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A RETROSPECTIVE ANALYSIS OF CLAIMS DATA TO DETERMINE SYMPTOMS ASSOCIATED WITH OVARIAN CANCER

DENISE MANON LANGABEER
UTHealth School of Public Health

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by

DENISE MANON LANGABEER
BBA, THE UNIVERSITY OF TEXAS SAN ANTONIO, 1990
BS, THE UNIVERSITY OF HOUSTON – CLEAR LAKE, 1995
MBA, THE UNIVERSITY OF HOUSTON – CLEAR LAKE, 1997
MPA, SUFFOLK UNIVERSITY, 2004

APPROVED:

TRUDY MILLARD KRAUSE, DRPH
ACADEMIC ADVISOR & COMMITTEE
CHAIR

TRUDY MILLARD KRAUSE, DRPH
CE/THESIS/DISSERTATION
SUPERVISOR

CECILIA GANDULIA CAZABAN, DRPH
COMMITTEE MEMBER

DAVID LOPEZ, PHD
COMMITTEE MEMBER

MICHAEL SWARTZ, PHD
COMMITTEE MEMBER

DEAN, THE UNIVERSITY OF TEXAS
SCHOOL OF PUBLIC HEALTH

DEDICATION

To my parents, Stacy and Marie-Luise Gales

A RETROSPECTIVE ANALYSIS OF CLAIMS DATA TO DETERMINE
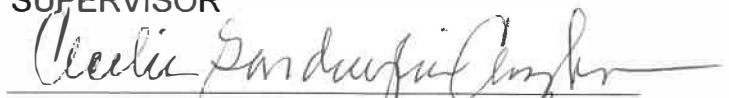
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Presented to the Faculty of The University of Texas

School of Public Health

in Partial Fulfillment

of the Requirements

for the Degree of

DOCTOR OF PHILOSOPHY

THE UNIVERSITY OF TEXAS
SCHOOL OF PUBLIC HEALTH
Houston, Texas
May 2019

PREFACE

I began my career in healthcare over twenty years ago, with the last fourteen in the field of oncology. While I'm not a clinician, the disease is multifaceted and is constantly evolving. Today, in 2019, we are seeing breakthroughs in which one drug can treat different types of cancer. I foresee over the next 20 years, cancer will not be cured, but I am confident many cancers will be managed as a chronic disease, giving survivors not a death sentence but an opportunity to experience a fulfilled quality of life. This has already been demonstrated in certain breast cancers as well as prostate, colon, and lung. Patients are experiencing remission within these cancer indications due to standard of care practices associated with annual screenings, public health organizations promoting methods to reduce exposures to the disease, as well as through outcomes from clinical research. When I first considered the topic for my dissertation, I knew it would be directed in cancer. I was led to ovarian cancer by reading the literature and hearing about patient stories, where many are diagnosed at such a late stage. No annual or effective screening is available, and more importantly, as the patient population is relatively small, commercializing a multi-million dollar therapy is cost prohibitive. When I came across Dr. Goff's research efforts associated with symptoms and further discussed my thoughts around this project with advisors, Drs. Krause and Cazaban, it became clear that evaluating symptoms in commercial claims would be relevant to this field and the findings could potentially contribute to detecting this disease at an earlier stage, receiving treatment before the cancer has spread.

A RETROSPECTIVE ANALYSIS OF CLAIMS DATA TO DETERMINE SYMPTOMS

ASSOCIATED WITH OVARIAN CANCER

Denise Manon Langabeer MBA, MPA, PhD
The University of Texas
School of Public Health, 2019

Dissertation Chair: Trudy Millard Krause, DrPH

According to the American Cancer Society, approximately twenty percent (20% of women with ovarian cancer are diagnosed at an early stage (e.g. stage I or II), which subsequently means eighty percent (80%) of women diagnosed with this disease are at the late stage (e.g. stage III or IV) and are likely not to survive. No cure exists and, concurrently, studies show mixed results in utilizing blood tests and transvaginal ultrasounds to screen for ovarian cancer. While symptoms are not easily discernable, some oncologists have validated there are common symptoms women experience prior to diagnosis. As these symptoms are not routinely recognized by general practitioners as an indicator to detect ovarian cancer, we conducted a retrospective study to determine whether certain types of symptoms are evident prior to the diagnosis. Our two specific aims included: (1) conduct an exploratory study to determine if certain symptoms were prevalent in women that are diagnosed with ovarian cancer; and (2) assess and compare symptoms experienced by women diagnosed with ovarian cancer to women that have not been diagnosed with any type of cancer.   The symptoms were identified by forty-seven (47) International

Classification of Disease, 9th revision (ICD-9), diagnosis codes and categorized into four primary groups: (i) abdominal-pelvis; (ii) bladder; (iii) digestive; and (iv) pain. In conjunction with identifying the type of symptoms experienced, reoccurrence and combination of symptoms were also analyzed. The data to support this study was derived from health insurance claims between 2008 through 2013 from a commercial payer. All subjects for both studies were residents in the state of Texas and were a minimum of 24 years old.

The analysis of the first aim of the study was primarily descriptive to assess symptoms and frequencies experienced prior to diagnosis. Of the 3,601 women diagnosed with ovarian cancer, 2,292 (64%) experienced a related symptom prior to or at diagnosis. Over 60% (n=1544) of women experienced a first symptom associated with abdomen and pelvis and 85% of overall complaints were associated with this group of symptoms. Pain was the second most frequent complaint at 45%, followed by digestive at 24% and bladder at 18%. This was also confirmed in women who experienced a combination of symptoms where abdomen and pelvis along with pain was shown to be the highest complaint at 41%.

The results of the first study consequently led to pursue the second aim which included a nested case control study comparing a subset of 789 women diagnosed with ovarian cancer to women who did not have any history of cancer. The results supported statistical significance in symptoms experienced specific to abdomen and pelvis in conjunction with pain as well as digestive.

While these symptoms are ordinary and are difficult to distinguish as having an association with ovarian cancer, the findings of this research appear to affirm that a

symptom index may prove to be a useful method when recurring complaints are presented in women.

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Background & Literature Review

Ovarian Cancer

Worldwide over 200,000 women are diagnosed with ovarian cancer and 125,000 die on an annual basis (Sankaranarayanan R., 2006). In the U.S., the National Cancer Institute estimates that 22,000 new women are diagnosed with this disease each year. Nearly 50% of the diagnosed cases occur in women under the age of 65 and overall survival is generally less than 5 years (Ovarian Cancer, 2015). It accounts for three percent of cancers among women (Cancer, 2015). While this may appear to be a low figure compared to other cancer mortalities, it unfortunately results in more deaths than any other oncologic disease of the reproductive system (Cancer, 2015). Ovarian cancer begins in the ovaries and is distinguished by three different types of tumors: a) Epithelial, b) Germ Cell, and c) Stromal. Epithelial is the most common type of ovarian cancer, representing 85%-90% of all cases (Cancer, 2015).

This cancer is recognized as an asymptomatic disease and thus is identified as a "silent killer" (Goff B. A., 2007). Unlike other cancers, such as breast, lung, cervical, prostate, colon or skin, no standard screening requirements to evaluate the risk of ovarian cancer are supported by professional organizations such as The American Congress of Obstetricians and Gynecologists or the United States Preventative Services Task Force (USPSTF). While studies show mixed results in utilizing blood

test and transvaginal ultrasounds to diagnose ovarian cancer, leading gynecological experts, such as Dr. Barbara Goff, have validated there are common symptoms women experience prior to diagnosis.   These symptoms are not recognized routinely within clinical practice to detect ovarian cancer and subsequently this may lead to women being misdiagnosed, causing the disease to advance to a later stage. Continued research is necessary to further assess if recurring symptoms are shown to have an association to ovarian cancer and, if so, whether these symptoms can be applied as part of standard of care practice, offering earlier diagnosis, and subsequently leading to earlier treatment and possibly long-term survival.

Symptoms of Ovarian Cancer

Ovarian cancer is difficult to diagnose and when it is discovered, many women are at such an advanced stage of the disease that the therapy is provided for palliative reasons. The survival rate is highly dependent on whether the cancer has spread to other organs, the woman's age, and response to treatment (NCI, 2015). If the disease is confined to the ovary, also known as Stage 1 (localized), five year survival rates can range between 70% and 90% (Cannistra, 2004; NCI, 2015).   Once the disease advances beyond Stage I or Stage II, the average five year survival rate begins to diminish as the cancer has either spread beyond the pelvis and has potentially penetrated the lymph nodes (regional) or metastasized (distant) into other organs. The National Cancer Institute's SEER data suggests that between 2005 and 2011, sixty percent (60%) of women are diagnosed as "distant" and a mere fifteen percent

(15%) are "localized" (NCI, 2015), further affirming that prognosis of this disease is not only dismal, but also requires research to assess opportunities to detect this disease as early as possible (Figure 1).

Figure 1: 5-Year Relative Survival
SEER 18 2005-2011, All Races, Females by SEER Summary Stage 2000
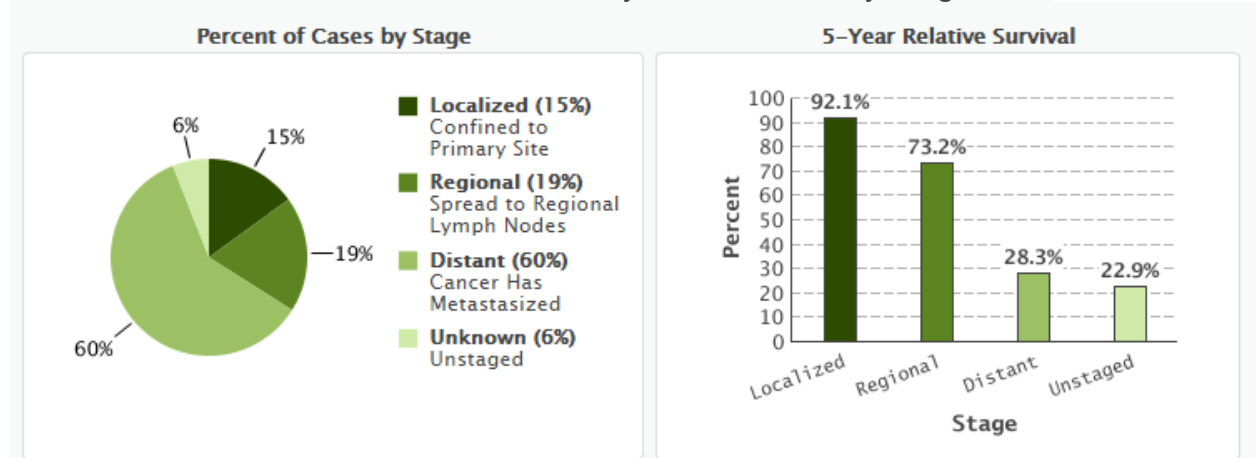
Symptom management of this disease has been limited. In the 1970s, a study of over 5,000 women showed that most patients with ovarian cancer experienced symptoms anywhere from two weeks to ten years prior to diagnosis (Ranney, 1979). This research subsequently has paved the framework for Dr. Barbara Goff, an oncological gynecologist and leading expert in ovarian cancer. Her studies in the last 10 years reveal that common targeted symptoms are evident between six and twenty-four months prior to diagnosis (Goff B. A., 2007) (Goff B. M., 2004). As a result of her research, clinicians now are beginning to recognize common ailments in women that require further investigation.

Several related symptoms addressed in Dr. Goff's research, otherwise known as the "symptom index" set the basis on what other investigators use as part of their methodological framework when evaluating symptoms associated with ovarian cancer. The categories to support these symptoms include areas associated with pain, eating, abdomen, bladder, bowels, menses, intercourse, and other (Goff B. M., 2004). The symptom index is shown to be positive if one or more symptoms occur for less than one year but for more than 12 days per month (Goff B. A., 2007).

Screening

Today, there are several types of screening tests that have shown to identify the risk of breast, lung, cervical, prostate, colon, and skin cancer. These screening tests are endorsed by national organizations such as the U.S. Preventive Services Task Force, American Cancer Society, and American Society of Clinical Oncology and are recognized as standard of care procedures by payers and clinicians. In contrast, there are no standard of care screening methods for ovarian cancer. Over sixty percent (60%) of ovarian cancer cases are found at Stage III and IV (Clarke-Pearson, 2009), which ultimately impacts a woman's survival rate, as the cancer has more than likely spread to other organs, making it very difficult to treat and place the cancer into remission.

Should a physician detect that a woman is at risk of the disease, there are two procedures that are initially performed prior to performing surgery to confirm diagnosis. One is the transvaginal ultrasonography and the other is a blood test known as a CA-125. While both procedures are noninvasive and can offer some

indication if a woman may or may not have ovarian cancer, the specificity and sensitivity of these tests remain questionable on whether early detection (e.g. Stage I) can be determined, thus potentially leading to needless surgeries (Clarke-Pearson, 2009) .

Importance of Earlier Diagnosis

While routine screening methods are not endorsed as standard of care, studies show women that are detected at an early stage (e.g. Stage I) are able to experience five year survival rates as high as 90%. This is primarily because the cancer has not spread outside of the ovary. Unfortunately, though, only a small percentage of women are diagnosed at this stage. Therapeutic options in this disease are beginning to evolve, especially in the field of personalized medicine (i.e. use of genetic profiles in the treatment of cancer), but effective screening, early detection, and cure remain obscure (Rauh-Hain, 2011). For women to benefit from the chemotherapies and simultaneously improve their survival rates, some form of early detection is needed. Although screening tests are not routinely performed, oncologists, such as Dr. Goff, are attempting to implement clinical decision strategies by incorporating a symptom index that will enable physicians to possibly identify whether their patient is at risk of the disease. If the symptoms are evident, then further diagnostic tests can be pursued.

Public Health Significance

Ovarian cancer remains a lethal disease world-wide. While the overall prevalence is much smaller compared to breast and lung cancer, the long-term

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survival rates are one of the worst where 10-year survival is expected to be less than 50%. The main areas that influence the current state of why women are not currently screened as well as why symptoms are not recognized as indicators in this disease include patient awareness, the ordinariness of the symptoms, and current clinical practice. Patient awareness is affected by the lack of information and knowledge in recognizing that certain patterns could be associated with signs of ovarian cancer.

Target symptoms as distinguished in the literature by experts such as Dr. Barbara Goff and others remains in question by clinicians and organizations such as the Centers of Medicare and Medicaid, U.S. Preventative Task Force, American Congress of Obstetricians and Gynecologists, and American Society of Clinical Oncology. In addition to the lack of both patient awareness and understanding of target symptoms, clinicians, in general, do not appear to be familiar with symptoms that are evident in this field of medicine. Unless a physician is trained as an oncologist, the primary care physician or gynecologist is generally not leaning towards cancer as the initial diagnosis. The combination of the patient, the healthcare industry, and the clinicians collectively not recognizing the correlation of the symptoms to ovarian cancer may lead to delays in earlier diagnosis as well as treatment. The proposed research objectives have the potential to contribute to a better understanding of symptom indicators that may be associated with the disease, offering further awareness.

This research is intended to explore whether symptoms are evident in women diagnosed with this disease, and if so, how long and how frequent did the symptoms occur prior to diagnosis.

Specific Aims

The main objective of this research is to determine if there is an association of certain symptoms women experience prior to the diagnosis of ovarian cancer. Outlined below are the primary research questions and related aims for this research:

Research Question 1: What are the frequencies and types of symptoms prior to diagnosis of ovarian cancer?

Aim 1: To evaluate and compare whether certain symptoms exist prior to diagnosis in claims data. Primary symptoms include bloating, increased abdominal size, abdominal pain, pelvic pain, difficulty eating, feeling full quickly and the frequency (Andersen, 2014).

Research Question 2: What is the frequency and type of the symptoms prior to diagnosis in comparison to an aged-matched control group of women who are not diagnosed with cancer?

Aim 2: To determine whether women diagnosed with ovarian cancer indicate a different frequency of target symptoms than the aged-match control group.

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Overview of Methods

Study Design: Both studies involved a retrospective analysis of insurance claims over a five year period. Symptoms for both study aims were identified based on 47 International Classification of Disease (ICD-9) codes specific to pain, abdominal and pelvis, digestive, and bladder. The first study aim (1st Journal Article) was exploratory and descriptive, evaluating symptom complaints prior to diagnosis. The second study aim (2nd Journal Article) supported a nested case control study, which included a cohort of women diagnosed with ovarian cancer and were randomly matched to women who had no history of cancer. The second aim would compare type of symptom complaints and frequencies experienced by women with ovarian cancer to women with no history of cancer.

Study Subjects: Subjects were identified as women diagnosed with ovarian cancer (both studies) and women with no history of cancer (second study aim only).

Sample Size:

Study Aim 1 (1st Journal Article)
- o Women diagnosed with ovarian cancer n= 3601

Study Aim 2 (2nd Journal Article)

- o Women diagnosed with ovarian cancer n=789

- o Women with no history of cancer n=789

- o Total sample size n = 1578

Data Collection: Extraction of claims and related member files (inclusive of date of birth) were based on: a) women diagnosed with ovarian cancer based on ICD-9

diagnosis codes 183.x, malignant neoplasm of ovary, and 233.39, carcinoma in situ of the ovary), b) women with no history of cancer based on the exclusion of any history of cancer based on ICD-9 diagnosis codes of 140.x through 239.x; and lastly c) included all visits (claims) within the observation period.

Data Analysis: Analysis for the first study aim *(1st Journal Article)* was exploratory and descriptive; Analysis for the second study aim *(2st Journal Article)* was descriptive and odds ratios and p values were determined based on conditional logistic regression.

Human Subjects, Animal Subjects, or Safety Considerations: No human or animal subjects were involved in these studies. This study was approved by the Institutional Review Board of The University of Texas – School of Public Health.

Journal Article (1ˢᵗ)

Are Certain Types of Symptoms Experienced Prior to the Diagnosis of Ovarian Cancer?

AUTHORS: Denise Manon Langabeer[1], Cecilia Ganduglia Cazaban[2], Michael D Swartz[2], David Lopez[2], and Trudy Millard Krause[2]

[1]The University of Texas MD Anderson Cancer Center, Houston, Texas   [2]The University of Texas School of Public Health, Houston, Texas

ABSTRACT (236 words)

Are Symptoms Experienced Prior to the Diagnosis of Ovarian Cancer? A Retrospective Study of Insurance Claims Over a Five-Year Period

Denise Manon Langabeer, Cecilia Ganduglia Cazaban, Michael D Swartz, David Lopez, Trudy Krause; The University of Texas MD Anderson Cancer Center, Houston, TX; The University of Texas School of Public Health, Houston, TX

Abstract Text:

Background: The US healthcare system does not support a standard screening method for ovarian cancer, a disease where over 60% of ovarian cancer cases are found at a late stage. The purpose of this study is to determine whether certain types of symptoms are evident prior to the diagnosis. **Methods:** A retrospective analysis of health insurance claims between 2008 through 2013 from a commercial payer based on the following eligibility criteria: 1) women diagnosed with ovarian cancer, 2) at the time of diagnosis, 24 years of age or older, 3) continuously enrolled in healthcare plan for a minimum of 6 months prior to diagnosis, and 4) a Texas resident. Symptoms were based on 47 ICD-9 diagnosis codes and categorized specific to pain, abdominal and pelvis, digestive, and bladder. **Results:** Of the 3,601 of women diagnosed with ovarian cancer, 2,292 (64%) experienced a related symptom prior to or at diagnosis. Over 60% (n=1380) of women experienced symptoms associated with abdomen and pelvis. Over twelve hundred women age 30 and over 65 experienced a first symptom greater than 90 days prior to diagnosis, with the number of unique visits ranging from 1 to 41 per woman. A combination of symptoms occurred in over 50% of women (n=1230). **Conclusions:** Of the 3,601 women diagnosed with ovarian cancer, the majority experienced symptoms prior to diagnosis. Complaints specific to abdomen and pelvis appear to be the most common across all age groups.

INTRODUCTION

While cancer research is producing remarkable outcomes in the field of oncology, ovarian cancer remains a disease with short-term survival. Worldwide, over 200,000 women are diagnosed with this disease and 125,000 die on an annual basis[1]. In the U.S., the National Cancer Institute estimates that over 22,000 new cases occur annually and 14,070 women die due to this cancer[2]. Nearly 50% of the diagnosed cases occur in women under the age of 65 and overall survival is generally less than 5 years[3]. It accounts for three percent of cancers among women[4]. While this statistic may appear to be insignificant compared to other cancers, it results in more deaths than any other oncologic disease of the reproductive system[4].

Ovarian cancer is recognized as an asymptomatic disease[5]. The survival rate is highly dependent on whether the cancer has spread to other organs, the woman's age, race, and response to treatment[6]. Unlike other cancers, such as breast, lung, cervical, prostate, colon or skin, no standard screening requirements to evaluate the potential risk are supported by professional organizations such as The American Congress of Obstetricians and Gynecologists or the United States Preventative Services Task Force (USPSTF). In January 2018, the Journal of American Medical Association published USPSTF's decision that screening for ovarian cancer in asymptomatic women by performing a blood test, known as the cancer antigen 125 (CA-125), or the use of transvaginal ultrasounds are not beneficial, cost effective, and do not provide opportunities for an early diagnosis[7]. The USPSTF has taken this position as a result of recent research that has shown that these screening methods

are inconsistent leading to false positives or unremarkable findings. This was corroborated by the National Cancer Institute's Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial, where nearly 80,000 women were randomized to either obtain annual screening tests using both the CA-125 and the transvaginal ultrasound or proceed with usual care. For women randomized to annual ovarian cancer screening methods, more than 25,000 women were screened utilizing both tests in the first three years of the study, and then subsequently with CA-125 for a period of two years. In total, 6 annual CA-125 tests and 4 annual transvaginal ultrasounds were performed on each women involved in the study[8]. The investigators of the PLCO study followed the women for over 12 years and determined there was no statistically significant reduction in mortality in ovarian cancer between the women that were tested annually versus women who received usual care[8].

Today, innovative therapies are being offered to treat cancer in several indications (e.g. breast, lung, skin and liver). However, it remains a challenge to direct an effective clinical treatment to the ovarian cancer population that leads to long-term survival. The inability to diagnose at an *early* stage and inadequate therapies are two primary reasons this disease is extremely difficult to prevent or cure. Nearly 85% of women will be diagnosed when the cancer has spread or metastasized outside of the ovary, which sadly leads to a premature death[2]. A component of this research is to continue to stimulate awareness of the possible enduring symptoms that recur in ovarian cancer.

When symptoms tend to be ambiguous, time, inadvertently, is used as a diagnostic tool. Without an effective screening strategy to determine early detection of ovarian cancer, symptom research needs to continue and be part of a holistic approach that is inclusive of a diagnostic pathway. Symptom research has been monitored in this disease for several decades. In the 1970s, a study of over 5,000 women showed that most patients with ovarian cancer experienced symptoms anywhere from two weeks to ten years prior to diagnosis[9]. Other later clinical research revealed that common targeted symptoms are evident between six and twenty-four months prior to diagnosis[5, 10]. Goff et al established an ovarian cancer symptom index which has been used in several case-control studies[11]. The index measures whether women experienced certain symptoms specific to pelvic/abdominal pain, difficulty eating, urinary urgency, and bloating prior to diagnosis. The reporting of symptoms in this disease appear to be an indicator to ovarian cancer.

This study is a retrospective analysis of healthcare claims from a large U.S. commercial payer. The primary aim of this research is to assess whether certain symptoms are apparent prior to the diagnosis of ovarian cancer. The research is descriptive and will explore: a) the type of symptoms experienced, b) when the symptoms occurred, and c) how frequently women visited their provider.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board of The University of Texas – School of Public Health. To support the study aim, a retrospective analysis of health insurance claims from a commercial payer between 2008 through 2013 was

performed. A cohort of 4,406 women diagnosed with ovarian cancer was extracted from 3,596,696 unique women. Inclusion criteria for the analysis were the following: a) women diagnosed with ovarian cancer (ICD-9 diagnosis codes: 183, malignant neoplasm of ovary, and 233.39, carcinoma in situ of the ovary); b) residentially lived in the state of Texas, c) enrolled continuously in the plan for a minimum of 6 months prior to diagnosis, d) equal to or greater than 24 years of age at diagnosis. Of the 4,406 women diagnosed with ovarian cancer, 805 women were dropped from the cohort due to: a) diagnosis date was outside of the continuous enrollment periods; and b) diagnosis date before symptom date. This resulted in 3,601 women diagnosed with ovarian cancer to be analyzed (Figure 1).

Related symptoms were identified in the claims by 47 International Classification of Disease (ICD-9) codes specific to pain, abdominal and pelvis, digestive, and bladder (Table 1). As the hypothesis supports a review of symptoms *prior* to diagnosis, any claims that occurred subsequent to the diagnosis date were dropped from the analysis.   Associated symptoms were analyzed by age group, number of visits (based on claims), time period, and combination of symptoms.

The dataset for the analysis was compiled by two separate data files based on the research criteria noted above. The first dataset comprised of enrollees who met the demographic criteria specific to age, enrollment period, and residence.   The second dataset was based on member (n=3,601) claims specific to the cancer diagnosis and symptoms.   Once each dataset met the specifications, the datasets were matched based on member identification number and merged.

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The statistical package used for the analysis was STATA 13.1.   This research primarily reports descriptive analyses and includes the following: i) proportions of the number of women that experienced a visit with symptoms versus no symptoms, ii) the type of first symptoms experienced prior to diagnosis, iii) the number of days the first symptom occurred prior to diagnosis, iv) combination of symptoms experienced, and v) the range of recurring visits by symptom and age.

RESULTS

There were 3,601 women included in the analysis that met the study criteria. Women ranged in age from 24 through 89, with an average age of 53 (SD 12.20). Of the 3,601 women, symptoms prior to the diagnosis were found in 64% (n=2292) (Figure 2). Of the women that experienced symptoms prior to diagnosis, 32% (n=731) were between the age of 50 and 59. The analysis further revealed that 60% of women treated for their first symptom primarily presented with a complaint associated with abdomen and pelvis.   The second most frequent complaint as a first symptom was associated with pain (16%), followed by digestive (13%), and bladder (11%) (Figure 3).

Of the 2,292 women with symptoms, time and the number of visits was reviewed. The following results are described in figures 4 through 6. To understand the *time* between first symptom and diagnosis, the researchers performed an analysis on the number of days the initial symptom occurred prior to the diagnosis.   Women that experienced a symptom on the day of diagnosis were removed from the analysis and further analysis occurred on symptoms that ranged between 1 to greater than 365

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days. Of the 2,292 women, 46% (n=1063) experienced a first symptom under 90 days prior to diagnosis. Women in this analysis from age 30 to over 65 (n=739; 32%) had a first symptom visit over a year prior to diagnosis.

In conjunction with determining the number of days of the first symptom prior to diagnosis, the number of symptom visits by each of the 2,292 women was analyzed. A total of 10,970 visits (correlated with date of service) across all age groups were evaluated. Eighty-five percent (85%; n=1954) complained of symptoms associated with abdomen and pelvis with over 1,400 women experiencing more than one visit. Complaints associated with pain effected forty-five percent (45%; n=1031) of women, with digestive following at 24%, and bladder at 18% (Figure 4). Plot graphs were created to show the distribution of visits for each category of symptoms by number of women. Nearly 500 women experiencing symptoms for abdomen and pelvis went to their physician five or more times. Four women had over 30 recurring visits in this symptom (Figure 5). Each of the other category of symptoms also displayed a range of recurring visits. Over 100 women had five or more recurring visits associated with digestive, with one experiencing forty-one (41) visits (Figure 6). In regards to bladder, these symptoms appear to be less frequent than the other symptoms, however, 138 women did experience between two to eighteen recurring visits (Figure 7). Lastly, symptoms associated with pain ranged between 2 visits to 41, with seventy-two women experiencing five or greater (Figure 8).

Another segment to the analysis involved whether women may have experienced a combination of symptoms. Of the 2,292 women, 54% (n=1,230)

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experienced a combination of symptoms prior to diagnosis. A total of ten different combinations were analyzed. The results showed that 41% experienced symptoms associated with pain along with abdomen and pelvis, and 17% experienced digestive with abdomen and pelvis (Figure 9; Table 2). Combination of symptoms were experienced in all age groups, with 53% in women aged 40 to 59.

DISCUSSION

This research remains relevant as ovarian cancer continues to be recognized as a disease where long-term survival statistics are dismal. Currently, the female gender comprises of nearly 50% of the world population and life expectancy is expected to grow as a result of public health advances, which in turn is also projected to lead to an increase of cancers cases of nearly 10 million with 5.5 million deaths by 2030[12]. Agencies such as the National Cancer Institute, American Cancer Society, and other noteworthy coalitions assert that 50% of ovarian cancer cases occur under the age of 65, with the median age of 63. This statistic was further supported by the commercial claims data used for this research, where 80% of the 3,601 women diagnosed with this disease were between the ages of 30 through 64 (n=2895). This research shows that pre-existing symptoms, especially specific to abdomen and pelvis, appear to exist prior to diagnosis. Of the initial 3,601 women, 64% experienced a related symptom prior to or on the day of diagnosis. Further analysis of the 2,292 women that experienced a symptom, 54% (n=1233) had a first visit between 91 days to over a year *prior* to diagnosis. The frequency of symptom visits ranged from 1 to more than 40 visits.

The investigators recognize that this type of prescreening assessment cannot independently lead to a diagnosis of ovarian cancer.   However, this study does strongly suggest that a taxonomy of symptoms is beneficial as a prescreening approach prior to pursuing tests, such as a CA125 or transvaginal, which can be expensive and also lead to false positives[13]. With most hospitals both in the U.S. and abroad utilizing sophisticated electronic health records and big data analytics (e.g. IBM Watson), evaluation of symptoms in combination with a thorough risk assessment could lead to opportunities for better clinical decisions as well as offering earlier interventions.   While not extensively shown in ovarian cancer thus far, there is research that is demonstrating impactful results in other areas.   For example, in diabetic retinopathy, the investigators applied a clinical decision support system (CDSS) in conjunction with a lab data and patient demographics to detect susceptibility to diabetic retinopathy (DR) with high accuracy[14]. Similar to ovarian cancer, detection of DR is asymptomatic and requires specialized physicians (i.e. ophthalmologists) and expensive tests to assess the risk.   The researchers of the study were able to develop a predictive clinical application that could accurately detect DR at 93% based on a routine blood test[14].

Limitations and Strengths

Insurance claims were historically developed for the purpose to support physician documentation and charge reimbursement, which for purposes of research, such as the one presented, has limitations.   For example, for this study, detailed clinical information about the disease, demographics, and stage of the disease are not

captured in the claims data. Additionally, the claims associated with this study are from a commercial payer, which eliminates any data from women who may be on primary healthcare plans associated with the Centers for Medicare and Medicaid Services. This limits extrapolation of our findings to other populations such as uninsured and lower income women as well as women over the age of 65.

Apart from the limitations of the analysis, this research exhibits strengths. The database used for this study has over 3.5 million women members in the state of Texas, and enabled the investigators to analyze age, time of symptoms to diagnosis, number of visits specific to related symptoms, as well as combination of symptoms without recall bias. Another advantage of using claims data is the ability to evaluate visits across multiple providers.

CONCLUSIONS

Patients routinely experiencing a type of symptom epidemiology want to be referred and diagnosed expeditiously[15]. While meaningful advancements continue to rapidly evolve in diagnostics and genetic testing, ovarian cancer still remains without any type of standard screening method along with limited treatment options. It is inferred that early detection increases the chances for long-term survival. This research supported that over 64% women experienced a related symptom, with the majority experiencing recurring symptoms.

Incorporating a symptomology index as part of the clinical diagnostic strategy may lead to earlier detection[16].   Although the results were not statistically significant, a recent United Kingdom Collaborative Trial of Ovarian Cancer Screening revealed a

15% reduction in ovarian cancer mortality with multimodal screening which included a CA125 based risk of ovarian cancer algorithm (known as ROCA) followed by transvaginal ultrasound, if the ROCA was abnormal[17]. Based on the outcomes of our exploratory retrospective analysis as well as other studies, including prospective clinical studies such as those supported by Dr. Goff, it does appear that more awareness needs to be directed to women and health care providers. In the United States, the National Cancer Institute is disclosing some early results of a NCI-funded study of an experimental pap screening test. The retrospective study detected endometrial and ovarian cancer through DNA collected from blood and tissue[2]. Further research needs to continue, both within the U.S. and globally, to not only validate the efficacy of symptoms related to ovarian cancer, but also whether recurring symptoms are red flags to subsequently promote diagnostic testing whether through traditional methods (i.e. CA-125 blood test, transvaginal ultrasound) or more advanced methods such as molecular pathways evaluating the cytology of the human cells.

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TABLES; ILLUSTRATIONS/FIGURES; UNITS OF MEASUREMENT; ABBREVIATONS AND SYMBOLS

Figure 1 Study Design

Table 1 Symptoms Categorized by ICD9 Diagnosis Codes *(47 codes*

Category	ICD9	Description
Pain	6250	*Dyspareunia*
	6255	*Pelvic congestion syndrome*
	6258	*Other specified symptoms associated with female genital organs*
	6259	*Unspecified specified symptoms associated with female genital organs*
	7245	*Backache*
Abdomen & Pelvis	5340	*Gastritis*
	5781	*Blood in stool*
	6262	*Excessive or frequent menstruation*
	6266	*Metrorrhagia; bleeding unrelated to menstrual cycle; irregular intermenstrual bleeding*
	6267	*Postcoital bleeding; bleeding from vagina after sexual intercourse*
	6268	*Dysfunctional or functional uterine hemorrhage*
	6269	*Disorders of menstruation & other abnormal bleeding from female genital tract; unspecified*
	7890	*Abdominal pain*
	78900	*Abdominal pain; unspecified*
	78901	*Abdominal pain; right upper quadrant*
	78902	*Abdominal pain; left upper quadrant*
	78903	*Abdominal pain; right lower quadrant*
	78904	*Abdominal pain; left lower quadrant*
	78905	*Abdominal pain; periumbilic*
	78906	*Abdominal pain; epigastric*
	78907	*Abdominal pain; generalized*
	78909	*Abdominal pain; other specified site*
	7893	*Abdominal or pelvic swelling, mass or lump*
	78930	*Abdominal or pelvic swelling, mass or lump; unspecified*
	78935	*Abdominal or pelvic swelling, mass or lump; periumbilic*
	78936	*Abdominal or pelvic swelling, mass or lump; epigastric*
	78959	*Ascites - fluid in peritoneal cavity; other specified site*
	7896	*Abdominal tenderness*
	78965	*Abdominal tenderness; periumbilic*
	78966	*Abdominal tenderness; epigastric*
	78960	*Abdominal tenderness; unspecified*
	7899	*Other symptoms involving abdomen and pelvis*
Digestive	5361	*Acute dilatation of stomach*
	5369	*Unspecified functional disorder of stomach*
	7830	*Anorexia (loss of appetite)*
	7831	*Abnormal weight gain*
	7832	*Abnormal weight loss*
	7873	*Flatulence, eructation & gas pain*
	7879	*Other symptoms involving digestive system*
	78791	*Diarrhea*
Bladder	7880	*Renal colic*
	7881	*Dysuria*
	7883	*Urinary incontinence*
	78840	*Frequency of urination & polyuria*
	78841	*Urinary frequency*
	78842	*Polyuria*
	78843	*Nocturia*

Figure 2 Women with Symptoms and No Symptoms

Women with Ovarian Cancer
n=3601

■ No Symptoms (n=1309) ■ Symptoms (n=2292)

	20	30	40	50	60	>65
■ No Symptoms (n=1309)	29	138	233	464	236	209
■ Symptoms (n=2292)	60	281	490	731	322	408

NUMBER OF WOMEN WITH / WITHOUT SYMPTOMS
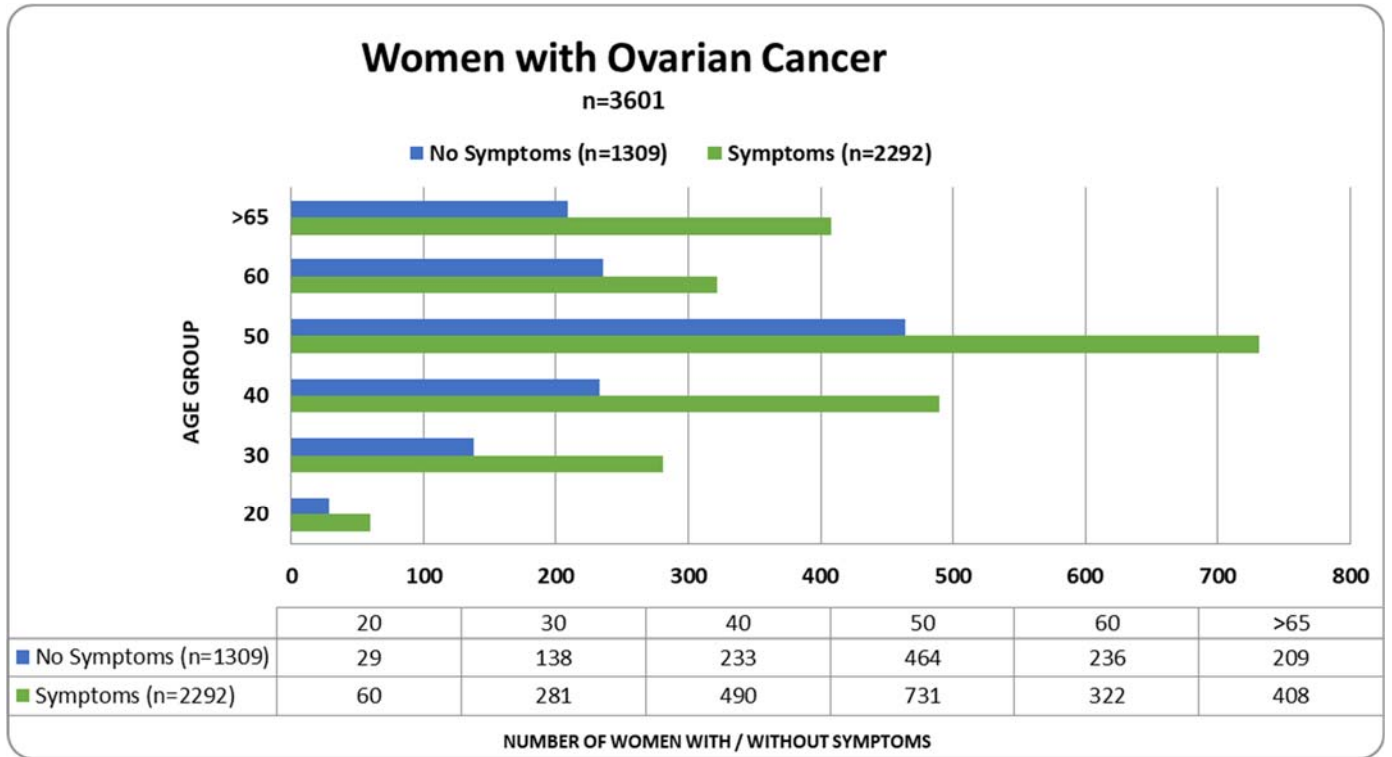
Figure 3 First Symptoms

First Symptom Prior to Diagnosis
n= 2292

- abdom_pelvis
- bladder
- digestive
- pain

1380, 60%
360, 16%
309, 13%
243, 11%
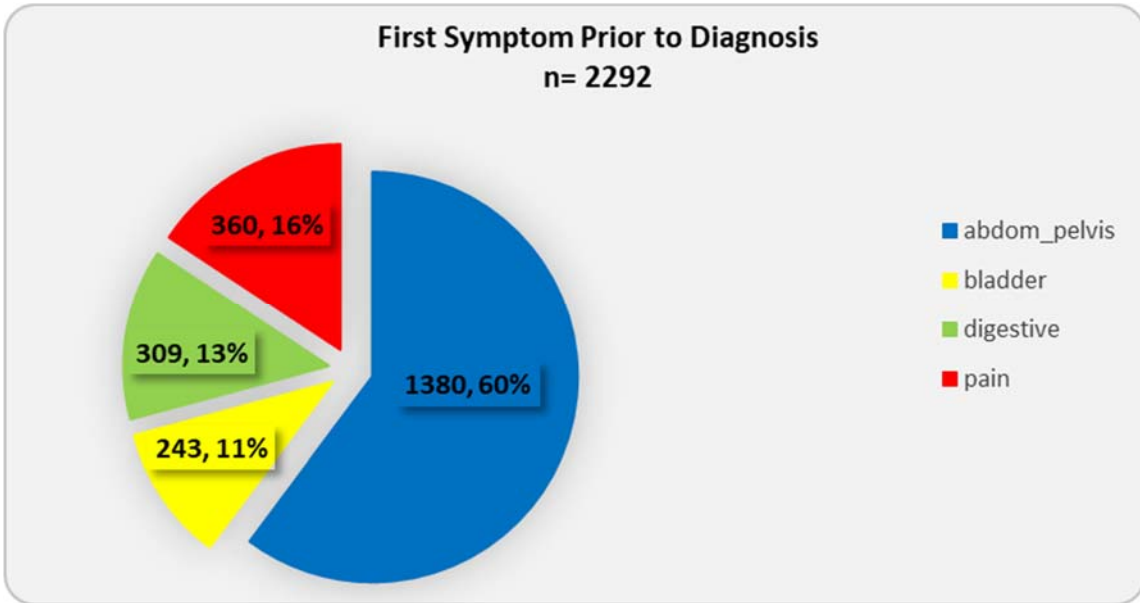
Figure 4 Number of Women Experiencing Recurring Symptoms

34
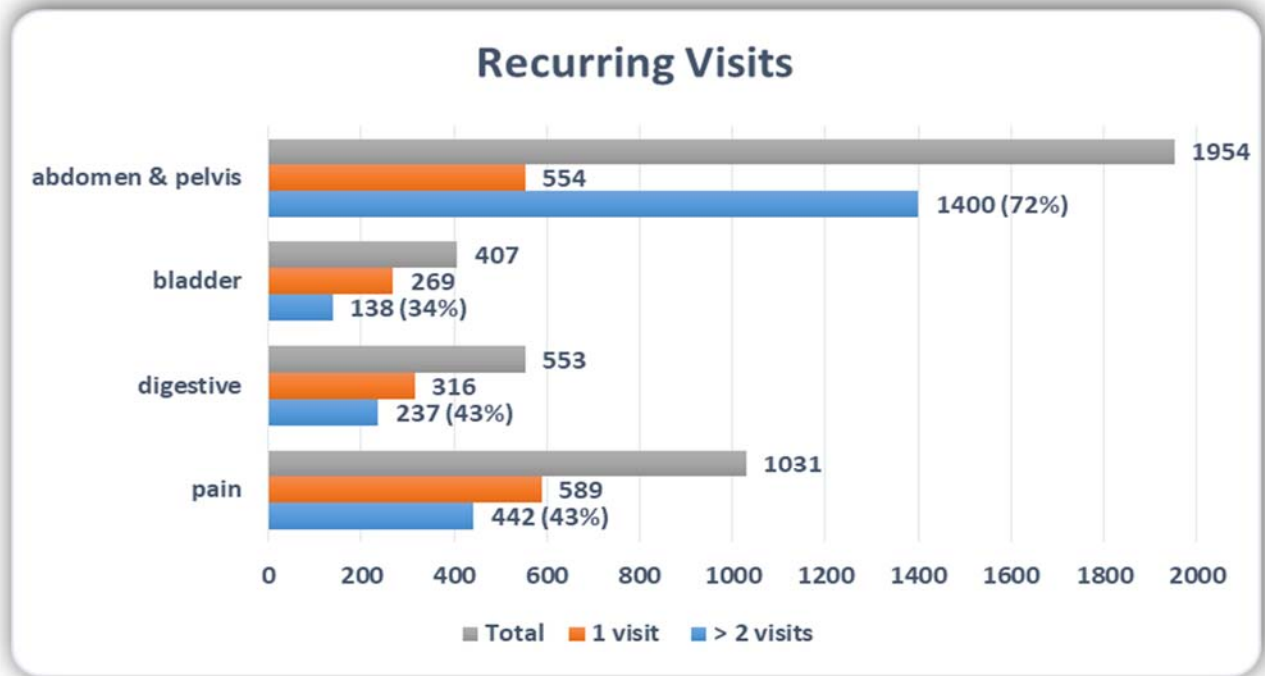
Figure 5 Frequency of Visits by Women for Each Symptom (Abdomen and Pelvis)

Visits	Women	Frequency of Abdomen and Pelvis Symptoms
0	338	*****************************
1	554	**
2	421	**
3	290	**************************
4	196	******************
5	146	*************
6	109	**********
7	67	******
8	42	****
9	33	***
10	18	**
11	16	**
12	13	*
13	15	*
14	5	
15	6	* *85% of women had abdom & pelvis symptoms*
16	3	
17	3	
18	1	
19	1	
20	2	
21	2	
22	2	
23	3	
27	1	
29	1	
31	1	
32	1	
35	1	
38	1	
Total	2,292	

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Figure 6 Frequency of Visits by Women for Each Symptom (Digestive)

Frequency of Digestive Symptoms

Visits	Women	
0	1739	**
1	316	**********
2	117	****
3	46	*
4	36	*
5	7	
6	9	
7	4	
8	4	
9	3	*24% of women had digestive symptoms*
10	1	
12	2	
13	2	
14	1	
16	1	
19	1	
20	1	
21	1	
41	1	
Total	2292	

Figure 7 Frequency of Visits by Women for Each Symptom (Bladder)

Frequency of Bladder Symptoms

Visits	Women	
0	1885	**
1	269	********
2	71	**
3	28	*
4	17	
5	8	
6	3	*18% of women had bladder symptoms*
7	3	
8	1	
9	1	
11	2	
12	1	
14	1	
18	2	
Total	**2292**	

Figure 8 Frequency of Visits by Women for Each Symptom (Pain)

Visits	Women	Frequency of Pain Symptoms
0	1,261	***
1	589	**********************
2	226	*********
3	100	****
4	44	**
5	23	*
6	14	*
7	14	* *45% of women had pain symptoms*
8	5	
9	4	
10	3	
11	1	
12	2	
17	1	
22	1	
23	2	
31	2	
Total	**2,292**	

Figure 9 Combination of Symptoms Experienced By Visits & Age
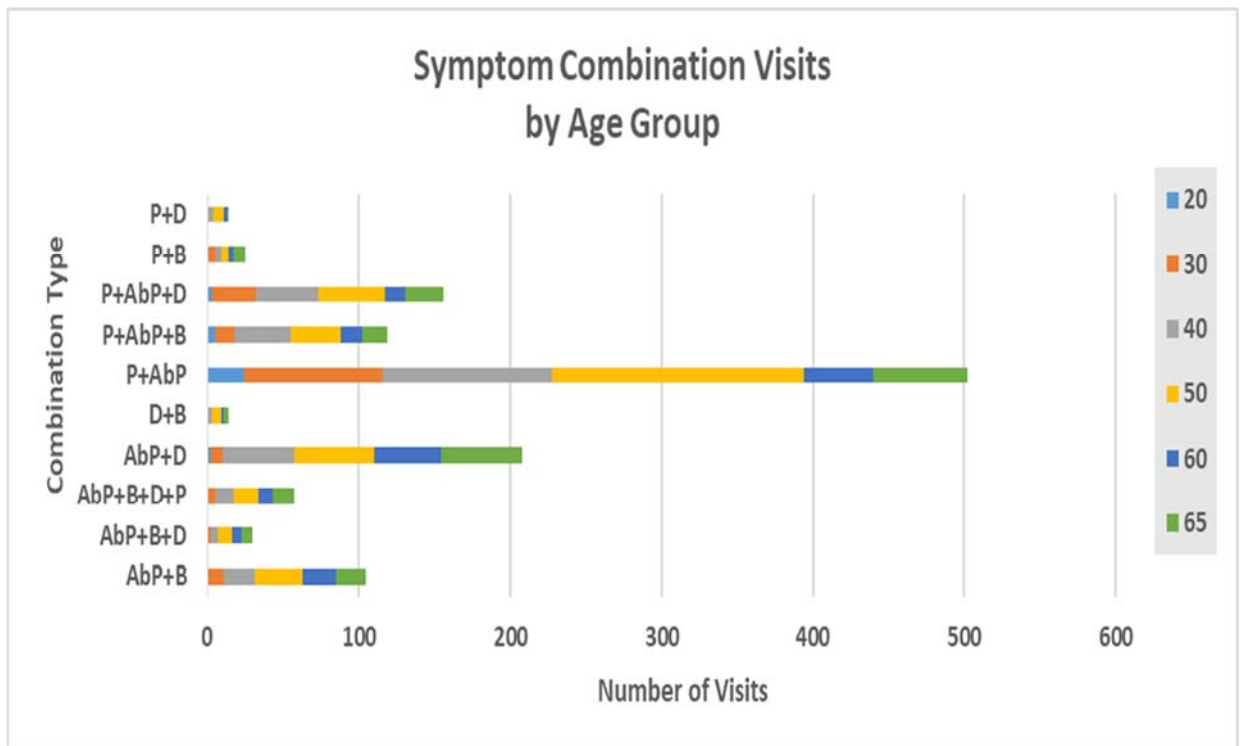
Table 2 Combination of Symptoms Experienced By Visits & Age

Symptom Combination by Age	Age Group						Grand Total	% by Symptom
	20	30	40	50	60	65		
AbP+B	0	11	20	32	22	20	105	9%
AbP+B+D	0	2	5	9	7	7	30	2%
AbP+B+D+P	0	5	12	17	9	14	57	5%
AbP+D	2	8	47	53	44	54	208	17%
D+B	0	1	2	6	2	3	14	1%
P+AbP	24	92	112	166	46	62	502	41% *
P+AbP+B	5	13	37	33	14	17	119	10%
P+AbP+D	3	29	41	44	14	25	156	13%
P+B	1	4	4	5	3	8	25	2%
P+D	1	0	3	7	2	1	14	1%
Grand Total	36	165	283	372	163	211	1230	100%
%	3%	13%	23%	30%	13%	17%	100%	

Legend:

AbP+B	Abdomen and Pelvis + Bladder
AbP+B+D	Abdomen and Pelvis + Bladder + Digestive
AbP+B+D+P	Abdomen and Pelvis + Bladder + Digestive + Pain
AbP+D	Abdomen and Pelvis + Digestive
D+B	Digestive + Bladder
P+AbP	Pain + Abdomen and Pelvis
P+AbP+B	Pain + Abdomen and Pelvis + Bladder
P+AbP+D	Pain + Abdomen and Pelvis + Digestive
P+B	Pain + Bladder
P+D	Pain + Digestive

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Journal Article (2nd Article)

Are Symptoms Distinguishable in Ovarian Cancer? A Nested Case Control Study of Insurance Claims

AUTHORS: Denise Manon Langabeer[1], Cecilia Ganduglia Cazaban[2], Michael D Swartz[2], David Lopez[2], and Trudy Millard Krause[2]

[1]The University of Texas MD Anderson Cancer Center, Houston, Texas   [2]The University of Texas School of Public Health, Houston, Texas

ABSTRACT (401 words)

Are Symptoms Distinguishable in Ovarian Cancer? A Nested Case Control Study of Insurance Claims

Denise Manon Langabeer, Cecilia Ganduglia Cazaban, Michael D Swartz, David Lopez, Trudy Millard Krause; The University of Texas MD Anderson Cancer Center, Houston, TX; The University of Texas School of Public Health, Houston, TX

Abstract Text:

Background: Over 60% of ovarian cancer cases are found at Stage III and IV. The US healthcare system does not support a standard screening method for ovarian cancer. The purpose of this study is to determine whether certain types of symptoms are distinguishable between women diagnosed with ovarian cancer and women without cancer. **Methods:**   Women diagnosed with ovarian cancer were randomly matched 1:1 to women without cancer to support a nested case-control analysis of health insurance claims between 2008 through 2013 from a commercial payer. The following eligibility criteria was applied: 1) 24 years of age or older; 2) continuously enrolled in healthcare plan for a minimum period of 6 months; 3) experienced more than 1 symptom over the observation period; 4) an observation period of a minimum of 6 months; and 5) a Texas resident. Symptoms were based on 47 ICD-9 diagnosis codes and categorized specific to pain, abdominal and pelvis, digestive, and bladder. A total of 1,578 women (789 cases; 789 controls) supported the analysis. **Results:** Sixty percent (60%) of women with ovarian cancer experienced the majority of associated pre-diagnosed symptoms analyzed for the study. Visits occurred over a period of 6 months to 70 months. Overall, ninety percent (90%; n=1,421) of the symptoms were experienced in abdomen and pelvis, with women with ovarian cancer visiting their physician for this complaint at 92% (n=725); OR of 1.66 (CI 1.14 to 2.41; P=.008). Pain was reported as a complaint by cases at nearly 60% (n=464) and controls at 48% (n=376); OR of 1.75 (CI 1.39 to 2.19; P<.001). Symptoms for bladder and digestive combined represented 68% of complaints for both cases (n=507) and controls (n=555), with results supporting no statistical significance to women diagnosed with ovarian cancer. Of the 1,578 women, 77% (cases=621; controls=595) experienced more than one type of symptom. Both cases (n=206) and controls (n=153) complained of both abdomen and pelvis along with pain; OR of 1.54 (CI 1.19 to 1.99; P=.001). A second combination including abdomen and pelvis with pain and digestive was experienced in 14% of women (cases n=99; controls n=67); OR 1.58; CI 1.13 to 2.22; P=.008. **Conclusions:** Certain recurring symptoms associated with abdomen and pelvis as well as pain appear to have indication of exposure to ovarian cancer, signifying that symptom awareness remains relevant to this disease that is diagnosed at a late stage and currently does not have routine screening methods to support early detection.

INTRODUCTION

According to the Centers for Disease Control and Prevention (CDC), average life expectancy for women in the US has risen from 70 years old in 1980 to 80.1 in 2015. Preventive healthcare screenings and innovative therapies are contributing to longer survival. This is evident in certain cancers, such as breast and lung, where the United States Preventative Services Task Force (USPSTF) recommends annual mammograms and low-dose CT scans to detect signs of breast or lung cancer, respectively. Early detection along with choices in therapies have offered women the ability to go into remission for many years.   This is not the case, however, for ovarian cancer, which accounts for 4% of all cancers in women[1]. Worldwide, over 200,000 women are diagnosed with this disease and 125,000 die on an annual basis[2]. In the U.S., the National Cancer Institute estimates that over 22,240 new cases occur annually and 14,070 women die from this cancer[3]. Nearly 50% of the diagnosed cases occur in women under the age of 65 and overall survival is generally less than 5 years[4]. The survival rate is highly dependent on whether the cancer has spread to other organs, the woman's age, race, and response to treatment[4].

Standard screening requirements to evaluate the potential risk are not supported by professional organizations such as The American Congress of Obstetricians and Gynecologists or the United States Preventative Services Task Force. In 2018, The Journal of American Medical Association published USPSTF's position that screenings for ovarian cancer in asymptomatic women with a blood test,

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known as the cancer antigen 125 (CA-125), or transvaginal ultrasound are not beneficial, cost effective, and do not provide opportunities for an early diagnosis[5]. The USPSTF has taken this position as a result of recent research that showed that these screening methods are inconsistent, leading to false positives or unremarkable findings. This was corroborated by the National Cancer Institute's Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial, where nearly 80,000 women were randomized to either obtain annual screening tests using both the CA-125 and the transvaginal ultrasound or proceed with usual care. For women randomized to annual ovarian cancer screening methods, more than 25,000 women were screened utilizing both tests in the first three years of the study, and then subsequently with CA-125 for a period of two years. In total, 6 annual CA-125 tests and 4 annual transvaginal ultrasounds were performed on each women involved in the study[6]. The investigators of the PLCO study followed the women for over 12 years and determined there was no statistically significant reduction in mortality in ovarian cancer between the women that were tested annually versus women who received usual care[6].

While clinical research in ovarian cancer is occurring, it remains a challenge to direct an effective treatment that leads to long-term survival. The inability to diagnose at an *early* stage and inadequate therapies are two primary reasons this disease is extremely difficult to diagnose or, subsequently, cure. Nearly 85% of women will be diagnosed when the cancer has spread or metastasized outside of the ovary, which leads to a premature death[3].

The primary objective of this research is to continue to draw awareness to this disease and to assess whether certain symptoms are able to predict signs of ovarian cancer. Symptom related research has been monitored in this disease for several decades. In the 1970s, a study of over 5,000 women showed that most patients with ovarian cancer experienced symptoms anywhere from two weeks to ten years prior to diagnosis[7]. Other more recent research revealed that common targeted symptoms are evident between six and twenty-four months prior to diagnosis utilizing an ovarian cancer symptom index[8,9]. The index measures whether women experienced certain symptoms specific to pelvic/abdominal pain, difficulty eating, urinary urgency, and bloating prior to diagnosis.

In general, ovarian cancer is perceived as having no disease specific symptoms[8]. Women have a tendency to ignore common symptoms and attribute them to ageing, weight gain or other natural physiological processes[10]. This lack of recognition contributes to a delay in seeking medical attention[10] and subsequently to a late presentation where the disease has metastasized within the lower abdomen[11]. Continuing to perform research to assess if symptoms in this disease are prevalent remains critical for both women as well as clinicians. Evidence-based symptomology of this disease may, at a minimum, provide earlier detection.

This study is a nested case-control analysis of healthcare claims from a large U.S. commercial payer. The primary aim of this research is to assess whether certain symptoms are distinguishable between women diagnosed with ovarian cancer and women who did not develop cancer. The research will explore a relationship between

the types of symptoms experienced as well as the frequency of recurring symptoms in women with ovarian cancer in comparison to women with no history of cancer.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board of The University of Texas – School of Public Health.

Database Description

The data and analysis for this case-control study was based on health claims data from a large U.S. commercial payer that provides health care coverage to over 100 million people. The insurance database and related medical claims were able to support demographic eligibility and study criteria.

Case-Control Study Design

The rationale for this study is to evaluate how associated symptoms compare between women with ovarian cancer (case) to women with no history of cancer (control). The analysis supported visits that occurred between January 1, 2008 through December 31, 2013. Symptoms were identified in both case and control groups by reported claims identified by 47 International Classification of Disease (ICD-9) codes specific to pain, abdominal and pelvis, digestive, and bladder (Table 1). All related symptoms were categorized and analyzed within one of the four symptom groups. Specific to ovarian cancer cases, a review of symptoms *prior* to diagnosis only occurred.   Any claims that occurred subsequent to the diagnosis date were

dropped from the analysis. Symptom visits for controls occurred over the continuous enrollment period.

The women diagnosed with ovarian cancer (case group) comprised of an initial cohort of 4,406 from 3,596,696 unique women. Inclusion criteria for the analysis were based on the following: a) women diagnosed with ovarian cancer (ICD-9 diagnosis codes: 183, malignant neoplasm of ovary, and 233.39, carcinoma in situ of the ovary); b) Texas resident; c) a minimum of 6 months of continuous enrollment in the plan; e) equal to or greater than 24 years of age at diagnosis; and f) experienced a related symptom documented by a specific ICD-9 code. Of the 4,406 women diagnosed with ovarian cancer, 2,308 were dropped due to enrollment periods occurring either prior to January 1, 2008 or subsequent to December 31, 2013, symptoms were identified either on or subsequent to diagnosis date, did not meet the six-month minimum continuous enrollment period prior to diagnosis, did not have an consecutive observation period of a minimum of 180 days, or experience a minimum of two symptoms over the course of the observation period. An additional 1,309 were dropped as no related symptoms were reported prior to diagnosis. This resulted in 789 women diagnosed with ovarian cancer to be matched 1:1 with women with no history of claims associated with cancer.

The control cohort was extracted from the claims database based on the same criteria as the cases with the exception of a cancer diagnosis. Women with history of any type of cancer based on the International Classification of Disease (ICD-9) codes

140.x through 239.x were exempt from the control group.   This resulted in 317,748 controls.

The match was randomly based on the following criteria of each of the 789 cases: a) age at first symptom; b) first symptom experienced; and c) observation period. If a control duplicated to a case based on criteria, a subsequent control with the same criteria was selected. At complete dataset of 1578 (789 cases/789 controls) was created for the analysis. A pair identifier was created to associate a case to control based on the match criteria. This group variable along with a dependent variable supporting women with ovarian cancer (case) or without cancer (control) was applied to the conditional logistic regression when determining the association of symptoms between cases and controls.

This research reports descriptive analyses as well as estimates of odds ratios (OR) with 95% confidence intervals (95%, CI) and statistical significance for the following: i) comparison of type of symptoms in cases and controls, ii) comparison of combination of symptoms experienced, and iii) a summary of visits and observation periods in each category of symptoms specific to cases and controls. The statistical package used for the analysis was STATA 13.1.

RESULTS

The total number of women included in the analysis that met the study criteria and matched was 1,578 (case: 789 / control: 789). Women ranged in age from 24 to 86, with an average age of 51 (SD 12.3065). Four hundred and eighty six women (n=486/1578; 31%) between the age of 50 and 59 represented the largest group of

women in the case control cohort. The analysis further revealed that 54% of women had a first symptom primarily presented with a complaint associated with abdomen and pelvis. The second most frequent complaint was associated with pain (17%), followed by digestive (15%) and bladder (14%). The observation period ranged from 6 months to 70 months. (Table 2).

Women in both cases and controls experienced multiple symptoms throughout the respective observation period. Both individual and combination of symptoms were constructed and analyzed based on the four primary symptom categories of abdomen and pelvis, bladder, digestive and pain. Women in both groups (n=1578) could experience multiple visits associated with one symptom or across multiple symptoms. Overall, ninety percent (90%; n=1,421) of the symptoms were experienced in abdomen and pelvis, with women with ovarian cancer visiting their physician for this complaint at 92% (n=725) and women without cancer at 88% (n=696) (Table 3). This particular group of symptoms produced an OR of 1.66 (CI 1.14 to 2.41; P=.008), indicating that recurring symptoms of abdomen and pelvis may be a predictive indicator of ovarian cancer compared to women without cancer. Following abdomen and pelvis were symptoms associated with pain at 53% (n=840). Cases (59%; n=464) had reported nearly 10% more complaints than controls (48%; n= 376). Results for pain appear to also show an association to risk of ovarian cancer with an OR of 1.75 (CI 1.39 to 2.19; P<.001). Symptoms for bladder and digestive combined represented approximately 68% of complaints for both cases (n=507) and controls (n=555). These

latter symptoms did not support they were predictive symptoms to the diagnosis of ovarian cancer with an odds ratio of .72 and .87, respectively (Table 3).

Of the 1,578 women, 77% (cases=621; controls=595) experienced more than one type of symptom.   In reviewing ten combinations of symptoms, 30% experienced symptoms associated with pain along with abdomen and pelvis, and 17% experienced digestive with abdomen and pelvis (Table 4).   Odds ratios and related confidence intervals support that a certain combination of symptoms experienced in women prior to diagnosis may be discernable in comparison to women without cancer. Compared to the analysis of the individual symptoms, 33% (n= 206) of women with ovarian cancer and 30% (n=153) of women without cancer complained of both abdomen and pelvis along with pain. The OR produced a result of 1.54 (P=.001) revealing that the odds of symptom complaints for women with ovarian cancer to women without cancer were significant, possibly demonstrating an associated risk to the disease. This also applied to symptoms which, again, include abdomen and pelvis, along with pain, and digestive (OR 1.58; CI 1.13 to 2.22; P=.008).

Total number of symptom visits reported within the respective observation months were evaluated in both cases and controls for each category of symptoms. The number of total visits equaled 13,126, with cases experiencing 60% (n=7890) of the visits. The average number of visits for controls equaled 6.63 (SD 5.27) and 10 for cases (SD 7.79). The average age of women experiencing symptoms during the 40 months of observation ranged between 49 and 53.   Visits occurred over an observation period between six months to seventy months. The analysis of each of

the category (digestive, bladder, pain and abdomen and pelvis) of symptoms showed that women with ovarian cancer had an average of more symptom visits per woman (Figures 1 through 4). Additionally, a review of symptoms occurred between 6 months to 40 months (3.33 years), which demonstrated that over 70% of symptoms during this period occurred prior to diagnosis on 80% of the women with ovarian cancer. Comparatively, women diagnosed with ovarian cancer appear to experience, on average, an increase of number of visits associated with all symptoms than women without cancer.

DISCUSSION

Ovarian cancer continues to be recognized as a disease where long-term survival statistics are dismal. Currently, the female gender comprises nearly 50% of the world population and life expectancy is expected to grow as a result of public health advances, which in turn is also projected to lead to an increase of cancer cases of nearly 10 million with 5.5 million deaths by 2030[12]. Agencies such as the National Cancer Institute, American Cancer Society, and other noteworthy coalitions assert that 50% of ovarian cancer cases occur under the age of 65, with the median age of 63. The primary objective of this research was to determine a correlation of symptoms experienced in women diagnosed with ovarian cancer to women who do not develop cancer through a nested case control analysis. The results of the research found that women diagnosed with ovarian cancer experienced 20% more symptom visits in comparison to women without cancer and the association was statistically significant in complaints associated with abdomen and pelvis along with pain.

The investigators recognize that this type of prescreening assessment cannot independently lead to a diagnosis of ovarian cancer. However, this study does strongly suggest that a taxonomy of symptoms remains beneficial as a prescreening approach prior to pursuing tests, such as a CA125 or transvaginal, which can be expensive and also lead to false positives[13]. Evaluation of symptoms in combination with a thorough risk assessment could lead to opportunities for better clinical decisions as well as offer earlier interventions. Additionally, while not part of this research, it would be of interest to possibly reevaluate a portion of the controls on this study who experienced recurring symptoms and assess if a diagnosis of ovarian cancer was eventually determined. The majority of women in this study were fifty and over which links to when the highest rates of diagnosis occur for this disease.

Limitations and Strengths

Insurance claims were historically developed for the purpose to support physician documentation and charge reimbursement, which for purposes of research, such as the one presented, has limitations. For example, for this study, detailed clinical information about the disease, demographics, and stage of the disease are not captured in the claims data. Additionally, the claims associated with this study are from a commercial payer, which eliminates any data from women who may be on primary healthcare plans associated with the Centers for Medicare and Medicaid Services. This limits extrapolation of our findings to other populations such as uninsured and lower income women as well as women over the age of 65. An additional limitation is that certain symptoms are subjective. For example, the

researchers recognize that pain was restricted to five (5) ICD-9 codes – dyspareunia, pelvic congestion syndrome, other to female genital organs, unspecified to female genital organs, and backache. The five types of symptom complaints were included based on prior research related to the symptomology of ovarian cancer. Future research in this area may need to expand the symptoms of pain and better define the type of pain experienced in order to better understand the association to ovarian cancer.

Apart from the limitations of the analysis, this research exhibits strengths. The database used for this study has over 3.5 million women members in the state of Texas, and enabled the investigators to analyze age, time of symptoms to diagnosis, number of visits specific to related symptoms, as well as combination of symptoms without recall bias. Another advantage of using claims data is the ability to evaluate visits across multiple providers.

CONCLUSIONS

Patients routinely experiencing a type of symptom epidemiology want to be referred and diagnosed expeditiously[14]. While meaningful advancements continue to rapidly evolve in diagnostics, genetic testing, and therapies, ovarian cancer still remains without any type of standard screening method along with limited treatment options. As with many cancer diagnoses, the assumption is that the earlier the disease is detected, the chances for long-term survival increase. Educating women and health care providers about related symptoms needs to be part of the diagnostic strategy to increase early detection[15]. This was recognized in the United Kingdom

Collaborative Trial of Ovarian Cancer Screening trial. Although the outcome was not statistically significant, the study did reveal a 15% reduction in ovarian cancer mortality with multimodal screening which includes a CA125 – based risk of ovarian cancer algorithm (known as ROCA) followed by transvaginal ultrasound, if the ROCA was abnormal[16].

In the United States, the National Cancer Institute is disclosing some early results of a NCI-funded study of an experimental pap screening test. The retrospective study detected endometrial and ovarian cancer through DNA collected from blood and tissue[3]. Further research needs to continue, both within the U.S. and globally, to not only validate the efficacy of symptoms related to ovarian cancer, but also whether recurring symptoms are red flags to subsequently promote diagnostic testing through traditional methods (i.e. CA-125 blood test, transvaginal ultrasound) or more advanced methods such as molecular pathways evaluating the cytology of the human cells. A recent prospective study conducted at the Seattle Cancer Care Alliance and the University of Washington incorporated both a symptom assessment and a biomarker marker test to predict ovarian cancer in women with adnexal mass[17]. Women were initially interviewed prior to surgery regarding their symptoms. Symptoms that were shown to recur greater than 12 times in a one month period and were present for less than one year would be considered eligible to participate in the biomarker collection[17]. The results of the study determined that incorporating both methods was effective in determining the risk of the disease and has the potential to improve patient outcomes.

The intent of this research is not to cause alarm, but to continue the awareness of symptoms associated of ovarian cancer and direct recurring symptoms of this disease into an integrative screening method that will lead to earlier referrals to gynecologic oncologists, that in turn, provide earlier diagnosis, which is considered essential in a disease that has dismal outcomes.

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TABLES; ILLUSTRATIONS/FIGURES; UNITS OF MEASUREMENT;

ABBREVIATONS AND SYMBOLS

Table 1: Symptoms Categorized by ICD9 Diagnosis Codes *(47 codes)*

Category	ICD9	Description
Pain	6250	*Dyspareunia*
	6255	*Pelvic congestion syndrome*
	6258	*Other specified symptoms associated with female genital organs*
	6259	*Unspecified specified symptoms associated with female genital organs*
	7245	*Backache*
Abdomen & Pelvis	5340	*Gastritis*
	5781	*Blood in stool*
	6262	*Excessive or frequent menstruation*
	6266	*Metrorrhagia; bleeding unrelated to menstrual cycle; irregular intermenstrual bleeding*
	6267	*Postcoital bleeding; bleeding from vagina after sexual intercourse*
	6268	*Dysfunctional or functional uterine hemorrhage*
	6269	*Disorders of menstruation & other abnormal bleeding from female genital tract; unspecified*
	7890	*Abdominal pain*
	78900	*Abdominal pain; unspecified*
	78901	*Abdominal pain; right upper quadrant*
	78902	*Abdominal pain; left upper quadrant*
	78903	*Abdominal pain; right lower quadrant*
	78904	*Abdominal pain; left lower quadrant*
	78905	*Abdominal pain; periumbilic*
	78906	*Abdominal pain; epigastric*
	78907	*Abdominal pain; generalized*
	78909	*Abdominal pain; other specified site*
	7893	*Abdominal or pelvic swelling, mass or lump*
	78930	*Abdominal or pelvic swelling, mass or lump; unspecified*
	78935	*Abdominal or pelvic swelling, mass or lump; periumbilic*
	78936	*Abdominal or pelvic swelling, mass or lump; epigastric*
	78959	*Ascites - fluid in peritoneal cavity; other specified site*
	7896	*Abdominal tenderness*
	78965	*Abdominal tenderness; periumbilic*
	78966	*Abdominal tenderness; epigastric*
	78960	*Abdominal tenderness; unspecified*
	7899	*Other symptoms involving abdomen and pelvis*
Digestive	5361	*Acute dilatation of stomach*
	5369	*Unspecified functional disorder of stomach*
	7830	*Anorexia (loss of appetite)*
	7831	*Abnormal weight gain*
	7832	*Abnormal weight loss*
	7873	*Flatulence, eructation & gas pain*
	7879	*Other symptoms involving digestive system*
	78791	*Diarrhea*
Bladder	7880	*Renal colic*
	7881	*Dysuria*
	7883	*Urinary incontinence*
	78840	*Frequency of urination & polyuria*
	78841	*Urinary frequency*
	78842	*Polyuria*
	78843	*Nocturia*

Table 2: Summary of Match Criteria

Match Criteria for case controls	case(n=789) / control (n=789)	%
Age at first symptom (years)		
20-29	50	3%
30-39	230	15%
40-49	414	26%
50-59	486	**31%**
60-69	186	12%
>65	212	13%
Total	**1578**	**100%**
First Symptom		
abdom_pelvis	858	**54%**
bladder	226	14%
digestive	232	15%
pain	262	17%
Total	**1578**	**100%**
Observation Months		
6-12 mo.	414	26%
12-24 mo.	520	**33%**
25-36 mo.	332	21%
37-48 mo.	156	10%
49-60 mo.	122	8%
61-70 mo.	34	2%
Total	**1578**	**100%**

First Symptom Experienced
n= 1578 (case & controls)

262, 17%

232, 15%

226, 14%

858, 54%

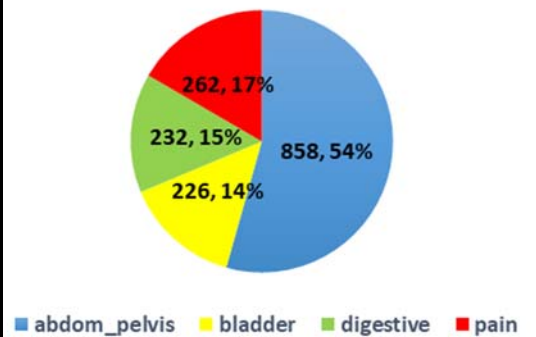■ abdom_pelvis   ■ bladder   ■ digestive   ■ pain

Table 3: Individual symptoms experienced in women with ovarian cancer (case) and women without cancer (controls)

| Symptom	case (n=789)	% Case	control (n=789)	% Control	Total Women	% Total	Odds ratio (95% CI)	P Value
Digestive	281	36%	297	38%	578	37%	.87 (.676 to 1.13)	0.298
Bladder	226	29%	258	33%	484	31%	.72 (.54 to .96)	0.024
Pain	464	59%	376	48%	840	53%	1.75 (1.39 to 2.19)	<.001
Abdom_Pelvis	725	92%	696	88%	1421	90%	1.66 (1.14 to 2.41)	0.008

Table 4: Combination symptoms experienced in women with ovarian cancer (case) and women without cancer (controls)

Combination Visits	case (n=789)	% Case	control (n=789)	% Control	Total Visits	% Total	Odds ratio (95% CI)	P Value
AbP+B	55	9%	73	12%	128	11%	.72 (.49 to 1.04)	0.09
AbP+B+D	22	4%	40	7%	62	5%	.53 (.31 to .90)	0.20
AbP+B+D+P	45	7%	34	6%	79	6%	1.37 (.85 to 2.19)	0.19
AbP+D	89	14%	120	20%	209	17%	.66 (.48 to .92)	0.01
D+B	13	2%	12	2%	25	2%	1.08 (.5 to 2.37)	0.84
P+AbP	**206**	**33%**	**153**	**26%**	**359**	**30%**	1.54 (1.19 to 1.99)	0.001
P+AbP+B	73	12%	63	11%	136	11%	1.85 (.83 to 1.70)	0.36
P+AbP+D	99	16%	67	11%	166	14%	1.58 (1.13 to 2.22)	0.008
P+B	10	2%	22	4%	32	3%	.40 (.18 to .91)	0.028
P+D	9	1%	11	2%	20	2%	.78 (.289 to 2.09)	0.62
Total Women Experiencing Combination of Symptoms	**621**	**100%**	**595**	**100%**	**1,216**	**100%**		

Figures 1 – 4: Frequency of Symptom Visits in women with ovarian cancer (cases) and women without cancer (controls)

Figure 1 – Summary of Digestive Visits

Summary of Digestive Visits (12%)
Case n=281 (817 visits) Controls n=297 (750 visits)
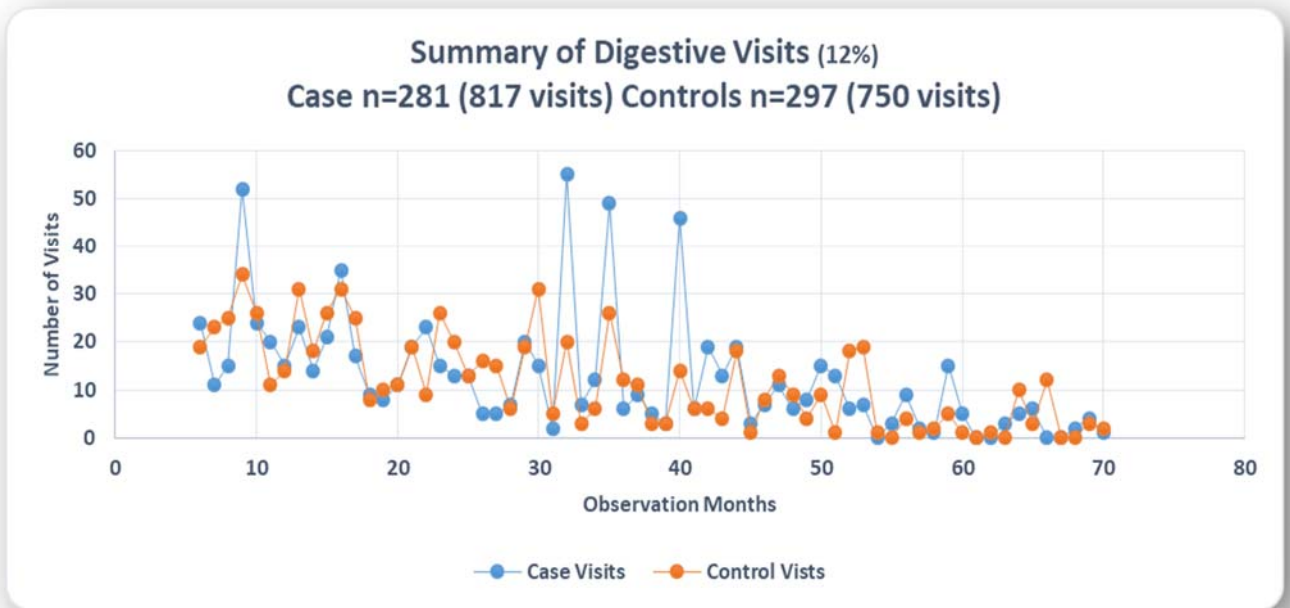
	Case (n=281)		Control (n=297)	
Avg. No. of Visits Per Women	2.91		2.53	
(SD)	2.5		1.9	
% of Visits between 6 mos. to 40 mos.	77%	(n=628)	79%	(n=589)
% of women experiencing digestive symptoms between 6 mos to 40 mos.	78%	(n=220)	81%	(n=461)
Average Age of women with visits between 6 mos. to 40 mos.	53		53	

Figure 2 – Summary of Bladder Visits

Summary of Bladder Visits (9%)
Case n=226 (593 visits) Controls n=258 (554 visits)
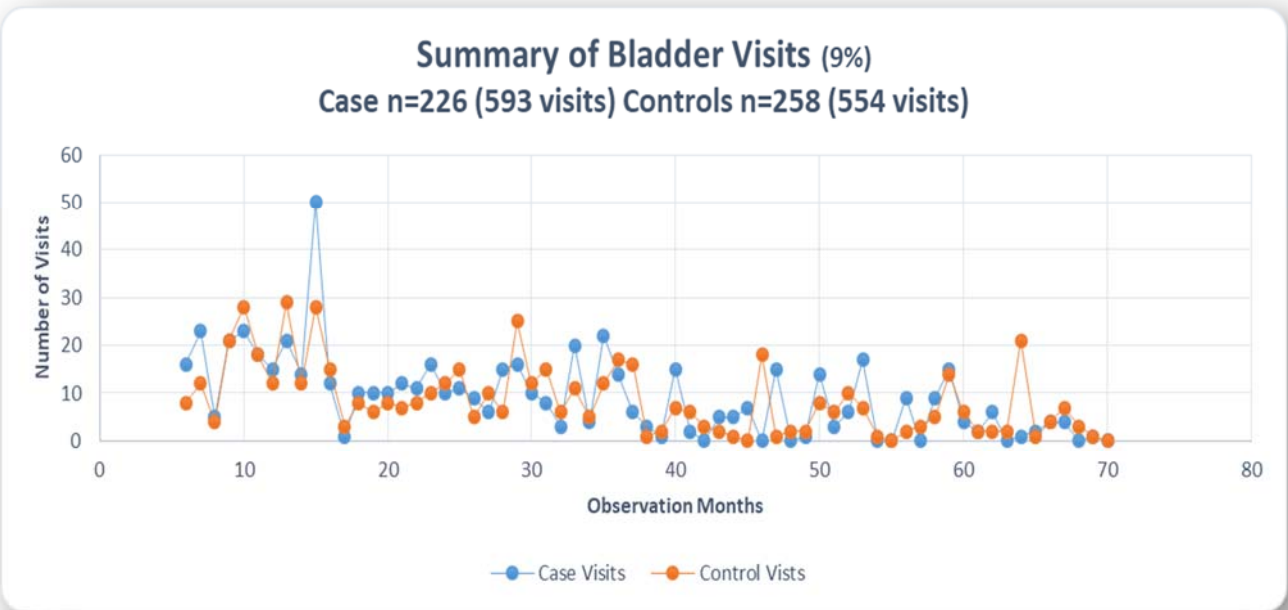
	Case (n=226)	Control (n=258)
Average No. of Visits Per Women	2.62	2.15
(SD)	1.7	1.5
Visits between 6 mos. to 40 mos.	78% (n=461)	75% (n=414)
% of women experiencing bladder symptoms between 6 mos to 40 mos.	81% (n=183)	79% (n=204)
Average Age of women with visits between 6 mos. to 40 mos.	53	53

66

Figure 3 – Summary of Pain Visits

Summary of Pain Visits (17%)
Case n=464 (1326 visits) Controls n=376 (953 visits)
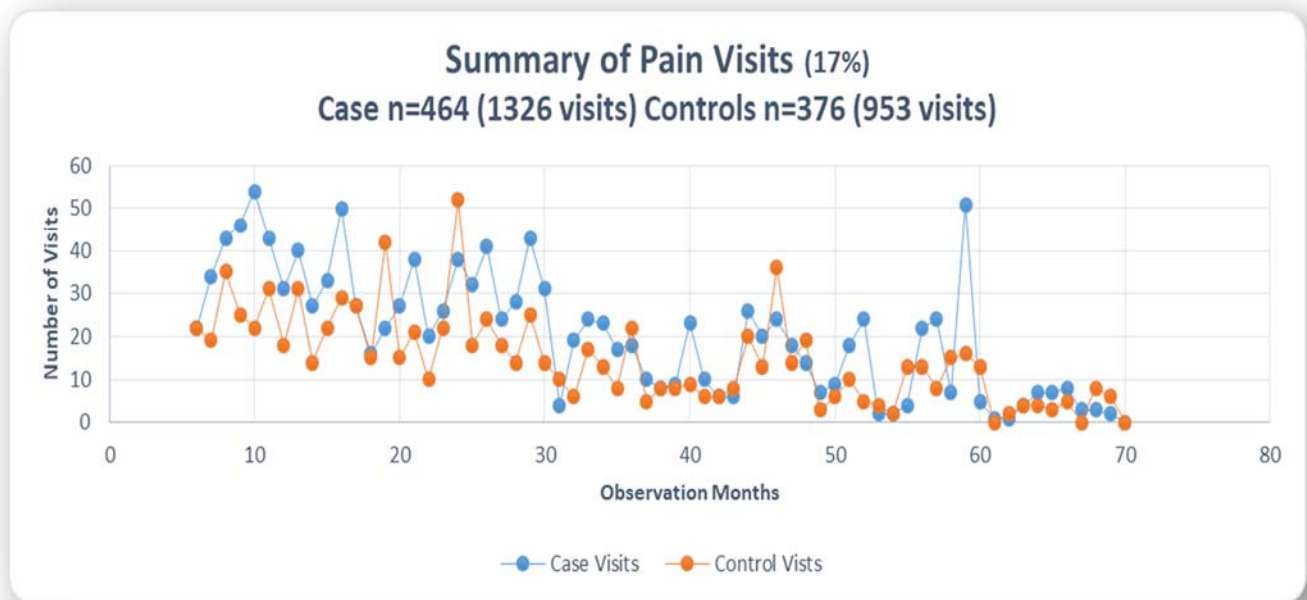
|	Case (n=226)	Control (n=258)
Average No. of Visits Per Women	2.86	2.53
(SD)	2.6	2.2
Visits between 6 mos. to 40 mos.	75% (n=991)	73% (n=691)
% of women experiencing pain symptoms between 6 mos to 40 mos.	82% (n=379)	79% (n=298)
Average Age of women with visits between 6 mos. to 40 mos.	49	50

*Between 50 mos to 60 mos 47 cases experienced 168 visits (~5 visits per women); 39 controls experienced 105 visits (~3 visits per

Figure 4 – Summary of Abdomen - Pelvis Visits

Summary of AbdomPelvis Visits (62%)
Cases n=725 (5154 visits) Controls n=696 (2979 visits)
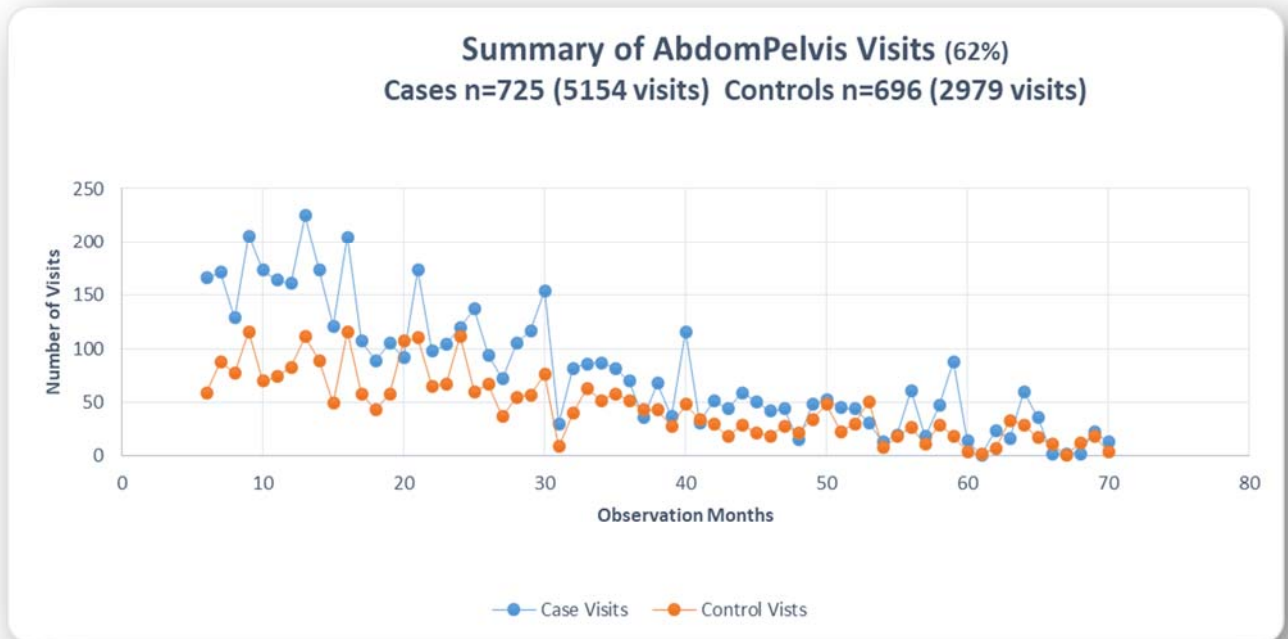
	Case (n=725)	Control (n=696)
Average No. of Visits Per Women	7.11	4.28
(SD)	5.9	3.9
Visits between 6 mos. to 40 mos.	81% (n=4155)	79% (n=2340)
% of women experiencing abdomen and pelvis symptoms between 6 mos to 40 mos.	84% (n=606)	83% (n=581)
Average Age of women with visits between 6 mos. to 40 mos.	51	51