetings discussing latent class analysis.

I am appreciative of the funding support from the National Cancer Institute's R25 Pre-doctoral Cancer Epidemiology Training Program. The opportunities to attend scientific conferences and collaborate with students and advisors in the program have been invaluable. In particular, I would like to thank Dr. Weissfeld, director of the R25 program, whose own wisdom and thoughtful approach to cancer epidemiology challenged me to consider all aspects of an issue. His critiques and insight during our meetings encouraged critical, independent thinking and has made me a better epidemiologist. I'd also like to extend my thanks to the staff at the University of Pittsburgh Cancer Institute who always found the time to help me, despite their many responsibilities. Specifically, I would like to express my appreciation to Kathy McDonough for

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Finally, I'd like to thank my family and friends for their patience and support during this process. In particular, I'd like to thank my mother, whose own battle with cancer has instilled in me the importance of facing challenges with courage, determination, and most importantly, humor. Without her unwavering encouragement and support throughout my academic career, this would not have been possible. For these reasons, and many others, I would like to dedicate this work to her.

1.0 INTRODUCTION

1.1 INCIDENCE AND MORTALITY

Ovarian cancer (OC) is the 8th most common cancer among women worldwide. Based on GLOBOCAN estimates, there were 225,500 new OC cases and 140,200 deaths attributed to OC globally in 2008. Incidence rates for OC are higher in developed countries compared to less developed countries with age-standardized rates per 100,000 of 9.4 and 5.0, respectively. It is likely that as developing countries progress, OC rates will begin to rise and mirror the higher rates currently found in more developed countries.[1] Within the United States, it is estimated that there will be 22,240 new cases of OC in 2013.[2] There are significant differences in OC rates between racial and ethnic groups in the United States.[3,4] Caucasian women have the highest risk of OC, with an age-adjusted incidence rate of 13.3 per 100,000 women during the 20. Age-adjusted rates for the same time period (2006-2010) for African Americans, Asian/Pacific Islanders, American Indian/Alaska Natives were 9.7, 9.4, 10.7, and 11.3 per 100,000 women, respectively.[5]

OC accounts for only 3% of cancers among women in the United States; however, it is the fifth most common cause of cancer death among women in this country.[2] Figure 1 presents overall 5-year relative survival rates for all cancer sites and the 5 most common causes of cancer death among women between 1975 and 2004. OC has a lower 5-year relative survival rate than all cancer sites among women and lower survival rates than the other most common causes of cancer death

among women, with the exception of lung/bronchus cancer. Based on Surveillance Epidemiology and End Results (SEER) data from 2002-2008, the overall 5-year relative survival between 2002 and 2008 was 43.7%. The majority of ovarian cancer cases are diagnosed once their disease has progressed to advanced stages (Figure 2). Cases diagnosed when disease is confined to the primary site have a 5-year relative survival of 91.5%. However, survival rates decrease drastically among cases whose disease has metastasized to regional and distant sites; 5- year relative survival rates for these cases are 71.9% and 26.9%, respectively.[5]

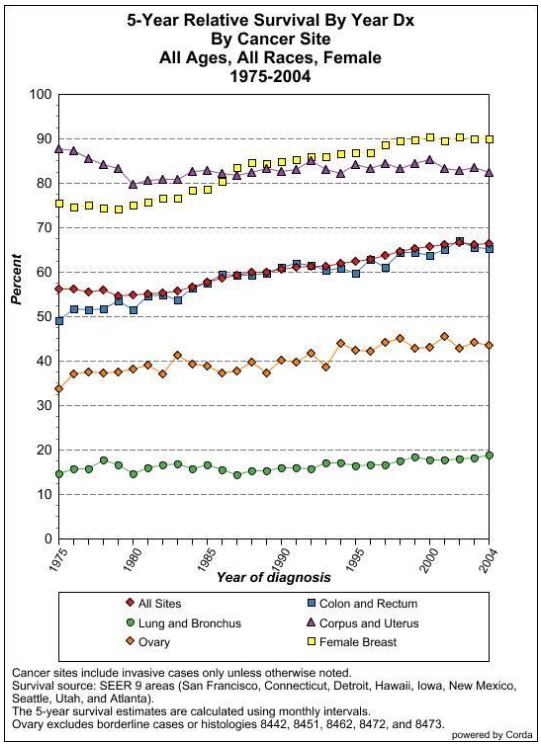

Figure 1. 5-year relative survival rates for all cancer sites and the 5 cancer sites responsible for the most cancer deaths among women, according to year of diagnosis

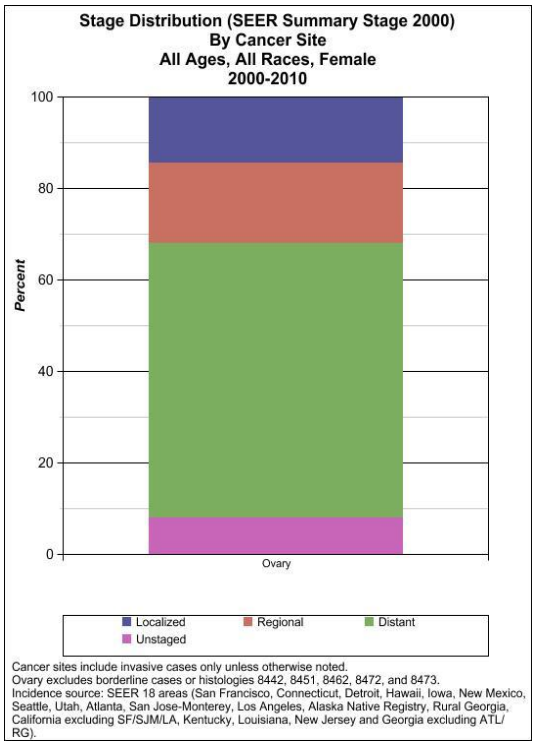

Figure 2. Stage distribution of ovarian cancer cases diagnosed between 2000-2010

1.2 PATHOLOGY

Ovarian tumors are classified according to the tissue in which they originated. The majority of ovarian tumors are epithelial in nature, arising from the epithelial surface of the ovary, and account for about 90% of ovarian malignancies, while 6% of cases originate in the stromal-cord and 3% of ovarian cancers originate in germ cells.[6] All epithelial subtypes are also classified as either invasive or borderline. Borderline tumors account for 10-15% of epithelial ovarian tumors and are characterized by their lack of invasive implants in the underlying stroma.[7] These low malignant

potential tumors have a more favorable prognosis than invasive tumors, with survival rates of 99%, 98%, 96%, and 77% for stages I, II, III, and IV, respectively.[8]

Ovarian tumors are further classified according to histologic subtype: serous, mucinous, endometrioid, clear cell, transitional (Brenner), and mixed histologies.[9] The most common of these histologic subtypes is serous, which accounts for approximately 52% of all ovarian tumors. Mucinous, endometrioid, clear cell, transitional, and mixed histologies each account for approximately 11%, 19%, 7%, <1%, and 4%, respectively.[9] Due to the differing morphologic, molecular, and clinical characteristics of histologic subtypes, ovarian tumors are categorized as being either type I or type II. Type I tumors include low-grade and borderline serous tumors, low-grade endometrioid, mucinous, and clear-cell tumors while type II tumors include high-grade serous, high-grade endometrioid, mixed mesodermal, carcinosarcomas, and undifferentiated tumors. Characteristics of type I and type II tumors vary greatly. Type I tumors more often present during earlier stages of disease, resist standard chemotherapy regimens but may be more responsive to hormone therapy. Type II tumors are more prevalent and are usually diagnosed at stage III/IV, are more aggressive, and typically respond well to chemotherapy but poorly to hormone-based treatments.[10,11] This suggests that the subtypes of OC have different etiologies and that treatments should be tailored according to the subtypes' molecular features.[12,13] It should be noted that tumors arising from the fallopian tubes and peritoneum share many molecular and clinical characteristics with OC and are often characterized as OC.[14]

1.3 RISK FACTORS

The causes of OC remain poorly understood, however, epidemiologic studies have successfully identified numerous demographic, reproductive, and lifestyle factors associated with OC risk. OC risk is strongly associated with age; most cases are diagnosed after menopause and the median age at diagnosis is 63 years old.[5] Race has also been identified as a risk factor, with Caucasian women having the greatest risk of OC. The factors that contribute to the reduced risk observed among other racial groups are unknown. Research has shown that protective risk factors established among Caucasian women are also protective among African-American women but that the difference in OC risk may be due in part to the disproportionate frequencies of risk factors between these racial groups.[3,15] Higher rates of OC risk among Caucasian women may also be due in part to the higher rate of BRCA1 and BRCA2 mutations among Caucasians.[16] However it is important to note that the proportion of OC cases with a positive family history of OC is relatively small.

Hereditary OC accounts for approximately 10% of all OC cases and includes breast-OC syndrome and hereditary non-polyposis colorectal cancer (HNPCC), or Lynch II, syndrome. Breast-ovarian cancer syndrome is responsible for 90% of hereditary cancers and is associated with germ-line mutations in the BRCA1 and BRCA2 tumor suppressor genes.[6] The lifetime risk of developing OC is 30-60% among BRCA1 mutation carriers and 15- 30% among BRCA2 mutation carriers.[13,17,18] OC patients that are also BRCA mutation carriers tend to be younger than non-hereditary OC patients and they often respond better to treatment with longer survival.[19,20] Patients with HNPCC carry a germ-line mutation in the DNA mismatch repair (MMR) genes, usually hMLH1 and hMSH2. HNPCC is associated with an 80% increased risk of colorectal cancer and women with HNPCC are 12% more likely to develop OC during their lifetime compared to

women without the syndrome. However, the percentage of OC patients that have germ-line mutations in the HNPCC genes is small (<1%).[21] Similar to OC patients with BRCA mutations, women affected by HNPCC who develop OC tend to be younger; they are also generally diagnosed at an earlier stage compared to OC patients in the general population.[22,23] In addition, OC patients with HNPCC are more likely to have non-serous ovarian tumors.[23] Studies assessing whether OC patients with HNPCC have improved survival compared to patients with sporadic OC have been inconclusive.[24,25]

Several reproductive factors have been identified as being protective of OC. Parity has consistently been linked to the risk of OC, with the protective effect increasing with each live birth. In line with this, nulliparous women are at a greater risk of developing OC compared to women with at least one live birth. [26-29] Breastfeeding has also been established as a protective factor against OC. Women who have ever breastfed have a reduced risk of developing OC and a dose-response relationship has been observed for the duration of time spent breastfeeding.[30-33] Tubal ligation is also associated with a decreased risk of OC and several theories have been proposed to explain the mechanism by which tubal ligation reduces the risk of OC [34-36]. The first of which hypothesizes that tubal ligation prevents the ascent of potential carcinogenic endometrial and fallopian tube epithelial cells to the ovaries.[37] A second hypothesis states that the surgery creates a mechanical barrier that prevents potential carcinogens associated with OC, such as talc, from reaching the ovaries via the genital tract.[6,38-40] Studies assessing the relationship between fertility drug use and OC risk have provided conflicting results. Early studies, including a study by Whittemore and colleagues found that women who used fertility drugs were more likely to develop OC.[26,41,42] Subsequent studies have suggested that there may be an increased risk of OC associated with fertility drug use among nulliparous women.[43,44] However, other studies have not observed

any association between OC and fertility drug use.[45-48] Hormonal factors linked to OC include oral contraceptive use[49-52] and hormone replacement therapy (HRT).[53,54] Oral contraceptive use has consistently been shown to decrease the risk of OC; however there is some controversy regarding the impact that HRT has on OC risk. [55-58]

Several theories have been proposed to explain the mechanisms by which hormonal and reproductive factors affect OC risk. The incessant ovulation hypothesis theorizes that the repeated damage and subsequent repair cycles that occur during ovulation on the epithelial surface of the ovary contributes to DNA damage and increases the risk of developing OC.[59-62] This hypothesis is consistent with reduced risk associated with parity, breast-feeding, and oral contraceptive use. The gonadotropin hypothesis postulates that exposure to high levels of circulating pituitary gonadotropins, which causes increased estrogen stimulation of the ovarian surface epithelium, plays a role in the development of OC.[63,64] The hypothesis is supported by the decreased risk associated with parity and oral contraceptives but is inconsistent with regards to the decreased risk linked to breastfeeding, which increases gonadotropins, and HRT, which reduces gonadotropin levels.[6] The pregnancy clearance hypothesis theorizes that the increased levels of progesterone during pregnancy results in the clearance of premalignant and malignantly transformed cells from the ovaries.[6,65] This hypothesis is also supported by the observed risk reduction associated with parity. Inflammation has also been proposed as a potential mechanism by which factors affect OC risk. The inflammation hypothesis proposes that local inflammation and inflammatory cytokines damage the epithelial surface of the ovary; ovulation, talc use, and endometriosis are all associated with inflammation and increased risk of OC.[6,66] Despite the different hypotheses of the biological mechanisms involved in ovarian carcinogenesis, the process itself remains poorly understood.

However, the identification of numerous risk factors has established that OC is multifactorial and complex in etiology.

Research regarding the impact of lifestyle factors on OC risk has been inconsistent.[6,67] Several studies have found an increased risk associated with obesity,[68-70] while others have found no association.[71,72] A recent pooled analysis of studies participating in the Ovarian Cancer Association Consortium (OCAC) analyzed the risk of OC associated with body mass index (BMI) at three different time points: recent BMI, maximum BMI and early adulthood BMI. Olsen and colleagues observed increased risks of borderline and invasive OC at all three time points; however, they only observed this association among the less common non-serous and low-grade serous subtypes of ovarian tumors.[73] The relationship between hormone levels and obesity has been proposed as the mechanism by which obesity affects the risk of OC. Specifically, obesity affects hormone levels by: increased conversion of androgens to estrogens in adipose tissue, increased insulin resistance that results in hyperinsulinemia that subsequently stimulates androgen production, increased free estradiol levels due to reduced hormone-binding globulin capacity, and hyperstimulation of the adrenal gland. The impact of lifestyle factors including alcohol use[33,74,75] and smoking on OC risk has been similarly inconsistent.[33,76,77]

1.4 DIAGNOSIS, TREATMENT, AND SURVIVAL

OC has traditionally been thought of as a "silent killer"; however, a 2000 study by Goff and colleagues provided evidence that the majority of women experience more than one symptom an average of 3 to 6 months before their diagnosis. Importantly, they observed that 88% of the women diagnosed with early stage disease experienced the same symptoms that women with late stage

disease reported. The most commonly reported symptoms in their study were: increased abdominal size, bloating, fatigue, abdominal pain, and indigestion.[78] Interestingly, before they were diagnosed with OC, women reported that they were initially diagnosed with irritable bowl syndrome (15%), stress (12%), gastritis (9%), or were diagnosed with another condition (47%), and 13% reported that they were told nothing was wrong with them. Goff *et al* reported that patients not recognizing that their symptoms were indicative of a serious illness and the misdiagnosis by clinicians both contributed to delays in their OC diagnosis.[78] Due to these factors, patients are typically diagnosed once their disease has progressed to advanced stages.

Usually, initial diagnostic findings include a palpable abdominal mass. Transvaginal ultrasonography (TVU) is then performed to visualize the mass and if ascites are present, paracentesis may be done to determine whether the ascitic fluid contains malignant cells. Cancer-antigen 125 (CA-125) is often collected prior to primary surgery in order to determine the probability of a primary ovarian tumor; however, CA-125 can be elevated due to non-malignant conditions, such as endometriosis and uterine fibroids.[79,80], and alone is not an accurate diagnostic measurement. Unless patients are poor candidates for surgery, an exploratory laparotomy is performed for diagnostic confirmation, cytoreduction, and staging. [81] The most commonly used staging system for OC is the Féderation Internationale de Gynécologie et d'Obstétrique (FIGO) system, which is presented in Table 1.[82]

Patients with low risk of recurrence generally do not require adjuvant chemotherapy. This group includes cases diagnosed with borderline disease or stage Ia, grade 1 disease. Depending on the perceived risk of recurrence, women with stage Ia, grade 2, or stage Ib grade1/2 may or may not receive adjuvant chemotherapy. The majority of patients are diagnosed with advanced disease and the current standard of care for these patients is adjuvant taxane and platinum-based

chemotherapy, which most commonly includes Taxol and Carboplatin. The majority of OC patients achieve clinical remission upon the completion of primary treatment. [83,84] Unfortunately, a large proportion of these women will ultimately develop recurrent disease.[85-88] The overall average 5-year relative survival rate is 44.2% among OC patients.[5] The most significant predictor of survival is stage; however, many other patient characteristics impact prognosis. Numerous studies have shown that optimal debulking (i.e., residual disease < 1 cm) is a significant predictor of survival and cases that are sub-optimally debulked have a poorer prognosis.[89-92] Other factors associated with prognosis include age,[90,93,94] tumor grade,[90,92,95] and histologic subtype.[89,90,94-96]

Upon completion of primary adjuvant chemotherapy, surveillance for recurrent disease is initiated. The European Society of Medical Oncology (ESMO) recommends physical examinations every 3 months for 2 years after remission is achieved, every 4 months during the third year, and every 6 months beginning in the fourth year of surveillance care. They also recommend that CA-125 levels are measured at each visit while imaging scans are recommended only if there is a rise in CA-125 levels or there is clinical evidence of recurrent disease.[97] However, there is controversy regarding whether these surveillance recommendations are able to meaningfully improve survival among OC patients.[98-101] Several studies have reported that physical examinations have a limited impact on detecting recurrent disease and that the majority of cases who have recurrent disease detectable by physical exam also present with symptoms or elevated CA-125 levels.[102,103] A recent, randomized trial assessed the effectiveness of initiating recurrent treatment based on rising levels of CA-125 alone compared to initiating treatment only when there was clinical evidence of recurrent disease. Rustin and colleagues observed no survival benefit among cases whose treatment was initiated based on CA-125 levels alone; in fact, they observed an earlier decline in quality of life among these patients.[104] Although the use of CA-125

levels for the early detection of recurrent disease has not improved OC survival, the majority of patients believe routine CA-125 testing was the most important factor in predicting cancer survival.[105] These results suggest that there is a need for improved clinician-patient communication regarding the goals and efficacy of surveillance care. Improved measures of prognosis, particularly the risk of recurrence, are needed to aid clinicians and OC patients in making informed decisions regarding their follow-up care.

Table 1. Féderation Internationale de Gynécologie et d'Obstétrique (FIGO) staging system for cancer of the ovary

1. Stage	Characteristics
I	Growth limited to the ovaries.
Ia	Growth limited to one ovary; no ascites present containing malignant cells. No tumor on the external surface; capsule intact.
Ib	Growth limited to both ovaries; no ascites present containing malignant cells. No tumor on the external surfaces; capsules intact.
Ic	Tumor either stage Ia or Ib, but with tumor on surface of one or both ovaries, or with capsule ruptured, or with ascites present containing malignant cells, or with positive peritoneal washings.
II	Growth involving one or both ovaries with pelvic extension.
IIa	Extension and/or metastases to the uterus and/or tubes.
IIb	Extension to other pelvic tissues.
IIc	Tumor either stage IIa or IIb, but with tumor on surface of one or both ovaries, or with capsule(s) ruptured, or with ascites present containing malignant cells, or with positive peritoneal washings.
III	Tumor involving one or both ovaries with histologically confirmed peritoneal implants outside the pelvis and/or positive regional lymph nodes. Superficial liver metastases equals stage III. Tumor is limited to the true pelvis, but with histologically proven malignant extension to small bowel or omentum.
IIIa	Tumor grossly limited to the true pelvis, with negative nodes, but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces, or histologic proven extension to small bowel or mesentery.
IIIb	Tumor of one or both ovaries with histologically confirmed implants, peritoneal metastasis of abdominal peritoneal surfaces, none exceeding 2 cm in diameter; nodes are negative.
IIIc	Peritoneal metastasis beyond the pelvis >2 cm in diameter and/or positive regional lymph nodes.
IV	Growth involving one or both ovaries with distant metastases. If pleural effusion is present, there must be positive cytology to allot a case to stage IV. Parenchymal liver metastasis equals stage IV.

Adapted from: Oncology FCoG. Current FIGO staging for cancer of the vagina, fallopian tube, ovary, and gestational trophoblastic neoplasia. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics.* Apr 2009;105(1):3-4.

1.5 SCREENING METHODS

To date, efforts to develop screening methods to detect OC during the early stages of disease development have not been effective. Given the significantly improved prognosis for patients

diagnosed when disease is confined to the ovaries, earlier detection of OC would likely result in significantly improved survival rates. There is currently no standard screening method for the detection of OC. CA-125 and TVU have been proposed as a potential screening method but based on results from screening trials the protocol has not proven to be effective in detecting early stage disease with acceptable false-positive rates.[106,107]

In an effort to utilize symptoms experienced by OC patients to predict the presence of cancer, several studies have aimed to develop a symptom-based screening tool.[108,109] Subsequent studies have shown that the use of a symptom index may improve the sensitivity and specificity of OC screening when used in combination with diagnostic biomarkers such as CA-125,[110] and has the potential to improve discrimination between malignant and benign tumors when used with transvaginal sonography.[111] These results indicate that evaluating symptoms could be useful for the identification of women who are at increased risk of having OC and should be referred for further screening. However, using an approximation of the Goff *et a*. OC symptoms index,[108] Rossing *et al* determined that the use of such a symptoms index in the general population would likely have a low positive predictive value and would result in unnecessary medical evaluations for women without OC.[112] Screening tools utilizing OC symptoms are promising; however, improved methods to distinguish between healthy women and women at high risk of having OC is needed in order to avoid sending a large number of women for ultimately unnecessary testing.

1.6 SPECIFIC AIMS

OC represents a significant public health challenge due to its complex and poorly understood etiology, the lack of effective screening methods, and poor survival rates. The goal of this research

is to address each of these aspects through the following specific aims: 1) determine whether fertility drug use significantly impacts OC risk when accounting for established OC risk factors; 2) characterize subgroups of OC cases that experience similar symptomatology prior to diagnosis and identify the factors that predict membership to these groups; and, 3) assess conditional disease-free survival among OC cases and identify the prognostic factors that impact survival.

2.0 ARTICLE 1: USE OF FERTILITY DRUGS AND FISK OF OVARIAN CANCER: RESULTS FROM A US-BASED CASE-CONTROL STUDY

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2.1 ABSTRACT

Background: Previous studies examining associations between use of fertility drugs and ovarian cancer (OC) risk have provided conflicting results. We used data from a large case-control study to determine whether fertility drug use significantly impacts OC risk when taking into account parity, gravidity, and cause of infertility.

Methods: Data from the Hormones and Ovarian Cancer Prediction (HOPE) study were used (902 cases, 1802 controls). Medical and reproductive histories were collected via in-person interviews. Logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI). Models were adjusted for age, race, education, age at menarche, parity, oral contraceptive use, breastfeeding, talc use, tubal ligation, and family history of breast/ovarian cancer.

Results: Ever use of fertility drugs was not significantly associated with OC within the total HOPE population (OR: 0.93, 95%CI: 0.65–1.35) or among women who reported seeking medical attention for infertility (OR: 0.87, 95%CI 0.54-1.40). We did observe a statistically significant increased risk of OC for ever use of fertility drugs among women who, despite seeking medical attention for problems getting pregnant, remained nulligravid (OR: 3.13, 95%CI 1.01-9.67).

Conclusions: These results provide further evidence that fertility drug use does not significantly contribute to OC risk among the majority of women; however, women who despite infertility evaluation and fertility drug use remain nulligravid, may have an elevated risk for OC.

Impact: Our results suggest that fertility drug use does not significantly contribute to overall risk of OC when adjusting for known confounding factors.

2.2 INTRODUCTION

Ovarian cancer (OC) is multifactorial and complex in etiology. Lifestyle factors shown to increase the risk of OC include low parity,[27-29,113] late onset of menopause[114,115] and perineal talc use.[38-40]

Oral contraceptive use,[49-52] breastfeeding[30-32] and tubal ligation[34-36] have been shown to have a protective effect on OC risk. Several theories have been proposed to explain the mechanisms by which these factors affect risk of OC. The incessant ovulation hypothesis theorizes that the repeated damage and subsequent repair cycles that occur during ovulation on the epithelial surface of the ovary contributes to DNA damage and increases the risk of developing OC.[59-62] The gonadotropin hypothesis postulates that exposure to high levels of circulating pituitary gonadotropins, which stimulates the ovarian surface epithelium, plays a role in the development of OC.[63,64] Both of these theories suggest that the use of fertility drugs, which often contain gonadotropins and stimulate ovulation, may increase the risk of OC.

Fertility drug use has increased markedly in the U.S.[116] Based on data from the 2002 National Survey of Family Growth, 12% of the 61.6 million U.S. women between the ages of 16 and 44 sought infertility services. The use of infertility services was more common among older women, women with higher incomes, and women who were childless.[117] The utilization of fertility drugs and other infertility services is expected to continue to rise as the percentage of women who postpone attempts to become pregnant until after the age of 35 increases. Stephen *et al* projected that the number of infertile women will increase to between 5.4-7.7 million in 2025.[118] Despite the growing number of women seeking fertility treatment, the effects of fertility drug use on OC risk remain uncertain. Several early studies reported an association between exposure to fertility drugs and the development of OC, which spurred concern regarding the safety of these drugs.[26,41,42] Subsequent studies did not provide evidence of an increased risk of OC with the use of fertility drugs.[43,45,47,48,119,120] However, concern regarding fertility drug use remains after other studies reported that women who were exposed to fertility drugs for more than 12 cycles were at an increased risk of OC.[121,122] Nulliparous women who failed to conceive after treatment have also

been reported to have an increased risk OC.[26,45] Finally, several studies have shown that fertility drug use may increase the risk of borderline ovarian tumors.[41,42,44,46,123,124]

The conflicting results from previous studies might be due to the generally small sample sizes and/or inability to control for important reproductive factors known to influence OC risk. Establishing the relationship between fertility drug use and OC risk is complicated by the fact that infertility itself increases the risk of OC.[52,125-127] It is also of particular importance to account for parity because the frequency of nulliparity is high among infertile women and nulliparity has been established as an important OC risk factor.[63,128,129] The increasing use of fertility drugs necessitates the separation of the effects of underlying infertility and other confounding factors from those of fertility drug use. Ours is one of the largest case-control studies of OC conducted to date. Our objective was to contribute to the debate regarding whether fertility drug use significantly impacts OC risk when taking into account parity, gravidity, and cause of infertility.

2.3 MATERIAL AND METHODS

2.3.1 Study population and data collection

We used data from the Hormones and Ovarian Cancer Prediction (HOPE) study, a population-based case-control study of OC described in detail elsewhere.[50,130] Briefly, subjects were residents of a contiguous region comprising Western Pennsylvania, Eastern Ohio, and Western New York State. All cases were histologically confirmed to have primary epithelial ovarian, peritoneal, or fallopian tube cancers diagnosed between 2003 and 2008. Eligible women were at least 25 years old and were within 9 months of initial diagnosis at the time of recruitment. A total of 902 cases

were enrolled. Controls, N=1802, were frequency matched to cases (~2:1) by 5-year age group and telephone area code through random-digit dialing. Women who had undergone a bilateral oophorectomy were ineligible. All study participants provided informed consent. The study was approved by the University of Pittsburgh Institutional Review Board and by the human subject committees at each hospital where cases were identified.

Trained interviewers collected questionnaire data that included detailed reproductive, gynecological, and medical histories as well as information regarding lifestyle and family medical history; a reference date of 9 months before the interview date was used for all participants.

2.3.2 Infertility and fertility drug use

All study participants were asked if they had ever sought medical attention for problems becoming pregnant. Women who responded with "yes" to this question were asked whether their partner was tested, they were personally tested, they were both tested, or if neither of them were tested for infertility. They were also presented with a list of infertility causes and asked whether each was found to be a probable cause for their problems becoming pregnant. Women were able to respond "yes," "no," or "don't know" to whether they were diagnosed with a problem involving: partner's sperm, their ovaries, ovulation, their fallopian tubes, their cervix, cervical mucous, their uterus, scarring of the uterus, menstruation, endometriosis, or some other problem. For the current analyses, we collapsed the cervix and cervical mucous variables into one cervical problem variable. Similarly, we combined the variables for uterus problems and scarring of the uterus. We chose to collapse these variables because the mechanism affecting infertility is similar for both cervical variables as well as both uterine variables. Combining similar causes of infertility resulted

in a greater number of exposed women and increased our power to determine whether uterine or cervical causes of infertility were significantly associated with OC risk.

All study participants were asked if they had ever used fertility drugs. Women who responded with "yes" to this question were asked the name of the fertility drugs used. The majority of women used clomiphene citrate, which we defined as one group of fertility drugs ("clomiphene"). We pooled follicle stimulating hormone (FSH), human chorionic gonadotropin (hCG), gonadotropin-releasing hormone (GnRH), urofollitropin, and human menopausal gonadotropin (hMG) drugs into one group of fertility drugs, "gonadotropins", because they utilize the same method of stimulating ovulation. We also created a group for women who had used a combination of gonadotropins and clomiphene citrate ("clomiphene + gonadotropins"). Finally, we grouped together any other fertility drugs, such as progesterone and unknown hormone pills, into an "other" fertility drug group ("other fertility drug"). Women who reported taking fertility drugs were also asked how many months they took each fertility drug. This information was collected for the first four periods of fertility drug use. We do not have information regarding type of fertility drug or the duration of use for fertility drugs used after the first four time periods of fertility drug use; however, only 9 women reported using fertility drugs for more than four time periods.

2.3.3 Covariates

Based on anthropometric data provided by the participants, we calculated body mass index (BMI) as weight (kg) at reference date divided by height (m) at reference date squared. Family history of ovarian and breast cancers was defined as having at least one reported diagnosis of, respectively, ovarian or breast cancer among a first-degree relative. Hormone replacement therapy (HRT) use

was defined as the use of hormones for menopause, to treat osteoporosis, or after hysterectomy/removal of ovaries; any use of estrogen or estrogen plus progesterone among postmenopausal women was also classified as HRT use. Women were classified as postmenopausal if they were 55 years or older, reported natural menopause, had used HRT, or reported no menstrual periods in the 6 months prior to the reference date. Women were considered to be premenopausal if they had never taken HRT and reported having menstrual periods in the 6 months prior to the reference date, and were younger than 55 years old.[131] All participants were asked if they had ever been pregnant. Women reporting at least 1 pregnancy were subsequently asked to provide information regarding the outcome of the pregnancy and the duration they breastfed. This information was repeated for up to four pregnancies. Duration of breastfeeding was calculated as the sum of the number of months they breastfed after each of their first four pregnancies. Information regarding pregnancy outcomes, and breastfeeding was not available for later pregnancies; however, women did report their total number of pregnancies and live births. Among women who reported more than four pregnancies, we calculated their average length of breastfeeding for their first four pregnancies, multiplied this average by the number of additional pregnancies resulting in live births, and added this to the total months of reported breastfeeding. Perineal talc use was defined as ever using dusting powder or deodorizing spray on: the genital or rectal areas, on sanitary napkins, on underwear, or on diaphragms or cervical caps.

2.3.4 Statistical analysis

Associations between OC risk and demographic and reproductive factors were evaluated using logistic regression models. These models were used to calculate odds ratios (OR) and corresponding 95% confidence intervals (95% CI), as well as p-trend values for continuous factors.

Backward stepwise regression was used to determine which demographic and reproductive variables should be included as covariates in the regression models used to evaluate the effect of exposure to fertility drugs on OC risk. Age was locked into the stepwise model as a continuous variable; a p-value criterion of 0.10 was used to identify additional covariates. The following variables were evaluated for inclusion: race (white, black, other), education (less than high school graduate, high school graduate, post-high school education), site (Pittsburgh, Cleveland, Buffalo), BMI (<25, 25-29.99, ≥30), family history (none, first-degree breast, first-degree ovarian, first-degree ovary and breast), tubal ligation (yes, no, missing), oral contraceptive use (continuous), number of live births (0, 1, 2, 3, 4, ≥5), breastfeeding (never, < 6, 6 < 12, ≥ 12 months), age at menarche (continuous), menopausal status (premenopausal, postmenopausal), perineal talc use (ever, never), and HRT use (ever, never). All models are adjusted for the covariates identified through this process with the exception of models in which collinearity occurred between these covariates and the variables of interest (indicated with the results).

Associations between OC risk and ever versus never use of fertility drugs and also duration of use, which was evaluated as a continuous variable and as a categorical variable (never, < 6 months, ≥ 6 months), were evaluated among the total HOPE population and separately among women who reported seeking medical attention for infertility. We chose 6 months as the cutoff for duration of use because this was the median duration of fertility drug use among all women who had taken fertility drugs and using this grouping provided adequate sample size for each group when stratifying for parity and gravidity. Among women who reported seeking medical attention for infertility, we additionally evaluated associations between OC risk and year medical attention was sought, who was tested, and underlying cause of infertility using unconditional logistic regression. We also determined whether the relationship between fertility drug use and OC risk

was modified by year medical attention was sought, age at which medical attention for infertility was sought, cause of infertility, and person tested for infertility problems by creating interaction terms between fertility drug use and these variables and including them in the adjusted model. Finally, we evaluated whether use of specific types of fertility drugs (clomiphene, gonadotropins, clomiphene + gonadotropins, other fertility drugs) was associated with OC risk. These analyses were repeated separately for invasive and borderline ovarian tumors; analyses were also repeated using all cases and controls within the HOPE study population.

To examine the impact of parity and gravidity on the association between fertility drug use and OC risk, we evaluated ever compared to never use of fertility drugs while stratifying by the following groups of women: parous, nulliparous-gravid, and nulligravid. These analyses were conducted among women who reported seeking medical attention for infertility and repeated using the total HOPE study population.

All significance tests were two-sided; *P* values <0.05 were considered statistically significant. All analyses were conducted using Stata version 12.1.[132]

2.4 RESULTS

Demographic and reproductive characteristics of the HOPE study population are presented in Table 2. Compared to Caucasians, African Americans had a significantly increased risk of OC. High-school graduates and women with post-high school education had a significantly decreased risk of OC compared to women with less than a high school education. The following variables were also significantly associated with OC risk: age at menarche, oral contraceptive use, parity, gravidity, duration of breastfeeding, perineal talc use, and tubal ligation. Seeking medical attention

for infertility was not significantly associated with OC risk (Table 3). Backward stepwise regression yielded a model that included age, race, education, age at menarche, oral contraceptive use, parity, duration of breastfeeding, perineal talc use, and tubal ligation. First-degree family history of breast/ovarian cancers was associated with a p-value of 0.14 using this method but was nevertheless included in the model because of its known association with OC risk.

Table 3 provides medical information for the 445 women who reported seeking medical attention for infertility. No statistically significant association with OC was observed for age at which women sought medical attention, year medical attention was initially sought or with person tested for infertility problems. None of the causes of infertility were significantly associated with OC risk; however, borderline significant associations were observed for ovulation problems and menstrual problems. Among the 47 women who reported ovulation problems, 11 had also reported an issue with their menstrual cycles.

Use of fertility drugs was reported by 148 (33%) of the women seeking medical attention for infertility (Table 3). The majority used fertility drugs for less than 12 months (66.7%); mean duration was 11.4 months (range: 1-134 months). Ever use of fertility drugs was not significantly associated with OC risk (Table 3) and remained non-significant after additional adjustment for cause of infertility (OR: 0.66, 95%CI: 0.36-1.22), age medical attention was sought (OR: 0.86, 95%CI: 0.53-1.40), year attention was sought (OR: 0.90, 95%CI: 0.58-1.38), and who was tested for infertility problems (no one tested or partner-only tested compared to self tested or partner and self tested, OR: 0.90, 95%CI: 0.54-1.49) (not in table). No significant interactions between fertility drug use and these variables were observed (data not shown). Similar results were observed for duration of fertility drug use (Table 3 and data not shown). Regarding specific types of fertility drugs, the majority of women who ever used fertility drugs reported using only clomiphene citrate

(56.1%). None of the drugs evaluated were significantly associated with OC risk when looking at ever compared to never use (Table 3) or duration of use (data not shown). Analyses were repeated excluding the 12 cases and controls that reported using unknown or other fertility drugs and the results were unchanged. Additionally, no significant associations between ever use of fertility drugs and OC risk were observed when separately assessing borderline (OR: 0.96, 95%CI: 0.31-2.94; adjusted for age, duration of oral contraceptive use, talc, and age at menarche) and invasive tumors (OR: 0.85, 95%CI: 0.52-1.39; adjusted for all covariates identified by stepwise regression).

Among all 2704 HOPE participants, 152 (5.6%) women reported ever using fertility drugs, this included the 148 women who reported seeking medical attention for infertility and 4 women who had used fertility drugs but had never sought medical attention for fertility issues. All 4 of these latter women were controls; 2 reported taking clomiphene only and 2 reported taking gonadotropins only. Data regarding why these four women reported taking fertility drugs without ever seeking medical attention for infertility were not collected. Ever use of fertility drugs was not significantly associated with OC risk in the total HOPE population (OR: 0.93, 95%CI: 0.65-1.35), nor was duration of use (never compared to <6 months of use, OR: 1.05, 95%CI: 0.61-1.80; never compared to ≥ 6 months of use, OR: 0.82, 95%CI: 0.50-1.34), adjusting for age, race, education, tubal ligation, age of menarche, duration of oral contraceptive use, number of live births, duration of breastfeeding, perineal talc use, and family history. Adjusting for the same covariates, no significant associations between OC risk and ever use of fertility drugs were observed when separately evaluating borderline (OR: 0.64, 95%CI: 0.26-1.55) and invasive tumors (OR: 1.02, 95%CI: 0.69-1.50).

Table 4 presents results of the evaluation of associations between fertility drug use and OC risk stratified by parity and gravidity. Among those seeking medical attention for infertility,

nulligravid women who used fertility drugs were significantly more likely to develop OC than nulligravid women who had never used fertility drugs. However, fertility drug use among parous and nulliparous-gravid women was not significantly associated with OC risk among this group of women. Within the total HOPE study population, the association between OC risk and ever use of fertility drugs was non-significant among parous and nulliparous-gravid women. OC risk was elevated among nulligravid fertility drug users; however, this was not significant (Table 4).

2.5 DISCUSSION

In this large case-control study, we evaluated whether fertility drug use significantly affects OC risk when taking into account, parity, gravidity, and cause of infertility. Consistent with results from previous studies, oral contraceptive use, breastfeeding, and tubal ligation significantly decreased OC risk in our study population while nulliparity, and perineal talc use increased risk.[34,43,44,63,133] Ever use of fertility drugs was not significantly associated with OC risk within the total HOPE population or among women who reported seeking medical attention for infertility. Risk did not differ significantly according to duration of use or type of fertility drug. However, we did observe a statistically significant increased risk of OC for ever use of fertility drugs among women who, despite seeking medical attention for problems getting pregnant, remained nulligravid.

When examining specific causes of infertility among those seeking medical attention for infertility, none of the evaluated causes were significantly associated with OC risk. Specifically, we observed no significant association between OC and endometriosis even though previous studies have reported an increased risk.[44,134-136] Endometriosis was also not significantly associated

with OC risk in the total HOPE population (data not shown). The mechanism by which endometriosis may affect OC risk is poorly understood; however, several studies have shown that endometriosis-associated tumors are most commonly linked to clear cell and endometrioid tumors (55-58).[137-140] The small number of women who reported being diagnosed with endometriosis among those who sought medical attention for infertility in addition to the homogeneity of tumor histologic subtypes among these women may have contributed to the null relationship we observed here. Interestingly, we observed a decreased risk of OC among women who reported an ovulation problem as their cause of infertility. Although this observation was of borderline significance, it suggests that women who ovulate less frequently throughout their lifetime may have a decreased risk of OC and provides further evidence for the incessant ovulation theory.

In a 2004 case-control study, Rossing *et al* observed that women whose infertility manifested past the age of 30 were at increased risk of OC.[43] We found no significant association between OC risk and the age at which women sought medical attention for infertility in our population; however, women who sought help between the ages of 35 and 45 did exhibit a non-significant increased risk compared to women who sought help before they were 25. Women who seek treatment for infertility past the age of 30 have a lower likelihood of success compared to women who seek infertility treatments at younger ages[141] and OC risk associated with infertility among older women may reflect additional risk associated with low parity among these women.

Although we did not observe any significant associations between fertility drug use and OC risk within the total HOPE study population or among the subset of women who reported seeking medical attention for infertility, we did observe, similar to previous reports, a statistically significant increased risk of OC associated with ever fertility drug use among nulligravid women who had infertility problems.[26,44,45] This suggests that women who never became pregnant despite

efforts to conceive are at uniquely increased risk of OC. This is further supported by the fact that we found no significant association between fertility drug use and OC risk among nulliparous women who had at least one pregnancy. Although our results are in line with those from previous studies, it should be noted that the number of nulligravid women who sought medical attention for infertility was relatively small (N=74). Therefore, confirmation of our results by other studies is necessary.

Our finding that fertility drug use does not significantly contribute to OC risk among the majority of women is in line with results from other, recent studies.[43,44,48,133] Early studies that reported an increased risk of OC among fertility drug users included small numbers of OC patients exposed to fertility drugs and were unable to adjust for risk factors known to impact OC risk.[26,41] We observed no risk difference between borderline and invasive tumors; these results are in agreement with a recent case-control study[142] but disagree with several previous studies.[41,42,44,46,123,124]

The strengths of this study include a large sample size and availability of detailed reproductive and medical histories of women included in the study. The ability to stratify and adjust for factors linked to OC risk allowed us to disentangle risk associated with these factors from risk associated with fertility drug use. A limitation of our study is that we were unable to identify women who were infertile but never sought medical attention. This differential misclassification may have attenuated the associations between infertility and OC risk. However, our ability to analyze associations between fertility drug use and OC risk in a relatively large subset of women who had sought medical attention for infertility greatly improved the comparability of fertility drug users to non-users. Being able to reduce the study population to only these women also limited biases associated with comparing fertility drug users with infertility issues to non-

fertility drug users with no history of infertility issues. Our study is also limited by its reliance on self-reported use of fertility drugs; however, the use of a life calendar during interviews may have improved the accuracy of recalling details about fertility drug use. This study includes a greater number of OC cases exposed to fertility drugs than previous studies. Despite this, our study had limited power when completing stratified analyses for fertility drug use and OC risk, which resulted in small subgroups and subsequently wide confidence intervals.

Our results build upon previous research and provide further evidence that fertility drug use does not significantly contribute to overall risk of OC when adjusting for known confounding factors. Our observation that fertility drug use was only significantly associated with increased OC risk among nulligravid women who had ever sought medical attention for infertility suggests that a biological mechanism associated with the inability to conceive may impact OC risk to a greater extent than fertility medications do.

To conclude, these results are reassuring for women and clinicians embarking on fertility drug usage in the setting of infertility treatment.

2.6 TABLES

Table 2. Demographic and reproductive characteristics of the total HOPE population

	Cases (902)		Controls (1802)		OR (95% CI) [a]	*p*-trend [b]
	N	%	N	%		
Site						
Buffalo	251	27.8	476	26.4	1.0 (ref.)	---
Cleveland	294	32.6	628	34.9	0.89 (0.72, 1.09) [c]	
Pittsburgh	357	39.6	698	38.7	0.97 (0.79, 1.18) [c]	
Age (in years)						
< 30	13	1.4	24	1.3	1.0 (ref.)	0.01
30 < 40	47	5.2	108	6.0	0.80 (0.38, 1.71) [c]	
40 < 50	164	18.2	393	21.8	0.77 (0.38, 1.55) [c]	
50 < 60	276	30.6	569	31.6	0.90 (0.45, 1.79) [c]	
60 < 70	211	23.4	403	22.4	0.97 (0.48, 1.94) [c]	
≥ 70	191	21.2	305	16.9	1.16 (0.57, 2.33) [c]	
Race						
White	856	94.9	1,758	97.6	1.0 (ref.)	---
Black	35	3.9	29	1.6	2.48 (1.51, 4.08) [c]	
Other	11	1.2	15	0.8	1.51 (0.69, 3.29) [c]	
Education						
Non-high school graduate	83	9.2	82	4.5	1.0 (ref.)	---
High school graduate	303	33.6	535	29.7	0.59 (0.42, 0.83) [d]	
Post-high school	516	57.2	1,185	65.8	0.46 (0.33, 0.64) [d]	
Smoking Status						
Never Smoker	458	50.8	913	50.7	1.0 (ref.)	---
Former Smoker	286	31.7	545	30.2	1.02 (0.84, 1.22)	
Current Smoker	158	17.5	344	19.1	0.86 (0.69, 1.08)	
Body Mass Index (in kg/m^2) [e]						
< 25	300	33.3	671	37.2	1.0 (ref.)	0.08
25 - 29.99	267	29.6	528	29.3	1.09 (0.89, 1.33)	
≥30	334	37.0	602	33.4	1.18 (0.97, 1.43)	
Family History (1st degree)						
No	715	79.3	1,491	82.7	1.0 (ref.)	---
Breast Cancer Only	147	16.3	255	14.2	1.21 (0.96, 1.51)	
Ovarian Cancer Only	32	3.5	44	2.4	1.51 (0.95, 2.42)	
Breast and Ovarian Cancers	8	0.9	12	0.7	1.21 (0.48, 3.00)	
Age at Menarche (in years)						
<12	182	20.2	444	24.6	1.0 (ref.)	0.22
12	257	28.5	463	25.7	1.38 (1.09, 1.74)	
13	243	26.9	484	26.9	1.26 (0.99, 1.59)	
≥14	220	24.4	411	22.8	1.27 (1.00, 1.62)	
Menopausal Status						
Premenopausal	234	25.9	482	26.8	1.0 (ref.)	---
Postmenopausal	668	74.1	1,320	73.2	0.80 (0.63, 1.03)	

Table 2. (*Continued)*

	Cases (902)		Controls (1802)		OR (95%CI) [a]	*p*-trend [b]
	N	%	N	%		
Oral Contraceptive Use (months) [f]						
Never	367	40.7	531	29.5	1.0 (ref.)	< 0.01
< 6	96	10.6	161	8.9	0.88 (0.65, 1.18)	
6 < 24	135	15.0	282	15.6	0.69 (0.53, 0.89)	
24 < 60	122	13.5	297	16.5	0.61 (0.47, 0.79)	
60 < 120	123	13.6	299	16.6	0.63 (0.48, 0.82)	
≥ 120	58	6.4	232	12.9	0.37 (0.27, 0.52)	
Hormone Replacement Therapy Use						
Never	543	60.2	1039	57.7	1.0 (ref.)	---
Ever	359	39.8	763	42.3	0.87 (0.73, 1.03)	
Number of Pregnancies						
0	167	18.5	167	9.3	1.0 (ref.)	< 0.01
1	114	12.6	188	10.4	0.57 (0.41, 0.78)	
2	216	24.0	458	25.4	0.44 (0.33, 0.58)	
3	167	18.5	426	23.6	0.36 (0.27, 0.47)	
4	112	12.4	284	15.8	0.34 (0.25, 0.46)	
≥5	126	14.0	279	15.5	0.34 (0.25, 0.47)	
Number of Live Births						
0	213	23.6	230	12.8	1.0 (ref.)	< 0.01
1	117	13.0	228	12.7	0.51 (0.38, 0.68)	
2	263	29.2	593	32.9	0.45 (0.35, 0.57)	
3	170	18.8	418	23.2	0.39 (0.30, 0.51)	
4	73	8.1	190	10.5	0.32 (0.23, 0.45)	
≥5	66	7.3	143	7.9	0.32 (0.22, 0.47)	
Duration of Breastfeeding (months)						
Never	610	67.6	928	51.5	1.0 (ref.)	< 0.01
< 6	117	13.0	296	16.4	0.60 (0.47, 0.76)	
6 < 12	66	7.3	199	11.0	0.54 (0.40, 0.72)	
≥ 12	109	12.1	379	21.0	0.46 (0.36, 0.59)	
Perineal Talc Use						
No	653	72.4	1426	79.1	1.0 (ref.)	---
Yes	249	27.6	376	20.9	1.40 (1.16, 1.69)	
Tubal Ligation						
No	666	73.8	1162	64.5	1.0 (ref.)	
Yes	201	22.3	616	34.2	0.55 (0.46, 0.67)	---
Unknown	35	3.9	24	1.3	2.66 (1.57, 4.53)	
Sought Medical Attention for Infertility						
Never	747	82.8	1512	83.9	1.0 (ref.)	---
Ever	155	17.2	290	16.1	1.15 (0.93, 1.43)	

[a] Odds ratios and corresponding confidence intervals are adjusted for age (continuous), race (white, black, other), and education (non-high school graduate, high school graduate, post high-school), unless otherwise noted.
[b] P-trend values were obtained from logistic regression models by using continuous versions of these factors; all models were adjusted for age, race, and education with the exception of age, which was unadjusted.
[c] Unadjusted.
[d] Adjusted for age and race.
[e] 1 case and 1 control were missing weight information.
[f] 1 case was missing oral contraceptive use information.

Table 3. Medical information, infertility causes, and ovarian cancer risk among HOPE participants seeking medical attention for infertility (N=445)

	Cases (155)		Controls (290)		OR (95% CI) [a]
	N	%	N	%	
Year Medical Attention was Sought					
≤1970	55	35.5	97	33.5	1.0 (ref.)
1970≤1980	39	25.2	76	26.2	1.13 (0.55, 2.31) [b]
1980≤1990	31	20.0	74	25.5	0.77 (0.31, 1.91) [b]
After 1990	30	19.3	43	14.8	1.09 (0.34, 3.47) [b]
Age at Which Medical Attention was Sought (in years)					
< 25	47	30.3	86	29.7	1.0 (ref.)
25 < 30	52	33.5	110	37.9	0.94 (0.55, 1.61) [b]
30 < 35	35	22.6	68	23.4	0.89 (0.48, 1.66) [b]
35 < 40	17	11.0	18	6.2	2.00 (0.84, 4.75) [b]
≥ 40	4	2.6	8	2.8	0.84 (0.21, 3.37) [b]
Fertility Testing Done					
None	20	12.9	50	17.2	1.0 (ref.)
Partner	12	7.7	17	5.9	1.41 (0.53, 3.75)
Self	55	35.5	84	29.0	1.32 (0.66, 2.67)
Both	68	43.9	139	47.9	0.92 (0.47, 1.81)
Fertility Drug Use					
Never	105	67.7	192	66.2	1.0 (ref.)
Ever	50	32.3	98	33.8	0.87 (0.54, 1.40)
Type of Fertility Drug					
Never	105	67.7	192	66.2	1.0 (ref.)
Clomiphene Only	28	18.1	55	19.0	0.87 (0.49, 1.56) [b]
Gonadotropin Only	7	4.5	20	6.9	0.51 (0.20, 1.32) [b]
Gonadotropin + Clomiphene Only	9	5.8	17	5.8	0.94 (0.37, 2.42) [b]
Other Only [c]	6	3.9	6	2.1	1.87 (0.53, 6.65) [b]
Duration of Fertility Drug Use (in months) [d]					
Never	105	67.7	192	66.2	1.0 (ref.)
< 6	22	14.2	41	14.1	0.92 (0.48, 1.74) [b]
≥ 6	27	17.4	57	19.7	0.75 (0.42, 1.34) [b]
Low Sperm Count [e]					
No	130	83.9	229	79.0	1.0 (ref.)
Yes	25	16.1	55	19.0	0.68 (0.39, 1.18) [b]
Problems with ovaries (cysts) [e]					
No	141	91.0	264	91.0	1.0 (ref.)
Yes	14	9.0	21	7.2	1.32 (0.61, 2.84) [b]
Ovulation Problems [e]					
No	144	92.9	248	85.5	1.0 (ref.)
Yes	11	7.1	36	12.4	0.51 (0.24, 1.09) [b]
Tubal Problems [e]					
No	137	88.4	245	83.5	1.0 (ref.)
Yes	18	11.6	40	13.8	0.62 (0.33, 1.18) [b]
Uterine Problems [e]					
No	147	94.8	274	94.5	1.0 (ref.)
Yes	8	5.2	11	3.8	1.04 (0.38, 2.83) [b]
Menstrual Problems [e]					
No	146	94.2	254	87.6	1.0 (ref.)
Yes	9	5.8	30	10.3	0.48 (0.20, 1.11) [b]
Endometriosis [e]					
No	141	91.0	259	89.3	1.0 (ref.)
Yes	13	8.4	25	8.6	0.75 (0.35, 1.59) [b]
Cervical Problems [e]					
No	152	98.1	277	95.5	1.0 (ref.)
Yes	3	1.9	8	2.8	0.53 (0.11, 2.59) [b]
Other Diagnosis [e]					
No	126	81.3	240	82.8	1.0 (ref.)
Yes	29	18.7	46	15.9	1.56 (0.87, 2.79) [b]

[a] ORs and corresponding 95% CIs are adjusted for age, race, education, tubal ligation, age of menarche, duration of oral contraceptive use, number of live births, duration of breastfeeding, perineal talc use, and family history of breast/ovary cancers.

[b] Due to collinearity, family history of breast/ovarian cancer was omitted from the adjusted logistic regression model. These ORs and corresponding 95% CIs are adjusted for all other variables listed in [a].

[c] Includes the following fertility drugs: roloxifene, danazol, unknown hormone pills, bromocriptine, progesterone, and metformin.

[d] Duration of fertility drug use was missing for one case and was therefore not included in the logistic regression model; percentages correspond to the entire population of women who sought medical attention for problems getting pregnant.

[e] These variables exclude women who responded "don't know" when asked if they were diagnosed with a particular infertility problem and these women were also not included in logistic regression models. Percentages correspond to the entire population of women who sought medical attention for problems getting pregnant.

Table 4. Ovarian cancer risk according to parity, gravidity, and fertility drug use in total HOPE population and separately among HOPE participants that sought medical attention for infertility

		Women Who Sought Medical Attention for Infertility				Total HOPE Population			
Parity	**Gravidity**	**Fertility Drug Use**	**Cases (N=155) N (%)**	**Controls (N=290)**	**OR (95% CI)**	**Fertility Drug Use**	**Cases (N=902)**	**Controls (N=1802)**	**OR (95% CI)**
Parous		No	80 (51.6)	156 (53.8)	1.0 (ref.)	No	666 (73.8)	1493 (82.8)	1.0 (ref.)
		Yes	23 (14.8)	75 (25.9)	0.57 (0.31, 1.05) [a]	Yes	23 (2.6)	79 (4.4)	0.72 (0.44, 1.19) [a]
Nulliparous	**Ever Pregnant**	No	8 (5.2)	9 (3.1)	1.0 (ref.)	No	37 (4.1)	52 (2.9)	1.0 (ref.)
		Yes	9 (5.8)	11 (3.8)	0.47 (0.09, 2.53) [b]	Yes	9 (1.0)	11 (0.6)	0.77 (0.26, 2.25) [d]
Nulliparous	**Never Pregnant**	No	17 (11.0)	27 (9.3)	1.0 (ref.)	No	149 (16.5)	155 (8.6)	1.0 (ref.)
		Yes	18(11.6)	12 (4.1)	3.13 (1.01, 9.67) [c]	Yes	18 (2.0)	12 (0.7)	1.52 (0.68, 3.41) [e]

[a] Adjusted for: age, age of menarche, duration of OC use, perineal talc use, education, family history of breast/ovarian cancers, tubal ligation, race, duration of breastfeeding, and number of live births.
[b] Adjusted for: age, age of menarche, duration of OC use, and perineal talc use.
[c] Adjusted for: age, age of menarche, duration of OC use, perineal talc use, education, and family history of breast/ovarian cancers.
[d] Adjusted for: age, age of menarche, duration of OC use, perineal talc use, education, family history of breast/ovarian cancers, and tubal ligation.
[e] Adjusted for: age, age at menarche, duration of OC use, perineal talc use, education, and tubal ligation.

3.0 ARTICLE 2: SYMPTOM PRESENTATION AMONG OVARIAN CANCER CASES PRIOR TO DIAGNOSIS: A LATENT CLASS ANALYSIS.

To be submitted for publication

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3.1 ABSTRACT

Background: Ovarian cancer (OC) has traditionally been considered an asymptomatic disease. However, recent studies have established that the majority of women experience symptoms prior to diagnosis. Improved knowledge of the symptoms associated with OC could lead to earlier detection. Unfortunately, identification of OC-related symptoms is hampered due to their non-specific nature.

Objectives: To determine whether there are subgroups of OC cases that experience similar symptom profiles prior to diagnosis, establish whether these profiles differ according to stage at diagnosis, and identify characteristics that predict membership to these subgroups.

Methods: We examined data from 902 ovarian, peritoneal, and tubal cancer cases enrolled in the Hormones and Ovarian Cancer Prediction (HOPE) study. Information regarding symptoms experienced prior to diagnosis was collected via in-person interviews. Latent class analysis (LCA) was used to identify symptom profiles among study participants. Differences in demographic, lifestyle, and disease characteristics between subgroups were evaluated using chi-square tests.

Results: LCA yielded a model with 3 classes which were primarily characterized by the total number of symptoms experienced prior to diagnosis and were labeled: "Low Symptomatology" (N=436), "Moderate Symptomatology" (N=397), and "High Symptomatology" (N=69). The median number of symptoms reported for each class was 2 (range 0-6), 6 (range 2-12), and 13 (range 10-20), respectively. LCA completed separately for early (I/II) and late (III/IV) stage cases yielded similar results. Among all study participants, class membership was significantly associated with study site (P<0.01), age (P <0.01), and oral contraceptive use (P<0.01). Smoking status and tumor type were significantly associated with class membership among early stage cases only.

Conclusion: Using LCA, we identified 3 subgroups of OC cases that were defined by the total number of symptoms experienced prior to diagnosis. Interestingly, the number of symptoms experienced prior to diagnosis did not significantly differ between early and late stage cases. Our data suggests that raising awareness of the seriousness of symptoms experienced in combination may result in more women seeking medical attention before their OC progresses to late stage disease.

3.2 INTRODUCTION

The majority of ovarian cancer (OC) cases are diagnosed with advanced-stage disease and, as a result, their prognosis is poor. Women diagnosed with early-stage (I/II) disease have significantly higher five-year survival rates than women with advanced-stage disease (III/IV).[5] Improved early detection strategies could therefore result in higher survival rates.

OC has traditionally been considered an asymptomatic disease. However, more recent studies have provided evidence that a significant proportion of women do experience symptoms prior to diagnosis, with many experiencing more than one.[78,109,112,143,144] This indicates that evaluating symptoms may be useful for identifying women who are at increased risk of having OC and should be referred for further screening. Unfortunately, the identification of OC symptoms and their use in early detection strategies is complicated due to the non-specific nature of the symptoms. As a result, the ability of symptoms to improve current OC screening methods has remained limited by the large number of women in the general population that experience OC-related symptoms but do not have OC. Previous studies have characterized OC symptom presentation based on the individual ability of symptoms to predict OC. These studies then created

symptom indexes by comparing the predictive values of models that included various combinations of these symptoms.[108,109] However, results reported by Rossing *et al* showed that the use of such a symptoms index in the general population would likely have a low positive predictive value and would result in unnecessary medical evaluations for many women without OC.[112] In order to develop a symptom-based method that can predict the presence of OC with high sensitivity and specificity, there is a strong need to increase knowledge of symptom presentation prior to OC diagnosis and identify factors related to symptom presentation that are unique to women with OC.

We hypothesized that OC cases experience many different symptoms prior to diagnosis that can be grouped into unique symptom profiles. We utilized latent class analysis (LCA) to identify these profiles. LCA is a model-based, person-centered method that defines and characterizes unobservable characteristics derived from individuals' response patterns to a number of categorical items.[145-148] We applied LCA to data collected as part of the Hormones and Ovarian Cancer Prediction (HOPE) study[50,130,149] to determine whether there are subgroups of OC cases that experience similar symptom profiles prior to diagnosis. We additionally evaluated whether the symptom profiles differed according to stage at diagnosis and whether demographic, lifestyle and disease characteristics predicted membership to the subgroups. To our knowledge, this is the first study to use LCA to examine the heterogeneity in OC symptoms experienced prior to diagnosis.

3.3 MATERIAL AND METHODS

3.3.1 Study population and data collection

Study participants included in our analyses were all enrolled as part of the HOPE study, a population-based case-control study (902 cases and 1802 controls), the details of which are described elsewhere. [50,130,149] Information on symptoms was not collected from controls; consequently, the current analysis is restricted to HOPE participants enrolled as cases. Cases, recruited between 2003 and 2008 from Western Pennsylvania (PA), Eastern Ohio (OH), and Western New York State (NY), were women 25 years or older who had been diagnosed with primary ovarian, peritoneal or fallopian tube cancers within 9 months prior to recruitment. Trained interviewers collected demographic, lifestyle, reproductive and medical history information via in-person interviews using life calendars to aid in the recollection of past exposures. A reference date of 9 months prior to the interview date was used in an effort to identify only the exposures that occurred before women were diagnosed with cancer. Cases were also asked to provide contact information for all clinicians from whom they received medical care. Disease characteristics were abstracted from surgical records, pathology reports, hospitalization records, oncologist notes and CA-125 lab results provided by the cases' healthcare providers. All study participants provided informed consent. The study was approved by the University of Pittsburgh Institutional Review Board and by the human subject committees at each hospital where cases were identified and enrolled.

3.3.2 Demographic and lifestyle characteristics

Based on anthropometric data provided by the participants, we calculated body mass index (BMI) as weight (kg) at reference date divided by height (m) at reference date squared. Study participants were considered to be never smokers if they had never smoked cigarettes daily for 6 months or more; former smokers if they had ever smoked cigarettes daily for 6 months or more but were not smoking daily at the reference date; and, current smokers if they had ever smoked cigarettes daily for 6 months or more and were smoking daily at the reference date. Alcohol use was quantified by adding the number of wine, beer, and hard liquor drinks consumed per week. Women who consumed less than 7 drinks per week were classified as light drinkers, cases who consumed 7-14 drinks per week as moderate drinkers, and cases who reported drinking more than 14 drinks per week as heavy drinkers. Family history of ovarian and breast cancers was defined as having at least one reported diagnosis of, respectively, ovarian or breast cancer among a first-degree relative, including biological mother, father, sisters, brothers, sons and daughters. Participants were asked to provide the duration of each time period that they took oral contraceptives. Based on this information, oral contraceptive use was categorized as never used, used for less than 5 years, and used for 5 years or longer. Hormone replacement therapy (HRT) use was defined as the use of hormones for menopause, to treat osteoporosis, or after hysterectomy/removal of ovaries; any use of estrogen or estrogen plus progesterone among postmenopausal women was also classified as HRT use. Women were classified as postmenopausal if they were 55 years or older, reported natural menopause, had used HRT, or reported no menstrual periods in the 6 months prior to the reference date. Women were considered to be premenopausal if they had never taken HRT and reported having menstrual periods in the 6 months prior to the reference date, and were younger than 55 years old.[131]

3.3.3 Disease characteristics

Information regarding type of cancer (borderline ovarian, invasive ovarian, fallopian tube, peritoneal, or other/unknown), histologic subtype (serous, endometrioid, mucinous, clear cell, Brenner, mixed, or other/unknown), grade (borderline tumor, well differentiated, moderately differentiated, or poorly differentiated/undifferentiated) and stage at diagnosis was abstracted from pathology reports. Women diagnosed with stage I or II OC were classified as having early stage disease and women diagnosed with stage III or IV were classified as having late stage disease. Pre-treatment CA-125 levels were obtained from lab results, oncologist notes, and hospital records. Using these sources, pre-treatment CA-125 levels were available for 688 (76.3%) cases. CA-125 levels were considered within normal range if they were less than 35 U/mL and elevated if they were 35 U/mL or greater.

3.3.4 Ovarian cancer symptoms

All cases were shown a card that listed 23 symptoms; please see Table 7 for this list. Participants were asked to indicate which of these symptoms they had experienced prior to their cancer diagnosis, regardless of whether they realized at the time that it were symptoms of their disease. For the purpose of the current analysis, women are considered to have had the symptom independent of whether or not they suspected, prior to diagnosis, that the symptom was indicative of a larger health problem. Women who reported telling a doctor about a specific symptom were also asked to provide the date and type of appointment as well as the type of doctor they told.

3.3.5 Statistical analysis

Differences in diagnosis-related factors (*e.g.*, primary reason for provider visit that led to diagnosis) between participants with early and late stage OC were assessed using chi-square tests. For each of the 23 symptoms, we first separately evaluated the associations with OC diagnosis and with stage of disease using logistic regression to calculate odds ratios (ORs) and corresponding 95% confidence intervals (CIs). In these analyses, women who had not experienced the symptom being evaluated were used as the reference group. Logistic regression was also used to evaluate the associations between both total number of symptoms experienced (0, 1, 2, 3, 4, 5, 6, 7, ≥8 symptoms) and time elapsed between onset of first symptom and diagnosis (<1, 1<3, 3<6, 6<9, 9<12, ≥12 months), and OC diagnosis and stage of disease. Linear trend was assessed for these two factors as well by including them as continuous variables in logistic regression models.

LCA was used to identify latent classes among OC cases based on symptoms experienced prior to diagnosis.[145-148] LCA is a data-driven method and information regarding the number of latent classes and the size of each class is not known a priori. To determine the optimal number of classes, latent class models were fit using 1, 2, 3, 4, and 5 classes, with the final model chosen by comparing the goodness-of-fit with the Bayesian information criteria (BIC), Akaike information criteria (AIC), and the Lo-Mendel-Rubin likelihood ratio test (LMR- LRT). Study participants were assigned to the class for which they had the highest probability of membership. This process was repeated separately for early and late stage cases. Once the optimal LCA model was identified, we assessed the associations between class membership and demographic, lifestyle, and disease characteristics using chi-square tests among all study participants as well as separately for early and late stage cases.

LCA was performed using Mplus version 6.12 (Muthén & Muthén, Los Angeles, CA).[150] Stata version 12 was used for all other analyses.[132]

3.4 RESULTS

Selected demographic and disease characteristics of the study population are presented in Table 5. The majority of women were older than 55 years, Caucasian, post-menopausal, and had been diagnosed with late stage cancer. Diagnosis-related factors (*i.e.*, reason for visit, pre-treatment CA-25 levels, etc.) are presented in Table 6. Symptoms were the most commonly reported primary reason for the provider visit that led to diagnosis and a gynecological oncologist diagnosed the majority of women. Both primary reason for visit and healthcare provider differed significantly between early and late stage cases: late stage cases more often reported having symptoms, a surgery other than hysterectomy, or another problem as the primary reason for the visit that led to their diagnosis. Women with late stage disease were also more likely diagnosed by a PCP/general practitioner and less likely by an obstetrician/gynecologist. Only 7.4% of the women were actively seeking treatment to watch for OC and the majority had an annual gynecological exam within one year prior to diagnosis. This did not differ significantly between early and late stage cases. The majority of women had elevated pre-treatment CA-125 levels; elevated CA-125 levels were significantly more common among late stage cases than early stage cases.

Only 2.7% of the study participants reported that their physician or gynecologist had ever explained the signs and symptoms of OC to them and only 13.0% reported that they were aware of the signs and symptoms of OC prior to their diagnosis. However, 93.0% reported experiencing at least one symptom prior to their diagnosis, regardless of whether they realized at the time that

it was a symptom of their disease (Table 6). In our study population, women with invasive tumors were 2.27 times more likely to experience at least one symptom than women with borderline tumors (95% CI: 1.19-4.35; not in Table). Among participants with available pre-treatment CA-125 level information, 77.9% experienced symptoms prior to diagnosis and had an elevated CA-125 level, 15.3% experienced symptoms prior to diagnosis but their CA-125 levels were not elevated, 5.5% had an elevated CA-125 level only, and 1.3% did not experience any symptoms prior to diagnosis and had CA-125 levels within normal limits (not in Table).

Table 7 summarizes results for each of the 23 symptoms listed on the card shown to the study participants. The most common symptoms experienced (experienced by ≥30% of the women) were bloating, weight gain or loss, and pelvic or abdominal discomfort. Women who experienced the following symptoms were significantly more likely to have made the health care visit that led to their diagnosis due to symptoms compared to a reason other than symptoms: bloating, weight gain or loss, pelvic or abdominal discomfort, ongoing fatigue, abdominal swelling, distended abdomen, gas, feeling full, severe pelvic pain, indigestion, heartburn, abnormal bleeding, decreased appetite, and hard abdomen. Most symptoms were not associated with tumor stage. However, abdominal swelling, distended abdomen, and decreased appetite were significantly more common among women diagnosed with late stage disease while abnormal bleeding and abdominal mass were significantly more often reported by women with early stage disease.

Table 8 presents data pertaining to the total number of symptoms experienced prior to diagnosis and the time elapsed between the onset of the first symptom and the date of diagnosis. We observed a significant association between the total number of symptoms (continuous) experienced and the likelihood that symptoms were the reason for scheduling the healthcare visit

that led to diagnosis, compared to all other reasons for scheduling the healthcare visit (*P*-trend: <0.01). The total number of symptoms (continuous) did not impact the likelihood of being diagnosed with early versus late stage disease (*P*-trend: 0.43). Time elapsed between onset of first symptom (continuous) and the date of the visit that led to the diagnosis was significantly associated with whether symptoms led to the diagnosis (*P*-trend: <0.01). Overall, the association between time elapsed between onset of first symptom (continuous) and stage at diagnosis was not significant (*P*-trend: 0.09). However, participants with late stage disease were more likely to have experienced their symptoms less than 3 months before their OC diagnosis compared to early stage cases.

A latent class model with three classes was chosen based on the comparatively low BIC value and the significance of the LMR-LRT, in addition to its parsimony and interpretability. Figure 3 presents the probabilities of experiencing each symptom according to class. As evidenced in Figure 4, the classes were primarily defined by the total number of symptoms experienced rather than by specific symptoms experienced. We therefore labeled classes 1, 2, and 3 "Low Symptomatology," "Moderate Symptomatology," and "High Symptomatology," respectively. Participants in the Low Symptomatology (*N*=436) class experienced 6 or fewer symptoms prior to their diagnosis (median: 2) while Moderate Symptomatology cases (*N*=397) reported experiencing 2 to 12 symptoms (median: 6) and High Symptomatology cases (*N*=69) 10 to 20 symptoms (median: 13).

When LCA was repeated separately for early and late stage cases we observed that 3-class models best fit that data as well. Figures 5 and 6 present the probability of experiencing each symptom according to class for early stage cases and late stage cases, respectively. Similarly to the LCA results using all study participants, classes for the early stage and the late stage models

were largely defined by the total number of symptoms experienced prior to diagnosis and were therefore also labeled Low Symptomatology (early/late: *N*=163/*N*=256), Moderate Symptomatology (early/late: *N*=170/*N*=192), and High Symptomatology (early/late: *N*=25/*N*=61) classes. Among early stage cases, the Low Symptomatology class had a range of 0 to 5 symptoms, and the Moderate and High Symptomatology classes reported experiencing 3 to 12 symptoms and 10 to 20 symptoms, respectively. Among late stage cases, the total number of symptoms in each class ranged from 0 to 6, 2 to 12, and 7 to 17, respectively.

Associations between demographic, lifestyle and disease characteristics and class membership among all study participants are presented in Table 9. Significant associations were observed between class membership and study site, age, and oral contraceptive use. Similar significant associations were observed when limiting analyses to late stage cases only (Table 10). In analyses limited to early stage, study site, age and oral contraceptive use were not significant. However, smoking status and tumor type were significantly associated with class membership among early stage cases only (Table 11).

3.5 DISCUSSION

In line with previous studies,[78,112,143,144,151,152] the majority of both early and late stage cases within our study population experienced at least one symptom prior to their diagnosis. Importantly, we found that only a small proportion of participants (13%) were aware of the symptoms associated with OC before their diagnosis. This is consistent with the results from a previous study that reported that only 15% of the women in a national survey were familiar with OC symptoms.[153] Despite the low awareness of OC symptoms among women, the majority of our cases reported that

symptoms were the primary reason for making the provider visit that led to their diagnosis, which is in agreement with previous findings.[152] This suggests that increased awareness of the symptoms associated with OC may prompt more women to seek medical attention during the earlier stages of disease progression.

Similar to others, we observed that women with invasive tumors were significantly more likely to have experienced at least 1 symptom prior to their diagnosis compared to borderline tumors.[112,144,151,152] The symptoms most frequently reported by HOPE cases were bloating, weight gain or loss, and pelvic or abdominal discomfort and were similar to those reported by OC cases in previous studies.[108,143,152,154,155] Of the 23 symptoms included in our analysis, only three were more likely to be reported by late stage cases than early stage cases (abdominal swelling, distended abdomen, and decreased appetite). These results are in agreement with previous studies that found that these symptoms are generally more common among women diagnosed with late stage disease.[108,112,144,152] Consistent with findings by Lurie *et al* and Webb *et al*,[109,144] participants diagnosed with early stage OC reported experiencing abnormal bleeding and abdominal mass significantly more often than participants with late stage disease; however, Vine *et al* did not observe the same associations.[152]

Using LCA, we determined that there were 3 distinct groups of OC cases that differed according to symptom experience prior to their diagnosis. Rather than identifying patterns of symptoms that frequently occur together, we found that the groups were defined according to the total number of symptoms experienced. We also found that the probability of experiencing each individual symptom is proportional in that women within the High Symptomatology class had a higher probability of experiencing each symptom compared to women in the Moderate and Low Symptomatology classes. This was true for all symptoms except for abdominal bloating,

abdominal mass, and 'other' symptoms. Participants who were in the High Symptomatology group had a lower probability of experiencing these symptoms than expected. It is possible that these symptoms were more indicative of a serious health problem and prompted women to seek medical attention before they developed a greater number of symptoms. Two of these symptoms, abdominal bloating and abdominal mass, were significantly more likely to have been reported by women with early stage disease. This further supports the idea that women perceived these symptoms to require medical attention and therefore resulted in their OC being diagnosed during earlier stages of disease progression. These results suggest that raising awareness of the seriousness of milder symptoms experienced in combination may also prompt women to seek medical attention before their OC progresses to late stage disease.

We observed a significant difference in class membership according to age. Older women were less likely to be in the High Symptomatology class, which may be related to their general health status. It is possible that symptoms were less worrisome or noticeable due to comorbidities and other health problems associated with increased age, making older women less likely to remember experiencing a specific symptom. We also observed a significant association between oral contraceptive use and class membership. Lurie *et al* reported that women who used contraceptive hormones were more likely to experience bowel irregularity, bloating, and nausea and this finding may support our observation that oral contraceptive use was associated with the number of total symptoms experienced.[109] Study site was also significantly associated with class membership, which may be indicative of interviewer bias. When separately assessing the association between class membership and demographic, lifestyle and disease characteristics among women with late stage disease, we observed similar results. However, study site, age and oral contraceptive use were not associated with class membership when evaluating only early stage

cases. Among early stage cases, smoking status was significantly associated with class membership, which indicates that smoking may exacerbate or attenuate the severity of symptoms associated with early stage OC. Tumor type also significantly differed according to class membership among early stage cases. This suggests that during early stages of disease some tumor types may be associated with experiencing a greater number of symptoms than other tumor types.

However, generally, we found that class membership to the Low, Moderate, or High Symptomatology classes was not significantly associated with specific participant or disease characteristics. This suggests that the total number of symptoms is not sensitive to individual characteristics and may improve the specificity of symptom-based screening protocols. Other studies have reported that the number of symptoms experienced by OC cases is greater than the number of symptoms experienced by healthy women, which provides further evidence that the number of symptoms may improve the specificity of symptom indexes.[108,109,152,156] In addition, our results highlight the diversity of symptoms experienced by OC cases and emphasizes the importance of accounting for total number of symptoms when developing symptom-based screening methods.

To our knowledge, this study is the first to utilize LCA to provide further insight into the diverse symptoms that are experienced by OC cases prior to their diagnosis. An advantage of using LCA to characterize OC symptom presentation is that it is a person-centered method based on individual response patterns. By examining many common OC symptoms simultaneously, we were able to obtain a more comprehensive assessment of the symptoms experienced by women prior to being diagnosed with OC. Another advantage of using LCA is that the identification of subgroups is data driven rather than specified by the investigator. Our study was further strengthened by our relatively large study population and the availability of clinical, demographic,

and lifestyle data. The availability of this information allowed us to determine whether these factors were associated with experiencing Low, Moderate, or High Symptomatology prior to diagnosis. Additionally, participants were questioned about a large number of symptoms previously linked to OC, which enabled us to compare our results with previous studies that assessed pre-diagnostic symptom presentation among women with OC. Our study also had several limitations. The retrospective design of our study relied on self-reported data and was therefore susceptible to recall bias. In addition, cases' ability to recall the symptoms they experienced prior to their diagnosis may have been influenced by their current health status or the effects of treatment, although, the use of a reference date and life calendar may have improved accuracy. Unfortunately, our questionnaire did not ask healthy controls whether they had experienced symptoms prior to the reference date and we were therefore unable to compare the symptom presentation among controls to those of cases.

Our finding that cases can be grouped into Low, Moderate, and High Symptomatology classes suggests that symptom screening protocols that are limited to only a few of the symptoms linked to OC may be ineffective. Furthermore, our observation that the number of symptoms experienced prior to diagnosis did not significantly differ between early and late stage cases also provides evidence that the total number of symptoms experienced may improve the ability of screening methods to successfully identify women with early stage OC. Future efforts to educate women about OC-related symptoms should emphasize that symptoms frequently occur in combination. The resulting increased awareness of symptom presentation may prompt more women to seek medical attention during the early stages of OC thereby improving overall survival.

3.6 TABLES

Table 5. Selected demographic and disease characteristics of the study population (N_{total}=902)

Study Site	***N***	**%**
Buffalo	251	27.8
Cleveland	294	32.6
Pittsburgh	357	39.6
Age (years)		
< 45	125	13.9
45 < 55	227	25.2
55 <65	261	28.9
≥ 65	289	32.0
Race		
Caucasian	856	94.9
African-American	35	3.9
Other	11	1.2
Family History		
No	715	79.3
Breast cancer only	147	16.3
Ovarian cancer only	32	3.6
Breast and ovarian cancers	8	0.9
Education		
Non-high school graduate	83	9.2
High school graduate	303	33.6
Post-high school	516	57.2
Menopausal Status		
Pre-menopausal	234	25.9
Post-Menopausal	668	74.1
Type of Cancer		
Ovarian, borderline	97	10.7
Ovarian, invasive	677	75.1
Peritoneal	75	8.3
Fallopian	32	3.5
Other / unknown	21	2.3
Tumor Type		
Brenner	4	0.4
Clear cell	54	6.0
Endometrioid	100	11.1
Mucinous	66	7.3
Serous	516	57.2
Mixed	77	8.5
Other/ unknown [a] *	85	7.9
Grade		
Borderline tumor	97	10.8
Well differentiated	76	8.4
Moderately differentiated	171	19.0
Poorly differentiated / undifferentiated	467	51.8
Other/ unknown	91	10.1
Stage at Diagnosis [b]		
I	249	27.6
II	109	12.1
III	450	49.9
IV	59	6.5
Unknown	35	3.9

[a] Includes 11 "Poorly/Undifferentiated," 56 "Other," 3 "Non-epithelial" & 15 missing tumor type information.

Table 6. Diagnosis-related factors of ovarian cancer cases, by stage

	All Cases *N*=902		Early Stage [a] *N*=358		Late Stage [a] *N*=509		*P*-value [b]
	N	%	N	%	N	%	
Primary reason for provider visit that led to diagnosis [c]							
Routine gynecologic exam	103	11.4	55	15.4	46	9.0	0.023
Routine health exam	57	6.3	25	7.0	30	5.9	
Routine screening (CA125, TVU, etc.)	18	2.0	8	2.2	9	1.8	
Symptoms of ovarian cancer	569	63.1	208	58.1	340	66.8	
Pregnancy	7	0.8	5	1.4	2	0.4	
Infertility evaluation	3	0.3	3	0.8	0	0.0	
Hysterectomy	3	0.3	1	0.3	2	0.4	
Other surgery	20	2.2	5	1.4	13	2.6	
Other problem	101	11.2	38	10.6	58	11.4	
Other reason	16	1.8	7	2.0	7	1.4	
Healthcare provider that made the diagnosis							
Gynecological oncologist	480	53.2	208	58.1	261	51.3	< 0.001
Obstetrician/Gynecologist	197	21.8	97	27.1	94	18.5	
PCP/ General practitioner	107	11.9	15	4.2	84	16.5	
Surgeon	49	5.4	16	4.5	28	5.5	
Infertility specialist	3	0.3	3	0.8	0	0.0	
Other	66	7.3	19	5.3	42	8.3	
Actively seeking treatment to watch for ovarian cancer							
No	835	92.6	331	92.5	471	92.5	0.967
Yes	67	7.4	27	7.5	38	7.5	
Had annual gynecological exam within a year prior to diagnosis							
No	362	40.1	144	40.2	198	38.9	0.695
Yes	540	59.9	214	59.8	311	61.1	
Pre-treatment CA-125 [d]							
< 35 U/mL	114	12.6	86	24.0	23	4.5	< 0.001
≥ 35 U/mL	574	63.6	182	50.8	375	73.7	
Unknown	214	23.7	90	25.1	111	21.8	
Experienced symptoms prior to diagnosis							
No	63	7.0	33	9.2	29	5.7	0.048
Yes	839	93.0	325	90.8	480	94.3	

[a] 35 cases are missing stage information.
[b] p-values were obtained using chi-square tests.
[c] 5 cases were missing reason for making the provider visit that led to diagnosis.
[d] Pre-treatment CA-125 levels were available for 677 (75.1%) of cases.
[e] 35 cases were missing stage information.

Table 7. Symptoms experienced prior to diagnosis, in order of symptom frequency, stratified by stage and by whether symptoms led to diagnosis

	All Cases *N*= 902		Symptoms Led to Their Diagnosis [a] *N*= 569		Cases That Were Diagnosed for a Reason Other than Symptoms [a] *N*= 332		Symptoms Led to Diagnosis vs Symptoms did Not Lead to Diagnosis [a,b] *N*= 901	Early Stage [c] *N*= 358		Late Stage [c] *N*= 509		Early vs Late Stage [b,c] *N*=867
	N	%	N	%	N	%	OR (95% CI)	N	%	N	%	OR (95% CI)
Symptoms Experienced Prior to Diagnosis												
No symptoms	63	7.0	N/A	N/A	N/A	N/A	N/A	33	9.2	29	5.7	0.6 (0.35, 1.00)
Bloating	321	35.6	231	40.6	90	27.1	1.84 (1.36, 2.50)	114	31.8	195	38.3	1.33 (1.00, 1.77)
Weight gain/loss	300	33.3	217	38.1	83	25.0	1.85 (1.36, 2.53)	114	31.8	172	33.8	1.09 (0.82, 1.46)
Pelvic/abdominal discomfort	299	33.2	224	39.4	75	22.6	2.22 (1.62, 3.07)	118	33.0	167	32.8	0.99 (0.74, 1.32)
Ongoing fatigue	257	28.5	180	31.6	77	23.2	1.53 (1.11, 2.12)	101	28.2	143	28.1	0.99 (0.74, 1.64)
Abdominal swelling	251	27.8	190	33.4	61	18.4	2.23 (1.59, 3.14)	73	20.4	167	32.8	1.91 (1.39, 2.62)
Distended abdomen	238	26.4	179	31.5	59	17.8	2.12 (1.51, 3.01)	78	21.8	147	28.9	1.46 (1.06, 2.00)
Frequent/urgent urination	223	24.7	151	26.5	72	21.7	1.30 (0.94, 1.83)	101	28.2	116	22.8	0.75 (0.55, 1.02)
Gas	221	24.5	154	27.1	66	19.9	1.50 (1.07, 2.11)	83	23.2	129	25.3	1.12 (0.82, 1.54)
Feeling full	215	23.8	149	26.2	66	19.9	1.43 (1.02, 2.02)	81	22.6	125	24.6	1.11 (0.81, 1.53)
Bowel irregularity	196	21.7	134	23.6	61	18.4	1.37 (0.96, 1.95)	79	22.1	107	21.0	0.94 (0.68, 1.31)
Severe pelvic pain	192	21.3	143	25.1	49	14.8	1.94 (1.34, 2.83)	80	22.4	104	20.4	0.89 (0.64, 1.24)
Change in how clothes fit	169	18.7	115	20.2	54	16.3	1.30 (0.90, 1.90)	59	16.5	104	20.4	1.30 (0.91, 1.85)
Indigestion	168	18.6	130	22.8	38	11.4	2.29 (1.53, 3.48)	63	17.6	94	18.5	1.06 (0.75, 1.51)
Constipation	163	18.1	109	19.2	53	16.0	1.25 (0.86, 1.83)	54	15.1	103	20.2	1.43 (1.00, 2.05)
Heartburn	154	17.1	110	19.3	44	13.3	1.57 (1.06, 2.35)	62	17.3	87	17.1	0.98 (0.69, 1.41)
Abnormal bleeding	153	17.0	113	19.9	40	12.0	1.81 (1.21, 2.74)	85	23.7	62	12.2	0.45 (0.31, 0.64)
Decreased appetite	129	14.3	101	17.8	28	8.4	2.34 (1.49, 3.79)	39	10.9	85	16.7	1.64 (1.09, 2.46)
Hard abdomen	122	13.5	96	16.9	26	7.8	2.39 (1.49, 3.93)	48	13.4	66	13.0	0.96 (0.65, 1.43)
Nausea	103	11.4	67	11.8	36	10.8	1.10 (0.70, 1.74)	43	12.0	52	10.2	0.83 (0.54, 1.28)
Chest pain/respiratory problems	101	11.2	69	12.1	32	9.6	1.29 (0.82, 2.08)	32	8.9	63	12.4	1.44 (0.92, 2.25)
Painful intercourse [d]	78	8.7	45	7.9	33	9.9	0.78 (0.47, 1.28)	39	10.9	36	7.1	0.62 (0.39, 1.00)
Abdominal mass	73	8.1	47	8.3	26	7.8	1.06 (0.63, 1.82)	44	12.3	28	5.5	0.42 (0.25, 0.68)
Other	175	19.4	102	17.9	73	22.0	0.77 (0.55, 1.10)	67	18.7	105	20.6	1.13 (0.80, 1.59)

[a] 5 cases was missing reason for making the provider visit that led to their diagnosis.
[b] Odds ratios and corresponding 95% CIs were calculated using the women who did not experience a specific symptom as the reference group.
[c] 35 cases were missing stage information.
[d] 1 women was missing pic information.

Table 8. Number of symptoms experienced prior to diagnosis and the time elapsed between the onset of first symptom and the visit that led to the diagnosis of ovarian cancer, stratified by stage and by whether symptoms led to diagnosis

	All Cases *N*= 902		Symptoms Led to Their Diagnosis [a] *N*= 569		Cases That Were Diagnosed for a Reason Other than Symptoms [a] *N*= 332		Symptoms Led to Diagnosis vs Symptoms did Not Lead to Diagnosis [a]	Early Stage [b] *N*= 358		Late Stage [b] *N*= 509		Early vs Late Stage [b]
Total Number of Symptoms Experienced												
0	63	7.0	N/A	N/A	N/A	N/A	N/A	33	9.2	29	5.7	Reference
1	119	13.2	66	11.5	53	16.0	Reference	46	12.9	67	13.2	1.66 (0.89, 3.17)
2	107	11.9	71	12.5	36	10.8	1.58 (0.92, 2.72)	42	11.7	62	12.2	1.68 (0.89, 3.17)
3	105	11.6	67	11.8	37	11.1	1.45 (0.85, 2.50)	40	11.2	62	12.2	1.76 (0.93, 3.34)
4	103	11.4	68	12.0	35	10.5	1.56 (0.90, 2.69)	49	13.7	47	9.2	1.09 (0.58, 2.07)
5	96	10.6	69	12.1	27	8.1	2.05 (1.16, 3.64)	34	9.5	62	12.2	2.08 (1.08, 3.98)
6	63	7.0	49	8.6	14	4.2	2.81 (1.40, 5.63)	21	5.9	37	7.3	2.00 (0.96, 4.17)
7	59	6.5	45	13.2	14	4.2	2.58 (1.28, 5.20)	21	5.9	37	7.3	2.00 (0.96, 4.17)
≥ 8	187	20.7	134	23.6	53	16.0	2.03 (1.25, 3.29)	72	20.1	106	20.8	1.68 (0.94, 3.00)
Time elapsed between onset of first symptom and the date of the doctor visit that led to the discovery of ovarian cancer [c]												
Had no symptoms	63	7.0	N/A	N/A	N/A	N/A	N/A	33	9.2	29	5.7	Reference
< 1 month	120	13.2	91	16.0	28	8.4	Reference	38	10.6	76	14.9	2.28 (1.21, 4.29)
1< 3 months	177	19.6	125	22.0	52	15.7	0.74 (0.43, 1.26)	64	17.9	107	21.0	1.90 (1.06, 3.42)
3 < 6 months	181	20.1	121	13.4	60	18.1	0.62 (0.37, 1.05)	72	20.1	102	20.0	1.61 (0.90, 2.89)
6 < 9 months	86	9.5	63	21.3	23	6.9	0.84 (0.45, 1.60)	35	9.8	48	9.4	1.56 (0.80, 3.03)
9 < 12 months	58	6.4	42	7.4	16	4.8	0.81 (0.40, 1.65)	22	6.1	33	6.5	1.71 (0.82, 3.56)
≥ 12 months	205	22.7	120	21.1	85	25.6	0.43 (0.26, 0.72)	90	25.1	107	21.0	1.35 (0.76, 2.40)

[a] 5 cases were missing reason for making the provider visit that led to their diagnosis.
[b] 35 cases were missing stage information.
[c] 12 cases were missing time elapsed between onset of first symptom and the date of the doctor visit that led to their diagnosis.

Table 9. Associations between demographic, lifestyle and disease characteristics and class membership among all study participants(*N*=902)

	Low Symptomatology *N*=436		Moderate Symptomatology *N*=397		High Symptomatology *N*=69		*P*-value
	N	**%**	***N***	**%**	***N***	**%**	
Study Site							
NY	155	35.6	87	21.9	9	13.0	<0.001
OH	119	27.3	146	36.8	29	42.0	
PA	162	37.2	164	41.3	31	44.9	
Age (years)							
< 45	57	13.1	58	14.6	10	14.5	0.003
45 < 55	94	21.6	103	25.9	30	43.5	
55 < 65	126	28.9	120	30.2	15	21.7	
≥ 65	159	36.5	116	29.2	14	20.3	
Smoking Status							
Never	236	54.1	184	46.4	38	55.1	0.173
Former	130	29.8	134	33.8	22	31.9	
Current	70	16.1	79	19.9	9	13.0	
Alcohol Use [a]							
Light (0-7 drinks per week)	372	85.3	317	80.1	56	81.2	0.337
Moderate (8-14 drinks per week)	34	7.8	45	11.4	8	11.6	
Heavy (15 or more drinks per week)	30	6.9	34	8.6	5	7.3	
BMI (kg/m2) [b]							
< 25	142	32.6	137	34.5	21	30.4	0.835
25 < 30	128	29.4	120	30.2	19	27.5	
≥ 30	165	37.9	140	35.3	29	42.0	
Family History of Breast/ Ovarian Cancer							
No	336	77.1	323	81.4	56	81.2	0.292
Breast cancer only	81	18.6	59	14.9	7	10.1	
Ovarian cancer only	15	3.4	12	3.0	5	7.3	
Breast and ovarian cancers	4	0.9	3	0.8	1	1.5	
Oral Contraceptive Use [c]							
Never	204	46.8	142	35.8	21	30.4	0.003
< 5 Years	153	35.1	164	41.3	36	52.2	
≥ 5 Years	78	17.9	91	22.9	12	17.4	
Number of Pregnancies							
0	83	19.0	69	17.4	15	21.7	0.952
1	54	12.4	55	13.9	5	7.3	
2	100	22.9	98	24.7	18	26.1	
3	85	19.5	69	17.4	13	18.8	
4	55	12.6	49	12.3	8	11.6	
≥ 5	59	13.5	57	14.4	10	14.5	
Menopausal Status							
Pre-Menopausal	108	24.8	105	26.5	21	30.4	0.580
Post-Menopausal	328	75.2	292	73.6	48	69.6	
Hormone Replacement Therapy							
Never	269	61.7	235	59.2	39	56.5	0.617
Ever	167	38.3	162	40.8	30	43.5	

Table 9. (*Continued*)

	Low Symptomatology *N*=436		Moderate Symptomatology *N*=397		High Symptomatology *N*=69		*P*-value
	N	**%**	***N***	**%**	***N***	**%**	
Stage							
I	126	28.9	99	24.9	24	34.8	0.246
II	61	14.0	45	11.3	3	4.4	
III	206	47.3	209	52.6	35	50.7	
IV	28	6.4	28	7.1	3	4.4	
Unknown	15	3.4	16	4.0	4	5.8	
Primary Tumor Type							
Ovarian, borderline	48	11.0	36	9.1	13	18.8	0.243
Ovarian, invasive	321	73.6	307	77.3	49	71.0	
Peritoneal	39	8.9	32	8.1	4	5.8	
Fallopian	20	4.6	11	2.8	1	1.5	
Other/unknown	8	1.8	11	2.8	2	2.9	
Borderline vs. Invasive Tumor							
Borderline	48	11.0	36	9.1	13	18.8	0.145
Invasive	380	87.2	350	88.2	54	78.3	
Other/unknown	8	1.8	11	2.8	2	2.9	
Histologic Sub-type							
Serous	255	59.0	222	57.2	39	58.2	0.901
Endometrioid	46	10.7	48	12.4	6	9.0	
Mucinous	28	6.5	31	8.0	7	10.5	
Clear cell	24	5.6	23	5.9	7	10.5	
Brenner	2	0.5	2	0.5	0	0.0	
Mixed	41	9.4	31	7.8	5	7.3	
Other/unknown	40	9.2	40	10.1	5	7.3	
Grade							
Well differentiated	44	10.1	28	7.1	4	5.8	0.172
Moderately differentiated	72	16.5	86	21.7	13	18.8	
Poorly differentiated / Undifferentiated	226	51.8	208	52.4	33	47.8	
Borderline malignancy	48	11.0	36	9.1	13	18.8	
Unknown	46	10.6	39	9.8	6	8.7	
Pre-treatment CA-125							
< 35 U/mL	62	14.2	43	10.8	9	13.0	0.533
≥ 35 U/mL	267	61.2	261	65.7	46	66.7	
Unknown	107	24.5	93	23.4	14	20.3	

[a] 1 woman was missing weekly alcohol intake information.
[b] 1 woman was missing weight information.
[c] 1 woman was missing oral contraceptive usage information.

Table 10. Associations between demographic, lifestyle and disease characteristics and class membership among all early stage cases (*N*=358)

	Low Symptomatology *N*=163		Moderate Symptomatology *N*=170		High Symptomatology *N*=25		*P*-value
	N	**%**	***N***	**%**	***N***	**%**	
Study Site							
NY	45	27.6	28	16.5	3	12	0.083
OH	53	32.5	71	41.8	11	44	
PA	65	39.9	71	41.8	11	44	
Age (years)							
< 45	29	17.8	37	21.8	5	20	0.106
45 < 55	47	28.8	55	32.4	11	44	
55 < 65	41	25.2	47	27.6	8	32	
≥ 65	46	28.2	31	18.2	1	4	
Smoking Status							
Never	100	61.4	81	47.6	17	68.0	0.020
Former	43	26.4	51	30.0	7	28.0	
Current	20	12.3	38	22.4	1	4.0	
Alcohol Use [a]							
Light (0-7 drinks per week)	140	85.9	141	82.9	20	80.0	0.863
Moderate (8-14 drinks per week)	11	6.7	16	9.4	3	12.0	
Heavy (15 or more drinks per week)	12	7.4	12	7.1	2	8.0	
BMI (kg/m2) [b]							
< 25	49	30.1	56	32.9	5	20.0	0.561
25 < 30	47	28.8	48	28.2	6	24.0	
≥ 30	66	40.5	66	38.8	14	56.0	
Family History of Breast/ Ovarian Cancer							
No	134	82.2	133	78.2	23	92.0	0.054
Breast cancer only	27	16.6	30	17.7	0	0.0	
Ovarian cancer only	2	1.2	7	4.1	2	8.0	
Breast and ovarian cancers	0	0.0	0	0.0	0	0.0	
Oral Contraceptive Use [c]							
Never	71	43.6	60	35.3	7	28.0	0.203
< 5 Years	64	39.3	70	41.2	14	56.0	
≥ 5 Years	27	16.6	40	23.5	4	16.0	
Number of Pregnancies							
0	41	25.2	42	24.7	8	32.0	0.791
1	25	15.3	24	14.1	1	4.0	
2	42	25.8	38	22.4	6	24.0	
3	28	17.2	30	17.6	3	12.0	
4	14	8.6	21	12.4	5	20.0	
≥ 5	13	8.0	15	8.8	2	8.0	
Menopausal Status							
Pre-Menopausal	54	33.1	64	37.7	9	36.0	0.689
Post-Menopausal	109	66.9	106	62.3	16	64.0	
Hormone Replacement Therapy							
Never	107	65.6	118	69.4	17	68.0	0.763
Ever	56	34.4	52	30.6	8	32.0	

Table 10. (*Continued)*

	Low Symptomatology *N*=163		Moderate Symptomatology *N*=170		High Symptomatology *N*=25		*P*-value
	N	**%**	***N***	**%**	***N***	**%**	
Stage							
I	112	68.7	115	67.6	22	88.0	0.113
II	51	31.3	55	32.4	3	12.0	
Primary Tumor Type							
Ovarian, borderline	38	23.3	25	14.7	7	28.0	0.010
Ovarian, invasive	112	68.7	140	82.4	17	68.0	
Peritoneal	0	0.0	1	0.6	1	4.0	
Fallopian	12	7.4	3	1.8	0	0.0	
Other/unknown	1	0.6	1	0.6	0	0.0	
Borderline vs. Invasive Tumor							
Borderline	38	23.3	25	14.7	7	28.0	0.261
Invasive	124	76.1	144	84.7	18	72.0	
Other/unknown	1	0.6	1	0.6	0	0.0	
Histologic Sub-type							
Serous	65	39.9	42	24.7	9	36.0	0.159
Endometrioid	31	19.0	45	26.5	4	16.0	
Mucinous	20	12.3	29	17.1	5	20.0	
Clear cell	17	10.4	18	10.6	4	16.0	
Brenner	0	0.0	3	1.8	0	0.0	
Mixed	15	9.2	18	10.6	3	12.0	
Other/unknown	15	9.2	15	8.8	0	0.0	
Grade							
Well differentiated	25	15.3	25	14.7	3	12.0	0.563
Moderately differentiated	35	21.5	47	27.7	7	28.0	
Poorly differentiated / Undifferentiated	50	30.7	59	34.7	6	24.0	
Borderline malignancy	38	23.3	25	14.7	7	28.0	
Unknown	15	9.2	14	8.2	2	8.0	
Pre-treatment CA-125							
< 35 U/mL	39	23.9	40	23.5	7	28.0	0.062
≥ 35 U/mL	77	47.2	92	54.1	13	52.0	
Unknown	47	28.8	38	22.4	5	20.0	

[a] 1 woman was missing weekly alcohol intake information.
[b] 1 woman was missing weight information.
[c] 1 woman was missing oral contraceptive usage information.

Table 11. Associations between demographic, lifestyle and disease characteristics and class membership among all late stage cases (*N*=509)

	Low Symptomatology *N*=256		Moderate Symptomatology *N*=192		High Symptomatology *N*=61		*P*-value
	N	**%**	***N***	**%**	***N***	**%**	
Study Site							
NY	107	41.8	51	26.6	10	16.4	<0.001
OH	54	21.1	74	38.5	21	34.4	
PA	95	37.1	67	34.9	30	49.2	
Age (in years)							
< 45	23	9.0	18	9.4	9	14.7	0.001
45 < 55	40	15.6	44	22.9	21	34.4	
55 < 65	72	28.1	65	33.9	18	29.5	
≥ 65	121	47.3	65	33.9	13	21.3	
Smoking Status							
Never	129	50.4	86	44.8	31	50.8	0.677
Former	81	31.6	73	38.0	19	31.2	
Current	46	18.0	33	17.2	11	18.0	
Alcohol Use [a]							
Light (0-7 drinks per week)	213	83.2	157	81.8	46	75.4	0.572
Moderate (8-14 drinks per week)	28	10.9	19	9.9	9	14.8	
Heavy (15 or more drinks per week)	15	5.9	16	8.3	6	9.8	
BMI (kg/m2) [b]							
< 25	86	33.6	69	35.9	26	42.6	0.770
25 < 30	81	31.6	58	30.2	16	26.2	
≥ 30	89	34.8	65	33.9	19	31.2	
Family History of Breast/ Ovarian Cancer							
No	189	73.8	158	82.3	48	78.7	0.136
Breast cancer only	50	19.5	29	15.1	9	14.8	
Ovarian cancer only	13	5.1	2	1.0	4	6.6	
Breast and ovarian cancers	4	1.6	3	1.6	0	0.0	
Oral Contraceptive Use [c]							
Never	125	48.8	73	38.0	14	23.0	0.003
< 5 Years	83	32.4	79	41.2	32	52.5	
≥ 5 Years	48	18.8	40	20.8	15	24.6	
Number of Pregnancies							
0	34	12.3	24	12.5	10	16.4	0.837
1	25	9.8	25	13.0	6	9.8	
2	56	21.9	53	27.6	14	23.0	
3	56	21.9	37	19.3	10	16.4	
4	38	14.8	21	10.9	9	14.8	
≥ 5	47	18.4	32	16.7	12	19.7	
Menopausal Status							
Pre-Menopausal	44	17.2	39	20.3	17	27.9	0.161
Post-Menopausal	212	82.8	153	79.7	44	72.1	
Hormone Replacement Therapy							
Never	148	57.8	97	50.5	30	49.2	0.223
Ever	108	42.2	95	49.5	31	50.8	

Table 11. (*Continued)*

	Low Symptomatology *N*=256		Moderate Symptomatology *N*=192		High Symptomatology *N*=61		*P*-value
	N	**%**	***N***	**%**	***N***	**%**	
Stage							
III	227	88.7	168	87.5	55	90.2	0.837
IV	29	11.3	24	12.5	6	9.8	
Primary Tumor Type							
Ovarian, borderline	10	3.9	5	2.6	6	9.8	0.286
Ovarian, invasive	193	75.4	158	82.3	45	73.8	
Peritoneal	42	16.4	22	11.5	9	14.8	
Fallopian	9	3.5	6	3.1	1	1.6	
Other/unknown	2	0.8	1	0.5	0	0.0	
Borderline vs. Invasive Tumor							
Borderline	10	3.9	5	2.6	6	9.8	0.154
Invasive	244	95.3	186	96.9	55	90.2	
Other/unknown	2	0.8	1	0.5	0	0.0	
Histologic Sub-type							
Serous	199	77.7	151	78.7	42	68.9	0.301
Endometrioid	8	3.1	8	4.2	4	6.6	
Mucinous	5	2.0	3	1.6	1	1.6	
Clear cell	2	0.8	7	3.7	3	4.9	
Brenner	0	0.0	1	0.5	0	0.0	
Mixed	26	10.2	10	5.2	5	8.2	
Other/unknown	16	6.3	12	6.3	6	9.8	
Grade							
Well differentiated	14	5.5	6	3.1	1	1.6	0.116
Moderately differentiated	35	13.7	36	18.8	11	18.0	
Poorly differentiated / Undifferentiated	178	69.5	133	69.3	36	29.0	
Borderline malignancy	10	3.9	5	2.6	6	9.8	
Unknown	19	7.4	12	6.3	7	11.5	
Pre-treatment CA-125							
< 35 U/mL	17	6.6	5	2.6	1	1.6	0.229
≥ 35 U/mL	183	71.5	146	76.0	46	75.4	
Unknown	56	21.9	41	21.4	14	23.0	

[a] 1 woman was missing weekly alcohol intake information.
[b] 1 woman was missing weight information.
[c] 1 woman was missing oral contraceptive usage information.

3.7 FIGURES

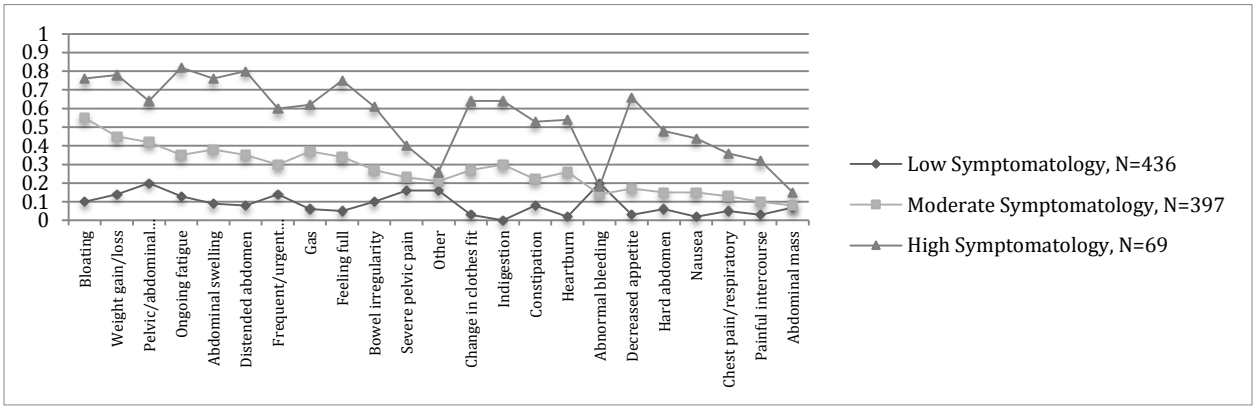

Figure 3. Probability of Experiencing a Symptom According to Class Membership (*N*=902)

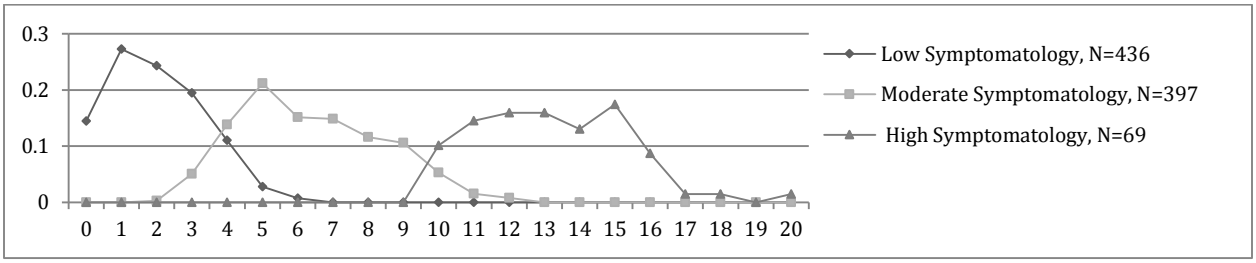

Figure 4. Probability of Experiencing Total Number of Symptoms According to Class Membership (*N*=902)

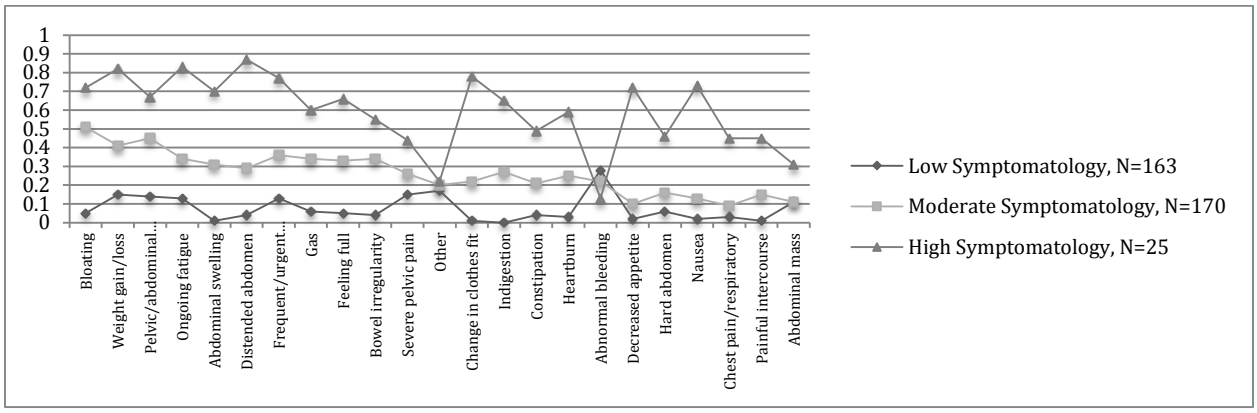

Figure 5. Probability of Experiencing a Symptom According to Class Membership Among Early Stage Cases (*N*=358)

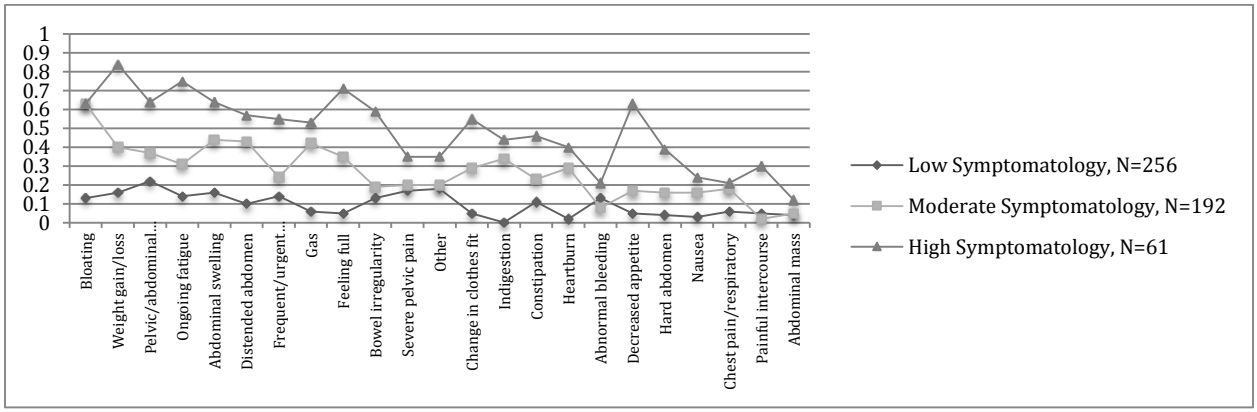

Figure 6. Probability of Experiencing a Symptom According to Class Membership Among Late Stage Cases (*N*=509)

4.0 ARTICLE 3: PROGNOSIS AND CONDITIONAL DISEASE-FREE SURVIVAL AMONG OVARIAN CANCER PATIENTS.

To be submitted for publication

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4.1 ABSTRACT

Background: Traditional disease-free survival (DFS) does not reflect how prognosis changes over time. Conditional DFS accounts for elapsed time since achieving remission and thereby provides more relevant prognostic information. The objective of this study was to estimate conditional DFS among ovarian cancer (OC) patients who had achieved remission and to identify the demographic, lifestyle, disease, and clinical factors that impact DFS.

Methods: Patients were recruited between 2003 and 2008 as part of the Hormones and Ovarian Cancer Prediction (HOPE) case-control study. They were included in the current study if they had originally been diagnosed with epithelial cancers of the ovary, fallopian tube, or peritoneum and had achieved remission (*N*=404). Information on demographic and lifestyle factors was collected at the time of enrollment; disease, treatment and clinical characteristics were abstracted from medical records. DFS was calculated by Kaplan-Meier method.

Results: Median DFS was 2.54 years (range 0.03-9.96 years) and the 5-year DFS was 44.6%. The probability of surviving an additional 5 years without recurrence, conditioned on having already survived 1, 2, 3, 4, and 5 years after remission, was 61.9%, 78.6%, 90.7%, 97.3% and 98.1%, respectively. Initial differences in DFS at time of remission between age and stage groups diminished over time. Backward stepwise Cox regression performed among all cases and among only those who had 1 and 2 years of remission yielded models with differing characteristics.

Conclusions: 5-year DFS estimates improved dramatically for patients who had already achieved a period of remission. Characteristics that are predictive of DFS at time of remission lose significance as the period of remission increases.

Impact: Conditional DFS is a more relevant measure for those OC patients who have already achieved a period of remission. It is particularly useful for patients as well as clinicians for informing follow-up care decisions.

4.2 INTRODUCTION

It is estimated that there will be 22,240 incident cases of ovarian cancer (ovarian cancer) and 14,030 deaths due to OC in the U.S. in 2013.[2] Although patients diagnosed with localized OC have an estimated survival rate of 92%, only approximately 15% of the cases are diagnosed at a localized stage. The majority of OC cases are diagnosed after the disease has progressed and survival rates for regional and distant disease are 72% and 27.3%, respectively.[5] In addition to stage, disease and clinical characteristics such as tumor histology, [94,157,158] residual disease after cytoreductive surgery,[94,159-162] and cancer antigen 125 (CA-125) levels during treatment [163-165] have been shown to impact prognosis.

Survival estimates are traditionally reported from the time of diagnosis (overall survival) or remission (disease free survival; DFS). Although these estimates provide important information to clinicians and patients, they are no longer applicable to patients who have survived for a period of time after their initial diagnosis and treatment. Conditional survival, which takes into account the changing risk of cancer death over time, offers a more accurate estimate of survival for these cancer patients. Several studies have previously assessed conditional overall survival among OC patients; three studies used data from the Surveillance, Epidemiology, and End Results (SEER) database,[166-168] and one used data from the European Network for Indicators on Cancer (EUNICE).[169] These studies found that overall survival estimates improved as time elapsed since

diagnosis and that the impact of prognostic factors such as age, stage, and histology diminishes over time. Furthermore, their findings provided evidence that survival probabilities change significantly when accounting for time elapsed since diagnosis.

Complete clinical remission is achieved by the majority of OC patients who are treated with cytoreductive surgery and platinum-based chemotherapy.[83,84] However, most OC survivors will eventually relapse.[85-88] Surveillance for recurrent disease generally includes physical exams, imaging tests, and the close monitoring of CA-125 levels; although, there is controversy regarding the effectiveness of these efforts to meaningfully impact disease outcomes.[99-101] Results from a recent clinical trial suggest that there was no survival benefit to initiating chemotherapy at the time CA-125 levels increased compared to delaying treatment until there was clinical evidence of disease. Additionally, earlier deterioration of quality of life was observed among women who were treated based on rising CA-125 levels alone.[104] Therefore, there is a need to provide accurate information regarding risk of recurrence to patients so that they are able to make informed decisions concerning their follow-up care.

To our knowledge, no prior studies have assessed conditional DFS among OC patients. The objective of this study is to estimate conditional DFS among OC patients who achieved remission and to identify the demographic, lifestyle, disease, and clinical factors that impact DFS.

4.3 MATERIAL AND METHODS

4.3.1 Study population and data collection

Patients included in our analysis were enrolled as part of the Hormones and Ovarian Cancer

Prediction (HOPE) case-control study, which has previously been described in detail elsewhere.[50,130,149] The HOPE study includes 902 ovarian, peritoneal, and fallopian tube cases from a contiguous region of Western Pennsylvania, Eastern Ohio, and Western New York. Cases were diagnosed between February 2003 and December 2008, were at least 25 years old, and were within 9 months of initial diagnosis at the time of recruitment. All study participants provided informed consent. The study was approved by the University of Pittsburgh Institutional Review Board and by the human subject committees at each hospital where cases were identified.

Trained interviewers collected demographic, lifestyle, and medical history information via in-person interviews. A reference date of 9 months prior to the interview date was used in an effort to identify only the exposures that occurred before cases were diagnosed with cancer. Contact information for all clinicians from whom patients received medical care was collected during the interview. Follow-up data for HOPE cases has been collected on an on-going basis through annual requests for patient's medical records from their treating physicians since time of recruitment into the HOPE study. Information collected includes CA-125 lab results, chemotherapy flow sheets, pathology reports, surgical and hospitalization records, imaging results, and oncologist notes. The Social Security Death Index (SSDI) and the National Death Index (NDI) are used to collect data on vital status as well. For the purposes of this study, the cutoff date for follow-up data collection was April 16, 2013.

Cases were eligible for inclusion in this study if they were recruited from OH or PA and had achieved complete clinical remission. Cases with borderline and non-epithelial ovarian, peritoneal, or fallopian tube tumors were excluded. Of the 651 cases recruited from OH or PA, 404 patients fulfilled these criteria and were included in the current analysis. We observed no significant differences in demographic and lifestyle factors between included and excluded OH/PA

cases [age (P=0.35), race (P=0.08), education (P=0.69), yearly income (P=0.40), body mass index (BMI; P=0.34), smoking status (P=0.30), weekly alcohol intake (P=0.92), family history of breast/ovarian cancers (P=0.54), menopausal status (P=0.14)].

4.3.2 Demographic and lifestyle characteristics

All demographic and lifestyle characteristics are based on data provided by participants during the initial HOPE interview at the time of recruitment. BMI was calculated as weight (kg) at reference date divided by height (m) at reference date squared. Participants were considered to be never smokers if they had never smoked cigarettes daily for 6 months or more; former smokers if they had ever smoked cigarettes daily for 6 months or more but were not smoking daily at the reference date; and, current smokers if they had ever smoked cigarettes daily for 6 months or more and were smoking daily at the reference date. Alcohol use was quantified by adding the number of wine, beer, and hard liquor drinks consumed per week. Participants who consumed less than 7 drinks per week were classified as light drinkers, those who consumed 7-14 drinks per week as moderate drinkers, and those who reported drinking more than 14 drinks per week as heavy drinkers. Family history of ovarian and breast cancers was defined as having at least one reported diagnosis of ovarian or breast cancer in a first-degree relative, including biological mother, father, sisters, brothers, sons and daughters. Women were classified as postmenopausal if they were 55 years or older, reported natural menopause, had used hormone replacement therapy, or reported no menstrual periods in the 6 months prior to the reference date. Women were considered to be premenopausal if they had never taken hormone replacement therapy, had reported having menstrual periods in the 6 months prior to the reference date, and were younger than 55 years old.[131]

4.3.3 Disease and clinical characteristics

Disease and clinical characteristics were abstracted retrospectively from participant medical records. Stage, primary cancer site, grade, histology, synchronous primary tumor, and lymph node involvement were collected from pathology reports; if this information was not stated in the pathology report, data was obtained from other medical records including surgical notes, hospital reports, and oncologist notes. Residual disease and debulking status after completion of cytoreductive surgery was determined from surgical notes. Cases were considered to be optimally debulked if their disease was < 1cm. If residual tumor size was unavailable, they were classified as optimally debulked if their surgeon/oncologist declared them to be optimally debulked at the time of their cytoreductive surgery. Cytology of ascites/pelvic washings was also obtained from pathology reports of either paracentesis of pre-treatment ascites or ascites/pelvic washings obtained at the time of primary surgery. The presence of ascites or pleural effusion was determined by imaging results. If no scans of the pelvis or chest were available, the presence of ascites or pleural effusion was considered to be "could not be assessed." Pre-treatment CA-125 levels and CA-125 levels throughout chemotherapy and follow-up care were abstracted from CA-125 lab results and oncologist notes. Chemotherapy agents were categorized into three groups: platinum-based (carboplatin, cisplatin, oxaliplatin, and abraxane), taxanes (taxol, taxotere, and xyotax), and "other" (all other chemotherapy agents, these were: avastin, doxil, topotecan, gemzar, Cytoxan, interferon, mytomycin, Erbitux, ifosphomaide, catumaxomab, and ovarex). Many of the "other" chemotherapies were given as part of a clinical trial and in some cases it was unclear whether participants received placebo or the active agent; cases that were reported to have received the placebo were considered to have received no chemotherapy. The total number of cycles received for each group was the sum of all neoadjuvant, adjuvant, maintenance, and persistent disease-

related chemotherapy. Persistent disease was defined as the presence of measurable disease after primary treatment and/or a CA-125 level greater than 35 U/mL.

Date of diagnosis was defined as the date of first positive cytology, in cases with no available cytology prior to primary surgery, the date of primary surgery was used as the date of diagnosis. The date of remission was the date that an oncologist first declared them to have no evidence of disease. If cases were missing oncologist notes in the interval immediately after completion of primary treatment, the first negative surgical result was used. If this too was unavailable, the date of remission was the date of first negative imaging results. Among the women who were missing the above information, a date of 4 weeks after completion of their adjuvant chemotherapy was used. In situations where the only available date did not specify a day, the 15th was assigned (N=8). If cases recurred, a similar process was used to determine the date of recurrence. If available, the date first diagnosed by an oncologist was used; in instances where this was not available, the date of first surgical, imaging or initiation of chemotherapy/radiation was used, respectively. Overall survival was defined as the time elapsed between date of diagnosis and date of death or last contact. DFS was defined as the interval between the date of remission and the date of recurrence or the date of last contact. Patients who were not diagnosed with recurrent disease during the period of follow-up data collection were censored at the date of last contact.

4.3.4 Statistical analysis

Chi-square tests were used to assess differences in demographic and lifestyle characteristics between included and excluded OH/PA cases. Traditional overall and DFS estimates were calculated using the Kaplan-Meier approach.[170] Log-rank tests were used to determine whether

survival differed according to demographic, lifestyle, disease and clinical characteristics. Conditional DFS was also estimated using Kaplan-Meier methods, conditioning on survival at 1, 2, 3, 4, and 5 years after achieving remission. For example, to estimate conditional survival at year 1, we used Kaplan-Meier methods to calculate DFS among only the participants who were disease-free at 1 year after the date of remission. Participants that had recurred prior to the 1-year time point were excluded from the analysis. The impact of demographic, lifestyle, disease and clinical characteristics at baseline and at 1, 2, 3, 4, and 5 years after achieving remission were assessed through the calculation of hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) using Cox regression. Improvements in conditional survival over time were assessed by comparing 5-year DFS estimates at 1, 2, 3, 4, and 5 years after achieving remission to baseline 5-year DFS. Backward stepwise Cox regression was used to identify models of the demographic, lifestyle, disease, and clinical factors that impact disease-free survival at baseline and 1, 2, 3, 4, and 5 years after remission was achieved. Age (continuous) was locked into the stepwise models with entrance/exit tolerance *P*-values of 0.05 and 0.10, respectively.

All significance tests were two-sided; *P*-values < 0.05 were considered statistically significant. All analyses were conducted using Stata version 12.1.[132]

4.4 RESULTS

Characteristics of the study population are presented in Table 12. The cohort consisted primarily of Caucasian women and most participants had at least some post-high school education. At the time of diagnosis, the median age was 58.6 years (range 24-90) and the majority of women were

post-menopausal. Only 5.5% of the women had a family history of ovarian cancer or a combination of ovarian and breast cancers.

Table 13 presents the disease and clinical characteristics for patients at baseline (i.e., at original diagnosis) as well as at 1, 2, 3, 4, and 5 years after achieving remission, given that they remained in remission at these time points. At baseline, the majority was diagnosed with primary ovarian tumors, the most common histologic subtype was serous, and most tumors were moderately or poorly differentiated. A small percentage of the cohort was diagnosed with a synchronous primary tumor (6.5%), the majority of which were endometrial tumors. Only three women in the cohort did not undergo cytoreductive surgery and most women were optimally debulked (76.0%); furthermore, a large proportion of the cohort had no residual disease at the conclusion of their cytoreductive surgery (59.4%). The majority of women received $3 \leq 6$ cycles of platinum-based and/or taxane chemotherapy and only a small percentage of women received "other" chemotherapy agents. Upon completion of their primary treatment, only 3.2% of the women had persistent disease.

Among the 404 women in this study, the median overall survival was 4.50 years after diagnosis (range: 0.82 – 9.89 years). At the cutoff date of April 16, 2013, 235 (58.2%) study participants were still alive. The median time elapsed between date of diagnosis and date of remission was 6.45 months (range: 0 – 26.2). This includes 12 women whose date of diagnosis was the date of their cytoreductive surgery, in which there was no residual disease and no further primary treatment necessary. Traditional DFS curves, stratified by stage, are depicted in Figure 7. Within our study, 222 (55.0%) women were diagnosed with recurrent OC and the median DFS was 2.54 years after achieving remission (range: 0.03 – 9.36 years). Using log rank tests to assess whether DFS differed according to the participant characteristics presented in Table 12, we found

that only age and menopausal status significantly impacted DFS (*P*-values: 0.02 and 0.01, respectively; data not shown). However, menopausal status was no longer significant when adjusting for age using Cox regression. Log rank tests were also used to assess the disease and clinical characteristics shown in Table 13. We found that survival was significantly different according to all disease and clinical characteristics, with the exception of synchronous primary tumor (*P*=0.06). Characteristics associated with better prognosis tended to have a greater proportion of women at later time points of DFS and included: early stage, negative cytology of ascites/pelvic washings, no residual disease at the completion of cytoreductive surgery, optimal debulking, and the normalization of CA-125 without/prior to chemotherapy, (Table 13). Only 30.8% of the study participants were diagnosed with stage I disease, however, 61.8% of the women who survived 5-years without recurrence had stage I disease. Similar relationships were observed for histologic subtypes, cytology of ascites/pelvic washings, pre-treatment ascites, lymph node involvement, presence of residual disease, residual disease size, and debulking status after cytoreductive surgery, and number of chemotherapy cycles before normalization of CA-125 (Table 13).

Hazard ratios for disease and clinical characteristics presented in Table 14 were calculated using Cox regression models adjusted for age. At baseline, we observed that the following characteristics significantly impacted survival: yearly income, family history, stage, primary site of cancer, grade, histology, pre-treatment CA-125 levels, pre-treatment pleural effusion, cytology of ascites/pelvic washings, pre-treatment ascites, lymph node involvement, presence of residual disease, size of residual disease and debulking status upon completion of cytoreductive surgery, number of platinum-based, taxane, and other chemotherapy cycles, maintenance chemotherapy, number of cycles before CA-125 normalization, and persistent disease. These same characteristics

remained significantly associated with survival among women who had already had periods of remission of 1 and 2 years, with the exception of pre-treatment CA-125 levels among women at 2 years of disease-free survival. In addition to pre-treatment CA-125 levels, the following variables were no longer significant among women who had survived 3 years without a recurrence: grade, pre-treatment pleural effusion, cytology of ascites/pelvic washings, residual disease after cytoreductive surgery, number of "other" chemotherapy cycles, and number of cycles before normalization. We were unable to assess the association between some characteristics and survival among these women due to limitations of strata size. Cox regression adjusting for age was also completed among women who had survived 4 and 5 disease-free years; however, the number of women in each stratum was too small to yield meaningful results (data not shown).

At baseline, 5-year DFS was 44.6%. The probability of attaining an additional 5 years without recurrence, conditioned on having already achieved 1, 2, 3, 4, and 5 year periods of remission, was 61.9%, 78.6%, 90.7%, 97.3% and 98.1%, respectively (Figure 8). Figure 9 illustrates unadjusted 5-year DFS for women at baseline and for women who had not recurred 1, 2, 3, 4, and 5 years after achieving remission. DFS estimates improved for all stages as time elapsed from the date of remission. Although women with stage III and IV disease had a much lower 5-year DFS rate at the time of achieving remission, the disparity in 5-year survival estimates decreased as more time elapsed from the date of remission. 5-year DFS also improved for all age groups as time elapsed since date of remission (Figure 10). Women in older age groups had lower 5-year DFS compared to younger women at baseline; however, the differences between the age groups also decreased as the period of remission increased.

Backward stepwise Cox regression yielded a model that included age (continuous), yearly income, BMI, race, family history, stage, grade, primary site of cancer, cytology of ascites/pelvic

washings, residual disease and debulking status after cytoreductive surgery, number of chemotherapy cycles before normalization of CA-125, maintenance chemotherapy, number of cycles of taxane and "other" chemotherapy. All study participants were included in the model, with the exception of the 3 women who did not have cytoreductive surgery. Repeating the process among only women who had achieved a period of remission of 1 year, we identified a model that included age, synchronous primary cancer, race, education, yearly income, maintenance chemotherapy, number of cycles prior to normalization of CA-125, grade, lymph node involvement, family history, pre-treatment ascites, cytology of ascites/pelvic washings, pre-treatment pleural effusion, and stage. Among women who had survived 2 years without recurrence, backward stepwise Cox regression included only age, pre-treatment ascites, pre-treatment pleural effusion, education, and grade. Both of these models excluded 1 woman who did not have cytoreductive surgery. We were unable to perform backward stepwise Cox regression among only cases that had achieved 3, 4, and 5 years of remission due to small subgroup sizes.

4.5 DISCUSSION

To the best of our knowledge, this is the first study to assess conditional DFS among OC patients. Our findings demonstrate that DFS estimates improve dramatically over time and that conditional DFS provides more relevant prognostic information than traditional estimates to patients who have already achieved a period of remission. Generally, we observed that DFS improves most for patients who initially had the poorest prognosis. Similar to previous studies examining conditional overall survival among OC patients, we found that the initial differences in DFS at diagnosis between age and stage groups diminished over time. [166-168] This was especially evident among

stage III/IV cases and cases that were diagnosed after the age of 65. Our findings suggest that the time elapsed since remission may be more important than prognostic factors collected at baseline when estimating survival among OC survivors.

At baseline, we observed significant associations between DFS and the majority of disease and clinical characteristics included in this study. Our results are in line with previous studies that have established these factors as significant predictors of overall or disease-free survival. These characteristics included: age,[90,93,94] family history,[171] stage,[89,92] primary site,[172], grade,[90,92,95] histology,[89,90,94,95]pre-treatment CA-125 levels,[173,174] pre-treatment pleural effusion,[175,176] cytology of ascites/pelvic washings,[96,177] and pre-treatment ascites.[89] Lymph node biopsies/involvement also significantly impacted DFS and is consistent with results from previous studies.[95,178-180] Significant associations between DFS and residual disease or debulking status after cytoreductive surgery were also significant.[89-91,94] Additionally, we found that the number of platinum, taxane, and "other" chemotherapy cycles also significantly impacted DFS.[87,89,95,181] Although the number of maintenance chemotherapy cycles was included in the number of platinum, taxane and "other" chemotherapy totals, receiving maintenance chemotherapy compared to not receiving maintenance chemotherapy was significantly associated with DFS.[182,183] Results from previous studies have provided conflicting results regarding the role of maintenance chemotherapy in improving overall survival.[184-186] The number of chemotherapy cycles before normalization of CA-125 also significantly affected DFS.[163-165] Persistent disease was significantly associated with DFS in our analysis; however, only 13 cases had persistent disease before achieving remission. The majority of HOPE cases that were found to have persistent disease after completion of primary therapy were excluded from our study because they never achieved remission.

Several factors that predicted DFS at baseline were no longer predictive of survival among women who had achieved longer periods of remission. When limiting DFS to only women who had achieved remission for a period of 1 or 2 years, we found that the same characteristics remained significant, with the exception of pre-treatment CA-125 levels among women who had achieved a remission period of 2 years. Among women who had survived a remission period of 3 years, grade, pre-treatment pleural effusion, cytology of ascites/pelvic washings, residual disease after cytoreductive surgery, number of "other" chemotherapy cycles, and number of cycles before normalization of CA-125 were also no longer predictive of DFS. The importance of these characteristics diminished over time, suggesting that time of remission already achieved provides more meaningful prognostic information to OC survivors than survival estimates based on baseline characteristics.

Backward stepwise Cox regression was used to identify the characteristics that together predict DFS and exclude characteristics that are interrelated. We identified 15 characteristics that should be included in a DFS prediction model among all women who achieved remission. Among patients who achieved 1 year of remission, the process yielded a model with 14 characteristics, some of which were not included in the baseline model. Furthermore, the backward stepwise Cox regression identified only 5 characteristics that were predictive of DFS among survivors who had achieved a remission period of 2 years. These results further suggest that prognostic tools based on prognostic factors identified through traditional survival estimates at baseline are no longer relevant to OC survivors that have achieved a period of remission.

OC follow-up care is a controversial topic with disagreement over whether increased surveillance for recurrent disease is effective in reducing overall survival.[99-101,187] Although the use of CA-125 for the early detection of recurrent disease has not resulted in meaningful

improvements in overall survival,[104] a study by Oskay-Oezcelik found that the majority of patients believe routine CA-125 testing was the most important factor in determining their cancer outcomes.[105] Their findings suggest that physician-patient communication regarding the goals and efficacy of follow-up care may be insufficient. Improved measures of recurrence risk, such as conditional DFS, may help clinicians provide more accurate prognosis information to survivors. Tailored risk assessments can then be used to develop individualized follow-up treatment plans.

The follow-up information collected from the HOPE participants enabled us to examine many prognostic characteristics that have not previously been assessed in OC conditional survival estimates. Our study was further strengthened by the fact that cases were recruited within a short time period, which limited the possibility that survival over time was influenced by changes in standard of care. However, this study has also several limitations that should be noted. The small sample sizes within subgroups, particularly within histology, chemotherapy regimens and persistent disease, resulted in large confidence intervals in our analyses and in the inability to estimate DFS for these variables among patients who had achieved 3 years of remission. Lifestyle characteristics were collected at the time of enrollment and therefore do not necessarily reflect the smoking status, BMI, weekly alcohol intake, or yearly income throughout treatment and follow-up care. The women included in this study were predominantly Caucasian, had completed at least some post-high school education, and had a yearly income of at least $25,000, which does not reflect the general U.S. population and therefore limits the generalizability of our study.

Future research should focus on the development and validation of prognostic tools that can be utilized in the clinical setting to inform follow-up care for OC survivors. Our results provide evidence that conditional DFS estimates are more meaningful than traditional DFS estimates to OC survivors that have already achieved a period of remission. Consequently, future efforts to

create prognostic tools that estimate the risk of recurrence for OC survivors should take the period of remission already achieved into account.

4.6 TABLES

Table 12. Characteristics of the study population at time of enrollment

	N=404	
	N	**%**
Study Site		
PA	236	58.4
OH	168	41.6
Age (years)		
< 45	50	12.4
45 < 55	104	25.7
55 < 65	117	29.0
≥ 65	133	32.9
Race		
Caucasian	391	96.8
African-American	9	2.2
Other	4	1.0
Education		
Non-High School Graduate	36	8.9
High School Graduate	131	32.4
Post-High School	237	58.7
Yearly Income		
≥ $90,000	47	11.6
$50,000 < $90,000	117	29.0
$25,000 < $50,000	113	28.0
< $25,000	80	19.8
Could Not Be Assessed	47	11.6
Body Mass Index (in kg/m^2)		
< 25	151	37.4
25 < 30	121	29.9
≥ 30	132	32.7
Smoking Status		
Never Smoker	202	50.0
Former Smoker	140	34.7
Current Smoker	62	15.4
Alcohol Use (drinks per week) [b]		
≤ 7	338	83.7
8 ≤ 14	38	9.4
≥ 15	28	6.9
Family History		
None	319	79.0
Breast Only	63	15.6
Ovarian Only	18	4.5
Breast and Ovarian	4	1.0
Menopausal Status		
Pre-menopausal	97	24.0
Post-menopausal	307	76.0

Table 13. Disease and clinical characteristics across years of disease-free survival

	Baseline *N*=404		1 Year *N*=281		2 Years *N*=219		3 Years *N*=185		4 Years *N*=148		5 Years *N*=104	
	N	***%***	***N***	***%***	***N***	***%***	***N***	***%***	***N***	***(%)***	***N***	***(%)***
Stage[a]												
I	124	30.8	118	42.1	112	51.4	108	58.7	89	60.5	64	61.8
II	44	10.9	37	13.2	31	14.2	28	15.2	25	17.0	19	18.6
III	205	50.9	113	40.4	69	31.7	44	23.9	30	20.4	17	16.7
IV	30	7.4	12	4.3	6	2.8	4	2.2	3	2.0	3	2.9
Primary Site												
Ovarian	341	84.4	239	85.1	189	86.3	165	89.2	130	87.8	94	90.3
Peritoneal	30	7.4	18	6.4	11	5.0	4	2.2	3	2.0	2	1.9
Fallopian	28	6.9	22	7.8	17	7.8	15	8.1	14	9.5	7	6.8
Could Not be assessed	5	1.2	2	0.7	2	0.9	1	0.5	1	0.7	1	1.0
Grade												
Well differentiated	42	10.4	39	13.9	34	15.5	32	17.3	28	18.9	16	15.5
Moderately differentiated	104	25.7	76	27.1	59	26.9	51	27.6	39	26.4	29	28.2
Poorly differentiated	203	50.3	127	45.2	94	42.9	80	43.2	61	41.2	45	43.7
Mixed	25	6.2	17	6.1	12	5.5	7	3.8	6	4.1	4	2.9
Could Not be Assessed	30	7.14	22	7.8	20	9.1	15	8.1	14	9.5	10	9.7
Histology												
Serous	216	53.5	125	44.5	81	37.0	60	32.4	45	30.4	29	28.2
Endometrioid	68	16.8	60	21.4	52	23.7	51	27.6	38	25.7	32	31.1
Mucinous	21	5.2	20	7.1	20	9.1	18	9.7	16	10.8	10	8.7
Clear cell	29	7.2	28	10.0	24	11.0	22	11.9	20	13.5	14	13.6
Brenner	5	1.2	4	1.4	4	1.8	3	1.6	3	2.0	3	2.9
MMT	9	2.2	7	2.5	6	2.7	5	2.7	5	3.4	4	3.9
Mixed	40	9.9	29	10.3	25	11.4	21	11.4	17	11.5	11	10.7
Other[b]	3	0.7	2	0.7	1	0.5	1	0.5	0	0.0	0	0.0
Could Not Be Assessed	13	3.2	6	2.1	6	2.7	4	2.2	4	2.7	1	1.0
Pre-treatment CA-125 Levels												
≤ 35 U/mL	60	14.9	54	19.2	49	22.4	45	24.3	38	25.7	28	26.2
>35 U/mL	274	67.8	178	63.4	136	62.1	112	60.5	94	63.5	68	66.0
Could Not Be Assessed	70	17.3	49	17.4	34	15.5	28	15.1	16	10.8	8	7.8
Pre-treatment Pleural Effusion												
No	58	14.4	36	12.8	29	13.2	29	15.7	27	18.2	19	18.5
Yes	44	10.9	23	8.2	15	6.9	10	5.4	7	4.7	6	5.8
Could Not Be Assessed	302	74.8	222	79.0	175	79.9	146	78.9	114	77.0	79	75.7
Cytology of Ascites/Pelvic Washings												
Negative	138	34.2	123	43.8	114	52.1	107	57.8	85	57.4	64	61.2
Positive	182	45.1	103	36.6	60	27.4	44	23.8	37	25.0	23	22.3
Atypical	16	4.0	11	3.9	9	4.1	7	3.8	7	4.7	4	3.9
Could Not Be Assessed	68	16.8	44	15.7	36	16.4	27	14.6	19	12.8	13	12.6
Pre-treatment Ascites												
No	153	37.9	128	45.6	112	51.1	99	53.5	83	56.1	60	57.3
Yes	246	60.9	148	52.7	103	47.0	84	45.4	63	42.6	43	41.8
Could Not Be Assessed	5	1.2	5	1.8	4	1.8	2	1.1	2	1.4	1	1.0
Lymph Node Involvement												
No Palpable Nodes, No Biopsies	152	37.6	83	29.5	55	25.1	42	22.7	31	21.0	18	17.5
Palpable Nodes, No Biopsies	6	1.5	5	1.8	1	0.5	0	0.0	0	0.0	0	0.0
Biopsies Negative	183	45.3	157	55.9	139	63.5	125	67.6	105	71.0	76	72.8
Biopsies Positive	57	14.1	33	11.7	21	9.6	16	8.7	10	6.8	8	7.8
Could Not Be Assessed	6	1.5	3	1.1	3	1.4	2	1.1	2	1.4	2	1.9
Synchronous Primary Tumor[c]												
No	375	93.5	261	93.2	202	92.7	170	92.4	135	91.8	96	93.1
Yes, Endometrial	20	5.0	15	5.4	14	6.4	13	7.1	11	7.5	7	6.9
Yes, Other[d]	6	1.5	4	1.4	2	0.9	1	0.5	1	0.7	0	0.0
Residual Disease after Cytoreductive Surgery[c]												
No	238	59.4	199	71.1	176	80.7	160	87.0	132	89.8	95	92.2
Yes	133	33.2	65	23.2	34	15.6	21	11.4	15	6.1	8	7.8
Could Be Assessed	30	7.5	16	5.7	8	3.7	3	1.6	0	0.0	0	0.0

Table 13. (*Continued*)

	Baseline *N*=404		1 Year *N*=281		2 Years *N*=219		3 Years *N*=185		4 Years *N*=148		5 Years *N*=104	
	N	***%***	***N***	***%***	***N***	***%***	***N***	***%***	***N***	***%***	***N***	***%***
Residual Disease after Cytoreductive Surgery (cm)[c]												
No Residual Disease	238	59.4	201	71.8	178	81.7	161	87.5	132	89.8	95	92.2
0.1 < 1.0	40	17.5	38	13.6	18	8.3	11	6.0	9	6.1	5	4.9
1.0 < 2.0	24	6.0	10	3.6	5	2.3	1	0.5	1	0.7	1	1.0
≥ 2.0	17	4.2	3	1.1	3	1.4	3	1.6	2	1.4	0	0.0
Could Not Be Assessed	52	13.0	28	10.0	14	6.4	8	4.4	3	2.0	2	2.0
Debulking at Cytoreductive Surgery[e]												
Optimal	307	76.0	244	86.8	196	89.5	171	92.5	138	93.2	97	93.2
Sub-Optimal	57	14.1	22	7.8	12	5.5	7	3.8	4	2.7	2	1.9
Received neo-adjuvant chemotherapy	27	6.7	9	3.2	8	3.7	5	2.7	4	2.7	3	2.9
No primary surgery performed	3	0.7	1	0.4	1	0.5	1	0.5	1	0.7	1	1.0
Could Not Be Assessed	10	2.5	5	1.8	2	0.9	1	0.5	1	0.7	1	1.0
Platinum Chemotherapy (# of cycles)[f]												
No	31	7.7	28	10.0	28	12.8	25	13.5	21	14.2	13	11.7
0 ≤ 3	21	5.2	20	7.1	18	8.2	16	8.7	13	8.8	11	10.7
3 ≤ 6	247	61.1	173	61.6	130	59.4	115	62.2	91	61.5	64	62.1
> 6	102	25.3	57	20.3	41	18.7	27	14.6	21	14.2	16	15.5
Yes, Number of Cycles Unknown	3	0.7	3	1.1	2	0.9	2	1.1	2	1.4	0	0.0
Taxane Chemotherapy (# of cycles)[f]												
No	41	10.2	37	13.2	35	16.0	30	16.2	24	16.2	16	14.6
0 ≤ 3	24	5.9	21	7.5	20	9.1	17	9.2	16	10.8	13	12.6
3 ≤ 6	235	58.2	163	58.0	126	57.5	109	58.9	87	58.8	60	58.3
> 6	99	24.5	55	19.6	34	15.6	25	13.5	19	12.8	15	14.6
Yes, Number of Cycles Unknown	5	1.2	5	1.8	4	1.8	4	2.2	2	1.4	0	0.0
Other Chemotherapy (# of cycles)[f,g]												
No	355	89.0	253	90.0	201	91.8	175	94.6	142	96.0	100	96.1
0 ≤ 3	3	0.8	5	1.8	3	1.4	2	1.1	1	0.7	1	1.0
3 ≤ 6	16	4.0	11	3.9	7	3.2	4	2.2	4	2.7	3	2.9
> 6	21	5.3	10	3.6	8	3.7	4	2.2	1	0.7	0	0.0
Yes, Number of Cycles Unknown	4	1.0	2	0.7	0	0.0	0	0.0	0	0.0	0	0.0
Maintenance Chemotherapy												
No	366	90.6	252	89.7	204	93.2	174	94.1	142	96.0	101	97.1
Yes	38	9.4	29	10.3	15	6.9	11	5.9	6	4.0	3	2.9
Number of Chemotherapy Cycles Before Normalization of CA-125												
Normalized Without/Prior to Chemotherapy	133	32.9	120	42.7	105	47.9	94	50.8	76	51.4	51	49.0
Normalized 1 < 3 Cycles	116	28.7	79	28.1	65	29.7	53	28.7	39	26.4	30	28.8
Normalized 3 < 6 Cycles	80	19.8	37	13.2	21	9.6	15	8.1	13	8.8	7	6.7
Normalized ≥ 6 Cycles	37	9.2	19	6.8	9	4.1	7	3.8	7	4.7	5	4.8
Could Not Be Assessed	38	9.4	26	9.3	19	8.7	16	8.7	13	8.8	11	10.6
Persistent Disease												
No	391	96.8	277	98.6	216	98.6	183	98.9	146	98.7	103	99.0
Yes	13	3.2	4	1.4	3	1.4	2	1.1	2	1.3	1	1.0

[a] 1 case was missing stage information because she never had staging or cytoreductive surgeries and was never formally staged by oncologist.
[b] Includes 1 micropapillary serous, 1 adenosquamous, 1 papillary serous with multiple psammoma bodies.
[c] Excludes 3 cases that did not have cytoreductive surgery.
[d] Includes 1 case of each of the following synchronous cancers: fallopian tube, granulosa cell tumor of the ovary, recurrent breast, gastrointestinal stromal, skin, and appendiceal.
[e] Cases were considered to be optimally debulked if their disease was < 1cm or their surgeon/oncologist declared them to be optimally debulked at the conclusion of their cytreductive surgery.
[f] Includes neoadjuvant, adjuvant and maintenance chemotherapies received as well as any chemotherapy received for persistent disease.
[g] Includes avastin, doxil, topotecan, gemzar, Cytoxan, interferon, mytomycin, Erbitux, ifosphomaide, catumaxomab, and ovarex. Many of these "other" chemotherapies were given as part of a clinical trial and in some cases it was unclear whether participants received placebo or the active agent; cases that were reported to have gotten the placebo were considered to have received no chemotherapy.

Table 14. Impact of participant characteristics on conditional disease-free survival[a]

	Baseline *N*=404	1 Year *N*=281	2 Years *N*=219	3 Years *N*=185
	HR (95% CI) [b]	**HR (95% CI) [b]**	**HR (95% CI)[b]**	**HR (95% CI) [b]**
Site				
PA	Ref.	Ref.	Ref.	Ref.
OH	0.98 (0.75, 1.28)	1.13 (0.77, 1.67)	1.09 (0.59, 2.00)	0.91 (0.31, 2.66)
Race				
Caucasian	Ref.	Ref.	Ref.	Ref.
African-American	0.56 (0.21, 1.50)	0.76 (0.24, 2.41)	1.21 (0.29, 5.11)	2.55 (0.31, 20.94)
Other	0.51 (0.07, 3.67)	1.04 (0.14, 7.75)	---	---
Education				
Non-High School Graduate	Ref.	Ref.	Ref.	Ref.
High School Graduate	1.46 (0.87, 2.44)	1.73 (0.76, 3.91)	5.48 (0.72, 41.61)	1.24 (0.14, 11.12)
Post-High School	1.24 (0.75, 2.07)	1.54 (0.68, 3.43)	4.79 (0.63, 36.29)	1.01 (0.12, 8.76)
Yearly Income				
≥ $90,000	Ref.	Ref.	Ref.	Ref.
$50,000 < $90,000	1.55 (0.94, 2.56)	0.88 (0.49, 1.57)	1.16 (0.44, 3.01)	---
$25,000 < $50,000	1.71 (1.03, 2.84)	0.70 (0.37, 1.32)	0.71 (0.24, 2.12)	---
< $25,000	1.52 (0.88, 2.59)	0.87 (0.46, 1.70)	1.35 (0.48, 3.79)	---
Could Be Assessed	1.64 (0.92, 2.94)	0.83 (0.39, 1.76)	1.08 (0.33, 3.55)	---
Body Mass Index (in kg/m^2)				
< 25	Ref.	Ref.	Ref.	Ref.
25 < 30	1.14 (0.83, 1.57)	0.84 (0.53, 1.35)	0.86 (0.42, 1.78)	0.56 (0.15, 2.18)
≥ 30	0.95 (0.69, 1.31)	0.68 (0.43, 1.09)	0.67 (0.32, 1.38)	0.78 (0.25, 2.48)
Smoking Status				
Never Smoker	Ref.	Ref.	Ref.	Ref.
Former Smoker	0.88 (0.66, 1.18)	1.06 (0.69, 1.63)	0.99 (0.51, 1.89)	0.88 (0.29, 2.70)
Current Smoker	0.94 (0.63, 1.40)	1.28 (0.74, 2.21)	0.96 (0.39, 2.37)	0.81 (0.17, 3.80)
Alcohol Use (drinks per week)				
≤ 7	Ref.	Ref.	Ref.	Ref.
8 ≤ 14	0.97 (0.61, 1.55)	0.89 (0.45, 1.78)	1.36 (0.57, 3.24)	3.00 (0.94, 9.60)
≥ 15	0.91 (0.53, 1.57)	0.80 (0.35, 1.82)	0.33 (0.05, 2.41)	1.13 (0.14, 8.80)
Family History				
None	Ref.	Ref.	Ref.	Ref.
Breast Only	0.84 (0.58, 1.22)	0.89 (0.53, 1.51)	1.15 (0.55, 2.40)	2.16 (0.74, 6.34)
Ovarian Only	0.69 (0.34, 1.41)	0.73 (0.27, 1.98)	0.47 (0.06, 3.41)	---
Breast and Ovarian	3.25 (1.20, 8.83)	4.23 (1.03, 17.44)	13.90 (1.82, 106.24)	---
Menopausal Status				
Pre-menopausal	Ref.	Ref.	Ref.	Ref.
Post-menopausal	1.14 (0.74, 1.77)	1.13 (0.61, 2.10)	1.11 (0.44, 2.79)	1.41 (0.34, 5.89)
Stage [c]				
I	Ref.	Ref.	Ref.	Ref.
II	3.47 (1.71, 7.02)	3.11 (1.26, 7.66)	2.16 (0.51, 9.07)	1.34 (0.14, 12.93)
III	12.59 (7.38, 21.49)	12.30 (6.35, 23.97)	14.78 (5.74, 38.02)	11.08 (3.07, 39.97)
IV	16.08 (8.40, 30.77)	11.00 (4.14, 29.21)	4.21 (0.49, 35.39)	---
Primary Site				
Ovarian	Ref.	Ref.	Ref.	Ref.
Peritoneal	1.70 (1.10, 2.61)	2.73 (1.53, 4.85)	5.33 (2.32, 12.21)	---
Fallopian	0.78 (0.44, 1.37)	0.94 (0.44, 2.04)	0.65 (0.15, 2.69)	0.81 (0.11, 6.16)
Could be assessed	1.63 (0.60, 4.43)	1.06 (0.15, 7.72)	3.00 (0.39, 23.06)	---
Grade				
Well differentiated	Ref.	Ref.	Ref.	Ref.
Moderately differentiated	3.46 (1.56, 7.63)	2.60 (0.99, 6.83)	2.30 (0.48, 10.94)	1.72 (0.15, 19.64)
Poorly differentiated	5.00 (2.32, 10.74)	3.73 (1.50, 9.36)	4.51 (1.06, 19.28)	6.38 (0.76, 53.21)
Mixed	4.81 (1.97, 11.73)	4.62 (1.54, 13.86)	7.10 (1.28, 39.21)	---
Could Not Be Assessed	3.20 (1.29, 7.93)	2.05 (0.62, 6.72)	3.66 (0.67, 20.05)	2.36 (0.14, 38.62)

Table 14. (*Continued)*

	Baseline *N*=404	**1 Year** *N*=281	**2 Years** *N*=219	**3 Years** *N*=185
	HR (95% CI) [a]	HR (95% CI) [a]	HR (95% CI) [a]	HR (95% CI) [a]
Histology				
Serous	Ref.	Ref.	Ref.	Ref.
Endometrioid	0.22 (0.13, 0.37)	0.23 (0.12, 0.43)	0.13 (0.04, 0.42)	0.30 (0.08, 1.11)
Mucinous	0.04 (0.01, 0.28)	---	---	---
Clear cell	0.20 (0.10, 0.44)	0.30 (0.13, 0.69)	0.19 (0.05, 0.80)	---
Brenner	0.36 (0.09, 1.47)	0.32 (0.04, 2.30)	0.59 (0.08, 4.36)	---
MMT	0.44 (0.16, 1.20)	0.40 (0.10, 1.62)	0.39 (0.05, 2.86)	---
Mixed	0.46 (0.28, 0.75)	0.37 (0.18, 0.77)	0.38 (0.13, 1.08)	0.25 (0.03, 1.92)
Other[d]	1.18 (0.28, 4.91)	1.47 (0.19, 11.23)	---	---
Could Not Be Assessed	0.87 (0.44, 1.70)	0.39 (0.10, 1.61)	0.87 (0.21, 3.67)	1.63 (0.21, 12.88)
Pre-treatment CA-125 Levels				
≤ 35 U/mL	Ref.	Ref.	Ref.	Ref.
>35 U/mL	2.93 (1.75, 4.90)	2.36 (1.21, 4.58)	2.27 (0.88, 5.88)	4.90 (0.63, 38.16)
Could Not Be Assessed	2.95 (1.66, 5.26)	2.99 (1.41, 6.32)	2.25 (0.71, 7.11)	6.46 (0.67, 62.37)
Pre-treatment Pleural Effusion				
No	Ref.	Ref.	Ref.	Ref.
Yes	1.98 (1.22, 3.23)	3.65 (1.53, 8.73)	16.99 (2.05, 141.55)	6.06 (0.55, 67.22)
Could Not Be Assessed	0.97 (0.66, 1.44)	1.90 (0.92, 3.95)	7.61 (1.04, 57.73)	2.43 (0.31, 18.87)
Cytology of Ascites/Pelvic Washings				
Negative	Ref.	Ref.	Ref.	Ref.
Positive	5.49 (3.72, 8.09)	5.59 (3.34, 9.33)	4.67 (2.20, 9.93)	2.42 (0.78, 7.52)
Atypical	3.20 (1.53, 6.72)	2.92 (0.99, 8.60)	3.10 (0.68, 14.22)	---
Could Not Be Assessed	3.52 (2.21, 5.59)	3.03 (1.59, 6.04)	3.68 (1.53, 8.86)	2.14 (0.54, 8.56)
Pre-treatment Ascites				
No	Ref.	Ref.	Ref.	Ref.
Yes	2.84 (2.08, 3.88)	2.76 (1.79, 4.28)	2.97 (1.52, 5.80)	8.25 (1.86, 36.59)
Could Not Be Assessed	1.09 (0.27, 4.47)	1.99 (0.47, 8.38)	2.54 (0.33, 19.71)	---
Lymph Node Involvement				
No Palpable Nodes, No Biopsies	Ref.	Ref.	Ref.	Ref.
Palpable Nodes, No Biopsies	1.48 (0.65, 3.38)	5.40 (2.11, 13.83)	6.54 (0.84, 50.99)	---
Biopsies Negative	0.30 (0.22, 0.42)	0.36 (0.23, 0.58)	0.43 (0.21, 0.88)	0.91 (0.19, 4.43)
Biopsies Positive	1.16 (0.82, 1.64)	1.41 (0.84, 2.37)	2.06 (0.94, 4.56)	7.41 (1.49, 36.85)
Could Not Be Assessed	0.59 (0.19, 1.86)	---	---	---
Synchronous Primary Tumor[e]				
No	Ref.	Ref.	Ref.	Ref.
Yes, Endometrial	0.43 (0.18, 1.04)	0.17 (0.02, 1.20)	0.36 (0.05, 2.64)	0.86 (0.11, 6.61)
Yes, Other[f]	1.20 (0.44, 3.24)	1.62 (0.39, 6.70)	---	---
Residual Disease after Cytoreductive Surgery[e]				
No	Ref.	Ref.	Ref.	Ref.
Yes	4.70 (3.50, 6.31)	4.94 (3.24, 7.54)	4.74 (2.46, 9.14)	2.42 (0.66, 8.86)
Could Not Be Assessed	5.32 (3.40, 8.34)	7.10 (3.78, 13.32)	10.14 (3.75, 27.39)	7.66 (0.92, 63.96)
Size of Residual Disease after Cytoreductive Surgery (cm)[e]				
No Residual Disease	Ref.	Ref.	Ref.	Ref.
0.1 < 1.0	4.40 (3.12, 6.21)	5.23 (3.22, 8.51)	4.23 (1.96, 10.02)	1.45 (0.18, 11.4)
1.0 < 2.0	5.64 (3.51, 9.04)	6.90 (3.34, 14.25)	11.16 (3.78, 32.90)	---
≥ 2.0	6.74 (3.86, 11.78)	1.41 (0.19, 10.22)	2.77 (0.37, 20.57)	8.14 (1.02, 65.24)
Could Not Be Assessed	4.90 (3.38, 7.13)	5.89 (3.48, 9.94)	5.56 (2.37, 13.04)	4.49 (0.97, 20.66)
Debulking at Cytoreductive Surgery[g]				
Optimal	Ref.	Ref.	Ref.	Ref.
Sub-Optimal	3.78 (2.73, 5.23)	3.41 (2.02, 5.80)	4.62 (2.03, 10.53)	4.81 (1.06, 21.76)
Received neo-adjuvant chemotherapy	2.98 (1.89, 4.71)	1.31 (0.48, 3.58)	2.50 (0.76, 8.21)	2.61 (0.34, 20.07)
No primary surgery performed	1.68 (0.41, 6.88)	---	---	---
Unknown	3.78 (1.92, 7.43)	4.29 (1.56, 11.74)	3.60 (0.49, 26.40)	---
Platinum Chemotherapy (# of cycles)[h]				
No	Ref.	Ref.	Ref.	Ref.
0 ≤ 3	2.22 (0.63, 7.86)	3.81 (0.74, 19.62)	2.33 (0.39, 13.97)	---
3 ≤ 6	5.69 (2.10, 15.39)	6.32 (1.55, 25.87)	2.39 (0.56, 10.16)	---
> 6	10.06 (3.68, 27.51)	10.82 (2.59, 45.18)	6.65 (1.53, 28.93)	---
Yes, Number of Cycles Unknown	2.47 (0.28, 22.14)	5.18 (0.47, 57.39)	---	---

Table 14. (*Continued)*

	Baseline *N*=404	1 Year *N*=281	2 Years *N*=219	3 Years *N*=185
	HR (95% CI) [a]	**HR (95% CI) [a]**	**HR (95% CI) [a]**	**HR (95% CI) [a]**
Taxane Chemotherapy (# of cycles)[h]				
No	Ref.	Ref.	Ref.	Ref.
0 ≤ 3	1.50 (0.55, 4.14)	1.34 (0.36, 5.00)	1.66 (0.34, 8.24)	---
3 ≤ 6	3.53 (1.73, 7.21)	2.97 (1.19, 7.39)	2.15 (0.65, 7.16)	---
> 6	6.88 (3.32, 14.27)	6.08 (2.37, 15.60)	4.52 (1.28, 16.02)	---
Yes, Number of Cycles Unknown	1.84 (0.39, 8.67)	2.96 (0.57, 15.30)	2.56 (0.26, 24.77)	---
Other Chemotherapy (# of cycles)[h,i]				
No	Ref.	Ref.	Ref.	Ref.
0 ≤ 3	1.01 (0.32, 3.16)	1.53 (0.38, 6.24)	---	---
3 ≤ 6	1.75 (1.03, 2.98)	2.59 (1.25, 5.36)	3.90 (1.35, 11.00)	3.40 (0.44, 26.30)
> 6	2.30 (1.40, 3.79)	2.13 (0.93, 4.89)	4.36 (1.54, 12.35)	4.29 (0.54, 34.20)
Yes, Number of Cycles Unknown	4.67 (1.72, 12.66)	18.18 (4.29, 76.96)	---	---
Maintenance Chemotherapy				
No	Ref.	Ref.	Ref.	Ref.
Yes	1.80 (1.22, 2.66)	3.53 (2.16, 5.75)	3.44 (1.52, 7.82)	4.41 (1.20, 16.28)
Number of Chemotherapy Cycles Before Normalization of CA-125				
Normalized Without/Prior to Chemotherapy	Ref.	Ref.	Ref.	Ref.
1 < 3 Cycles	2.03 (1.36, 3.06)	1.42 (0.83, 2.43)	1.89 (0.88, 4.08)	2.47 (0.72, 8.43)
3 < 6 Cycles	4.45 (2.96, 6.71)	3.44 (1.97, 6.01)	3.53 (1.46, 8.55)	4.07 (0.90, 18.31)
≥ 6 Cycles	4.14 (2.54, 6.74)	3.56 (1.79, 7.11)	1.73 (0.38, 7.87)	---
Could Not Be Assessed	2.34 (1.39, 3.95)	1.79 (0.88, 3.65)	1.56 (0.50, 4.91)	1.04 (0.12, 9.28)
Persistent Disease				
No	Ref.	Ref.	Ref.	Ref.
Yes	2.98 (1.58, 5.63)	0.84 (0.12, 6.01)	---	---

[a] Please see Tables 1and 2 for the number of participants in each stratum.
[b] Hazard ratios were calculated using Cox regression models adjusted for age(continuous).
[c] 1 case was missing stage information because she never had staging or cytoreductive surgeries and was never formally staged by oncologist.
[d] Includes 1 micropapillary serous, 1 adenosquamous, 1 papillary serous with multiple psammoma bodies.
[e] Excludes 3 cases that did not have cytoreductive surgery.
[f] Includes 1 case of each of the following synchronous cancers: fallopian tube, granulosa cell tumor of the ovary, recurrent breast, gastrointestinal stromal, skin, and appendiceal.
[g] Cases were considered to be optimally debulked if their disease was < 1cm or their surgeon/oncologist declared them to be optimally debulked at the conclusion of their cytreductive surgery.
[h] Includes neoadjuvant, adjuvant and maintenance chemotherapies received as well as any chemotherapy received for persistent disease.
[i] Includes avastin, doxil, topotecan, gemzar, Cytoxan, interferon, mytomycin, Erbitux, ifosphomaide, catumaxomab, and ovarex. Many of these "other" chemotherapies were given as part of a clinical trial and in some cases it was unclear whether participants received placebo or the active agent; cases that were reported to have gotten the placebo were considered to have received no chemotherapy.

4.7 FIGURES

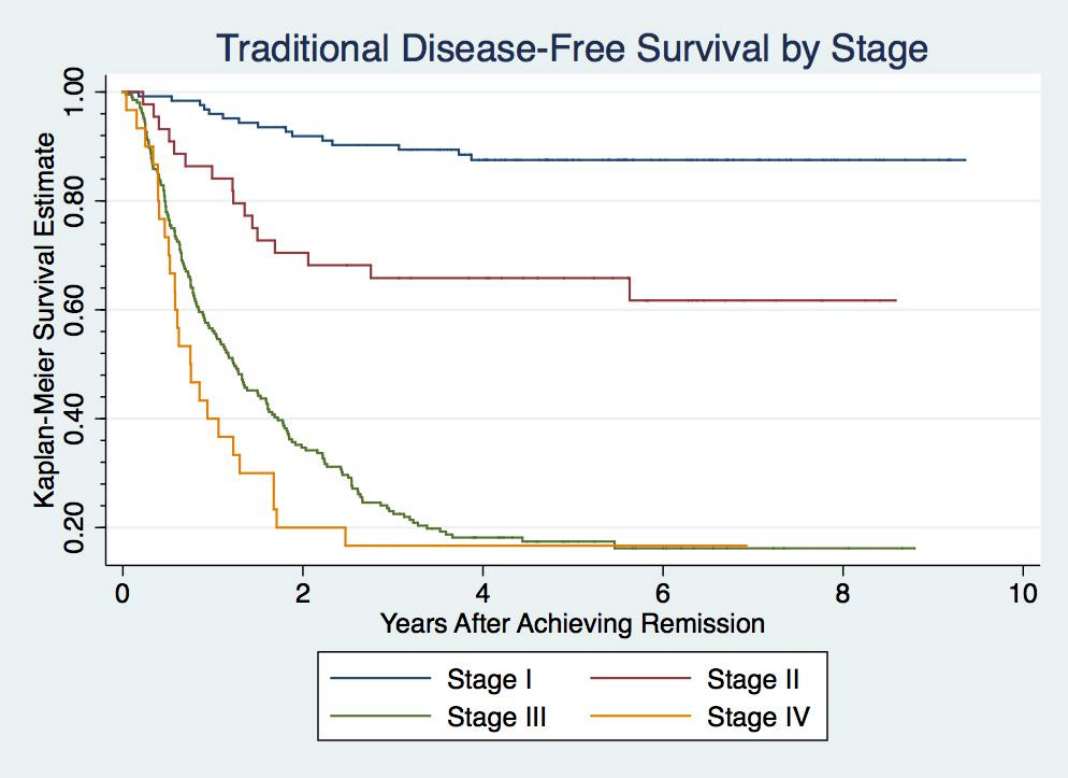

Figure 7. Traditional Disease-Free Survival (*N*=403) [a]

1 case was missing stage information because she never had staging or cytoreductive surgeries and was never formally staged by oncologist.

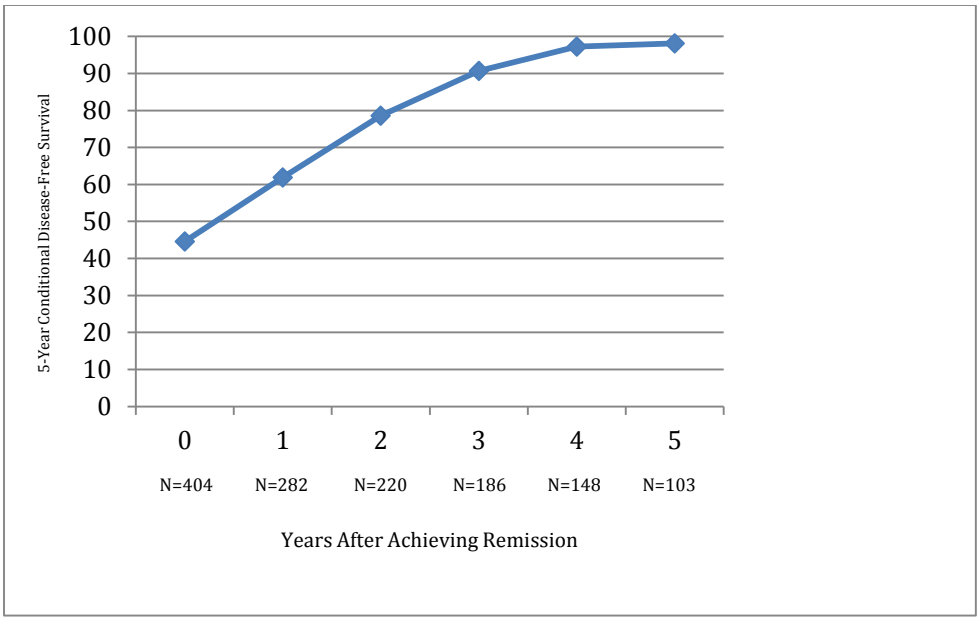

Figure 8. Improvements in 5-Year Conditional Disease-Free Survival

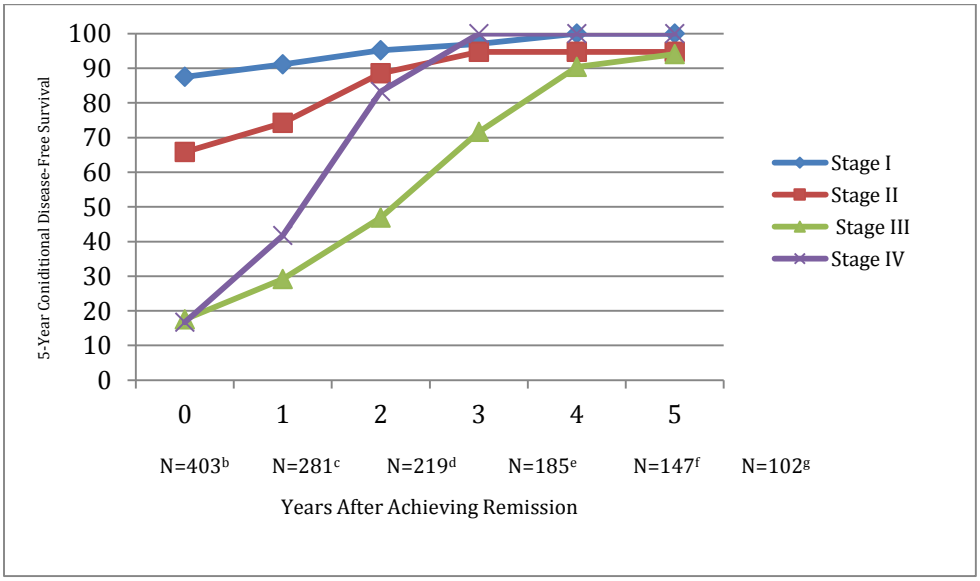

Figure 9. Improvements in 5-Year Conditional Disease-Free Survival, Stratified by Stage [a]

[a] 1 case was missing stage information because she never had staging or cytoreductive surgeries and was never formally staged by oncologist.
[b] Stage distribution at baseline: Stage I, 124; Stage II, 44; Stage III, 205; Stage IV, 30.
[c] Stage distribution after 1 year of remission: Stage I, 118; Stage II, 37; Stage III, 113; Stage IV, 12.
[d] Stage distribution after 2 years of remission: Stage I, 112; Stage II, 31; Stage III, 69; Stage IV, 6.
[e] Stage distribution after 3 years of remission: Stage I, 108; Stage II, 28; Stage III, 44; Stage IV, 4.
[f] Stage distribution after 4 years of remission: Stage I, 89; Stage II, 25; Stage III, 30; Stage IV, 3.
[g] Stage distribution after 5 years of remission: Stage I, 64; Stage II, 19; Stage III, 17; Stage IV, 3.

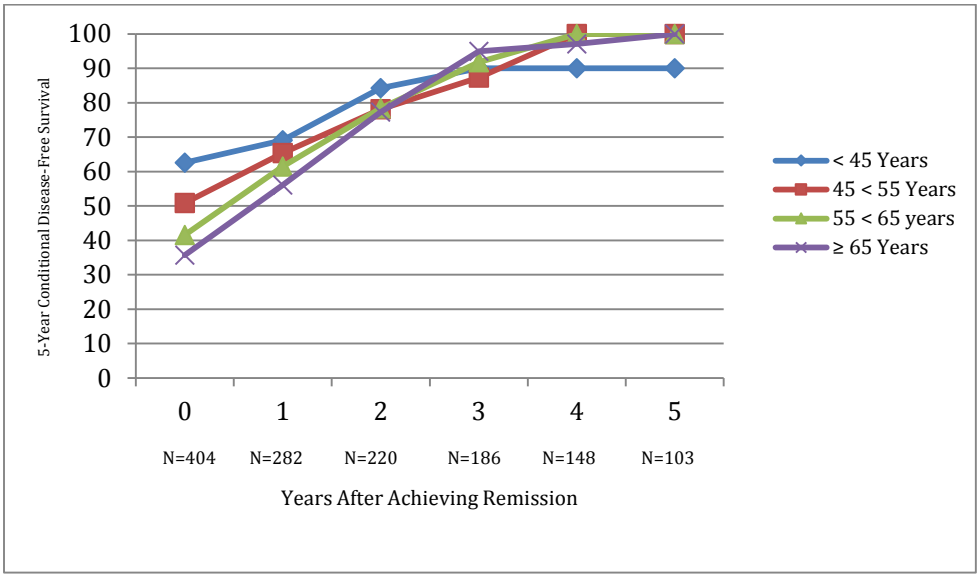

Figure 10. Improvements in 5-Year Conditional Disease-Free Survival, Stratified by Age

5.0 CONCLUSIONS AND PUBLIC HEALTH SIGNIFICANCE

OC accounts for only 3% of new cancer cases among women in the US; however, it is the 5th leading cause of cancer death among women in this country.[2] OC is a multifactorial, heterogeneous disease for which the etiology is not well understood. However, several risk factors have been found to impact the risk of OC. These include age,[5] oral contraceptive use,[49-52] parity,[26-29] breastfeeding,[30-33] and tubal ligation. [34-36] The relationship between OC and other risk factors, such as fertility drug use, remain poorly understood due to conflicting results from previous studies.[26,41-48] Understanding the relationship between fertility drug use and OC risk is complicated by the fact that many women who seek attention for infertility are also more likely to be nulliparous and to have never breastfed. Previous studies assessing the association between fertility drug use and the risk of OC were unable to account for these and other established OC risk factors. The results from the first project of this dissertation provide evidence that fertility drug use does not significantly contribute to the risk of OC in the majority of women. However, we did observe an increased risk of OC among women who remain nulligravid despite infertility evaluation and fertility drug use. This suggests that there may be an underlying biological mechanism associated with the inability to conceive that impacts OC risk to a greater extent than fertility drug use. Given the rising rate of fertility drug use,[116] these results are reassuring for women and their clinicians and build upon the results of previous studies. Although we did not observe a significant association between fertility drug use and OC risk among the majority of women, it is important to continue to evaluate the long-term effects of fertility drugs because this may provide additional insight into OC etiology.

The prognosis for women diagnosed with OC is poor, with an overall 5-year relative survival rate of 44.2%. Women diagnosed with localized disease have much higher estimated

survival, 91.5%, but unfortunately, the majority of women are diagnosed once the disease has metastasized to regional and distant sites. [5] Earlier diagnosis of OC would likely result in significantly improved survival rates; however, screening efforts to diagnosis OC during the early stages of disease have so far been ineffective. [106,107] Results from recent studies have provided evidence that the majority of women experience symptoms prior to their diagnosis and several studies have aimed to develop screening tools that utilize symptoms to identify women at high risk of having OC. [108,109,188] However, there is evidence that the implementation of such a tool would currently result in a high number of false-positives in the general population.[112] Consequently, there is a strong need to improve understanding of symptom presentation prior to diagnosis and identify factors related to symptom presentation that are able to distinguish between healthy women and those with OC. The second project of this dissertation was able to classify women into three groups according to their symptom presentation prior to diagnosis: low symptomatology, moderate symptomatology, and high symptomatology. These groups were defined largely by the total number of symptoms experienced. This suggests that symptom-based screening methods should consider the total number of symptoms. Importantly, we observed no significant differences in the number of symptoms experienced between early and late stage cases, which provides evidence that symptom-based screening methods may be useful in identifying early stage disease. Only a small percentage of the women in our study (13%) were aware of the signs and symptoms of OC prior to their diagnosis. These results suggest that future efforts to educate women about the symptoms of OC should emphasize the seriousness of symptoms when they occur in combination. Increased awareness of OC symptom presentation may prompt more women to seek medical attention for their symptoms during the early stages of disease progression, resulting in improved survival.

The current surveillance guidelines for recurrent OC include frequent physical exams, imaging tests, and the monitoring of CA-125 levels. [97] However, there is controversy regarding the effectiveness of such surveillance to result in improved survival. [98-101] Given the costs of medical testing and the negative psychological effects associated with disease surveillance, there is a need to create personalized surveillance plans. Our third project aimed to determine whether conditional DFS provides more relevant and accurate prognostic information to OC patients and their clinicians. Traditional survival estimates are estimated at the time of diagnosis and may not be relevant to OC patients who have already survived a period of remission. We observed increasing 5-year survival estimates as the time elapsed since the date of remission increased. Furthermore, we found that the initial disparities in survival between age and stage groups diminished over time. This was especially evident among women with late stage disease and those who were diagnosed after the age of 65. The results from this project suggest that the time elapsed since remission may be more important than prognostic factors collected at the time of diagnosis when estimating DFS among OC patients. More accurate methods to estimate the risk of recurrence may help clinicians and patients develop tailored follow-up treatment plans.

The public health implications of this dissertation include an improved understanding of the risk factors associated with OC, symptom presentation of OC prior to diagnosis, and DFS among OC patients. Our results have the potential to inform strategies for assessing the risk of developing OC, OC early detection, and follow-up care of OC. Improvements in each of these areas may lead to lower OC incidence and mortality rates.

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