CASE-CONTROL STUDIES OF VAGINAL AND VULVAR CANCERS AND GYNECOLOGIC SCREENING: A SEER-MEDICARE ANALYSIS

BY

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DISSERTATION

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ABSTRACT

The efficacy of performing pelvic examinations and Pap smears screening (gynecologic screening) in older women has been strongly debated among researchers and policymakers. Because of the rare nature of invasive vaginal and vulvar cancers, few epidemiological studies have been performed on this group (Mabuchi, et al. 1985, Brinton, et al. 1990a, Brinton, et al. 1990b) to determine if gynecologic screening reduces the risk of invasive vaginal and vulvar cancers. Previous studies, that have been published, utilized simulated mathematical models and small case-control designs to determine the etiology of vaginal and vulvar cancers, rather than to determine the efficacy of gynecologic screening.

This study utilized two large national population-based linked databases: the Medicare data set supported by the Centers for Medicare and Medicaid (CMS) and the Surveillance Epidemiology and End Results Registries (SEER) data set sponsored by the National Cancer Institute (NCI). The study cases included female Medicare beneficiaries with invasive vaginal and vulvar cancers diagnosed between 1991 and 1999 by the SEER Registries (representing approximately 14% of the United States population) who were 65 years or over and Medicare eligible. The age and residence matched controls were selected from a five-percent (5%) Medicare sample of female beneficiaries 65 years or older, who received care between 1991 and 1999, had not been diagnosed with cancer, and resided in the SEER areas.

This matched case-control design utilized incident vaginal (N=328) and vulvar (N=1,103) cancer cases, respectively from the Surveillance, Epidemiology and End Results (SEER). The study identified vaginal (N=2,624) and vulvar (N=8,825) cancer controls that were matched on age and geographical location to the cases. This study included women, covered by Medicare, who were enrolled in both Parts A and B coverage. These two matched case-control studies

compared cases of persons diagnosed with invasive vaginal or vulvar cancers with non-cancer controls who had not been diagnosed with cancer. The purpose was to investigate whether they had a history of gynecologic screening during the estimated combined duration of the pre-invasive detectable phase (PIDP) when screening is most beneficial, which occurs prior to the occult invasive phase (OIP) (Weiss, 1999).

Stratified analysis suggested that Pap smear and pelvic examination screenings have a stronger negative association among regional (odds ratio (OR) 0.78, 95% CI 0.40-1.51), distant (OR 0.31, 95% CI 0.09-1.03) and unstaged (OR 0.86, 95% CI 0.43-1.70) invasive vaginal cancers. Similar findings were observed for vulvar cancers suggesting that gynecological screening reduced the risk of regional (OR 0.71, 95% CI 0.51-1.00), distant (OR 0.68, 95% CI 0.27-1.70) and unstaged (OR 0.77, 95% CI 0.37-1.59) cancer stages. Borderline significant results were observed among women with invasive vaginal distant stage disease, as well as invasive vulvar regional stage disease. These findings suggest that gynecological screening may be effective in reducing the risk of later stages of disease of both vaginal and vulvar cancers. Women aged 65-74, who had been screened, have a slightly significant decreased risk of vulvar cancer (OR 0.55, 95% CI 0.31-0.97). These findings suggest that screening is most effective in reducing invasive vulvar cancer among women aged 65-74 years old.

Medicare gynecologic screening may be useful even in women who have had negative Pap smear results to reduce the risk of late-stage vaginal and vulvar cancers. This study was unique in that it utilized a larger population-based, matched case-control design that directly measured the effectiveness of these secondary prevention measures in women over the age of 65 years and serves to fill a gap in the current literature.

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CHAPTER 1: INTRODUCTION

Analyses were performed to determine if the use of gynecologic screening is effective in reducing the incidence of invasive vaginal and vulvar cancers in women aged 65 and older; to determine whether specific case and matched control subgroups will have unique gynecological screening histories based on the progression of disease; and to determine the association between gynecological screening test histories and risk of disease by age, race, education, and income subgroups.

Research hypotheses

H1: The use of pelvic examination and Pap smear screening is effective in reducing the incidence of vaginal and vulvar cancers in women aged 65 and older.

H2: Specific subgroups of cases will have unique screening pelvic examination and Pap smear history relationships based on the progression of disease (i.e., localized, regional and distant stages); the more advanced the disease the less likely that the case has had sufficient screening.

H3: There is an association between pelvic examination and Pap smear screenings histories and the risk of invasive vaginal and vulvar cancers, which differs by age (using 10-year strata), race, education and income of zip code areas.

Purpose of the study

The purpose of the study was to determine whether both pelvic examination and Pap smear screenings (gynecological screening) decrease the risk of invasive vaginal and vulvar cancers in women aged 65 or older using matched case-control designs.

The efficacy of performing pelvic examinations and Pap smears screenings in older women has been strongly debated among researchers and policymakers. Because of the rare nature of invasive vaginal and vulvar cancers, few epidemiological studies have been performed on women who had these invasive cancers (Mabuchi, et al. 1985, Brinton, et al. 1990a, Brinton, et al. 1990b). Previous studies have utilized simulated mathematical models and small case-control designs to determine the etiology of vaginal and vulvar cancers, rather than investigating the effects of screening.

Rationale

The purpose of screening tests is to detect pre-invasive cancers, decrease mortality and prevent the development of invasive disease (van den Akker-van Marle, et al. 2002). Screening is designed to detect disease at the preclinical or asymptomatic phase (Wang and Tang, 2010). The disease to be screened should have a long preclinical detectible phase; the severity of the disease must be considered a burden to the population in terms of disability and death, the disease should be be relatively prevalent in the population, and there must be available treatments (Wang and Tang, 2010).

Vaginal cancer is a rare malignancy that accounts for between one-percent (1%) to three-percent (3%) of all gynecological malignancies (Creasman, 2005, Tewari, et al. 2001, Tjalma, et al. 2001). Approximately 2,640 new cases of vaginal cancer and 840 deaths occurred last year (2011) according to the American Cancer Society (ACS, 2012b). Furthermore, the incidence of invasive vaginal cancer increases at older ages. The median age at diagnosis is 68 years (Howlader, et al. 2012).

Vulvar cancer is more common among older women than vaginal cancer. Vulvar cancers account for between five-percent (5%) percent and eight-percent (8%) of all gynecological

maligancies (Stehman and Look, 2006). There are estimated to be 4,490 new cases and 950 deaths for the year 2012 from vulvar cancer (ACS, 2012c). Similar to vaginal cancer, the incidence of invasive vulvar cancer, too, is more often observed at older ages with a median age at diagnosis of 68 years (Howlader, et al. 2012).

Treatment of both vaginal and vulvar cancers carries side-effects, both short and long term. Vaginal and vulvar cancers may be one of the most difficult types of surgery to cope with both emotionally and physically because these genital areas are the most private parts of a woman's body (Cancer Research UK, 2012a , Cancer Research UK, 2012b). Furthermore, many women who are of advanced age with these gynecological cancers may have other conditions that interfere with their recovery and may increase long-term chronic health issues (Fanfani, et al. 2006, Lagana, et al. 2001).

Significance of the study

It is well understood that, since the advent of the Pap smear, which generally is performed during a routine pelvic examination, the incidence of invasive cervical cancer has declined (Waxman, 2005). The Pap smear is a diagnostic laboratory test that is performed to detect inflammation, infection, or abnormal cells of the cervix or vagina for the purpose of early detection of cervical or vaginal cancers (Fischbach and Dunning, 2004). A pelvic examination is a physical examination of the uterus, vagina, vulva, ovaries, bladder and rectum, the purpose of which is to detect cancers, infections, sexually transmitted diseases and other reproductive abnormalities (Fetters, et al. 2003).

Screening measures, such as pelvic examinations and Pap smears, are an important aspect of gynecological health (NCI, 2007). Screening is especially important for the health of older women, because as women age the risk of invasive cancers such as vaginal and vulvar cancers

increases (NCI, 2007). The treatment of invasive disease may include radical surgery, chemotherapy, radiation therapy or a combination of therapies, all of which may result in disfigurement and sexual disability (Madeleine and Daling, 2006). The early detection of pre-invasive vaginal and vulvar cancers, through pelvic examination and Pap smear screening, may prevent the development of invasive disease and thereby, prevent the disabling aspects of treatment.

Based on the preventive nature of these screening protocols, policy recommendations by professional and governmental organizations (such as Centers for Medicare and Medicaid (CMS)) should be consistent in age recommendations at which to stop screening; however, recommendations vary among these organizations. Based on the rare nature of both invasive vaginal and vulvar cancers, few epidemiological studies have been performed to directly measure the effectiveness of screening protocols. Previous studies have utilized simulated mathematical models and small case-control designs that estimate the etiology of vaginal and vulvar cancers, rather than the preventive nature of screening . This study is unique in that it has a large population-based, matched case-control design that directly measured the effectiveness of these secondary prevention measures in women age 65 and older and serves to fill this gap in the literature.

Design and overview of the study

This study utilized two large national population-based linked databases: the Medicare data set supported by the Centers for Medicare and Medicaid (CMS) and the Surveillance Epidemiology and End Results (SEER) data set funded by the National Cancer Institute (SEER-Medicare, 2003). The study cases included those women with invasive vaginal and vulvar cancers diagnosed between 1991 and 1999 by the SEER Registries (representing approximately

14% of the United States population) who were 65 years or older and Medicare eligible. The age and residence matched controls were selected from a five percent (5%) Medicare sample of female beneficiaries receiving care between 1991 and 1999 who had not been diagnosed with cancer, were 65 years or older and resided in the SEER areas.

This study included women, covered by Medicare, who had enrolled in both Parts A and B coverage. This matched case-control design compared cases of persons diagnosed with invasive vaginal or vulvar cancers with controls to determine whether they had histories of screening during the estimated combined duration of the pre-invasive detectable phase (PIDP), which occurs prior to the occult invasive phase (OIP).

Conditional logistic regression was used to test the hypothesis that the presence of screening is effective in reducing the risk of invasive vaginal and vulvar cancers. Furthermore, specific groups of cases (i.e., with localized, regional and distant cancers) were stratified to estimate the efficacy of screening for different stages of invasive disease. Stratified regression analysis was performed to test the second hypothesis of whether the efficacy of screening varies among the various case strata during the OIP/PIDP interval. The OIP is the phase in which abnormal cancer cells have become invasive. Screening tests are intended to detect abnormal cancer cells during the PIDP, not after they have become invasive. The relationships between Pap smear and pelvic examination screenings and the risk of invasive vaginal and vulvar cancers was assessed in population subgroups based on strata defined by age, race and educational and income level of zip code area.

CHAPTER 2: REVIEW OF THE LITERATURE

Introduction

Carcinomas of the vagina and vulvar are both rare malignancies. While vaginal cancer is one of the most rare, accounting for approximately one-percent (1%) to three-percent (3%) of gynecological malignancies (Tjalma, et al. 2001, Creasman, 2005, Tewari, et al. 2001); vulvar cancer accounts for approximately five (5) to eight (8) percent of all gynecological malignancies (Higgins, 2011, Stehman and Look, 2006). Vaginal cancer is generally identified by direct visual examination of the vagina and an abnormal Pap smear (Creasman, 2005); while vulvar cancer is identified during a routine pelvic examination (Stehman, 1997).

The incidence rates for both invasive vaginal and vulvar cancers increase with increasing age (Creasman, 2005, Madeleine and Daling, 2006, Ozalp, et al. 2005), which suggest that, on the basis of epidemiological data, older women have a higher rate of gynecologic malignancies such as endometrium, myometrium, ovary, vulva and vagina, as well as other organ malignancies (Ozalp, et al., 2005). Furthermore, the side effects of invasive cancer treatment can be disabling (Quinn, 2007). This suggests the need for screening protocols specifically for older women (previously discussed in Chapter 1: Rationale section). However, few epidemiological studies that directly measure the association between screening tests, such as Pap smears and pelvic examinations on vaginal and vulvar cancers, provide useful information in the development of consistent screening protocols.

Structure of literature review

In order to understand the impact of studies and gaps in the literature it is important to understand the process by which both vaginal and vulvar cancers develop. To help explain these anomalies, the following literature review will progress as follows:

- *Vaginal cancer*
    - Natural history
    - Incidence and mortality
    - Demographic patterns
    - Histopathology and risk factors
    - Symptoms and treatment
    - Prior vaginal cancer research (case-control studies)
- *Vulvar cancer*
    - Natural history
    - Incidence and mortality
    - Demographic patterns
    - Histopathology and risk factors
    - Symptoms and treatment
    - Prior vulvar cancer research (case-control studies)
- *Prior research* (case-control studies) that relate specifically to both vaginal and vulvar cancers
- *Screening*
    - Definition and rationale for screening
    - Current policy recommendations for gynecologic screening

- Medicare gynecologic screening policies
- Definition of screening pelvic examinations and Pap smears
- Mechanism of vaginal and vulvar cancer screening
- Screening and diagnosis of vaginal cancer
- Staging of vaginal cancer
- Screening and diagnosis of vulvar cancer
- Staging of vulvar cancer

Vaginal cancer

Natural history

The natural history of vaginal cancer depends on the histologic distinction between squamous cell carcinoma and adenocarcinoma since each histologic type has a distinct pathogenesis (DiDonato, et al. 2011). However, the majority of invasive vaginal cancers are squamous cell carcinomas (approximately 86%-90%) (Madeleine and Daling, 2006, DiDonato, et al. 2011). Approximately five-percent (5%) of tumors are clear-cell adenocarcinomas that have a peak incidence between the ages of 17 and 21 (Madeleine and Daling, 2006, DiDonato, et al. 2011). Clear cell adenocarcinomas are rare and occur most commonly in patients younger than 30 years and are associated with vaginal adenosis (DiDonato, et al. 2011). Vaginal adenosis is most commonly arises from maternal diethylstilbestrol (DES) exposure during pregnancy (DiDonato, et al. 2011). Histologic types such as melanomas and sarcomas are rarely categorized as primary vaginal cancers (NCI, 2012). Therefore, these histologic types were not included this study's analysis data set.

Squamous cell carcinoma is the most common type of vaginal cancer and primarily affects older women (ACS, 2012c). Squamous cell carcinoma develops in the epithelial lining of

the vagina most often in the area closest to the cervix (ACS, 2012c). This type of cancer may exist over a period of many years at a premalignant stage called vaginal intraepithelial neoplasia (VAIN) (ACS, 2012c).

- *Squamous cell carcinoma*

  In the majority of cases (approximately 85%), vaginal cancer initially spreads superficially within the vaginal wall and later invades the paravaginal tissues and the parametria (NCI, 2012). In general, squamous cell carcinoma that originates in the epithelial lining of the vagina can be localized for many years (Stern, 2011). Eventually, the carcinoma invades the epithelial lining of the vaginal walls (Stern, 2011). Left untreated, the tumor will spread directly to the tissue that surrounds the vagina, the pelvic walls, bladder and/or rectum (Stern, 2011).

- *Adenocarcinoma and clear cell adenocarcinoma*

  This type of vaginal cancer typically develops in women over the age of 50 (ACS, 2012c). Adenocarcinoma is a type of cancer that begins in the epithelial cells that line the vagina and have glandular (secretory) properties (Kretschmann, 2002). This type of adenocarcinoma accounts for approximately five-percent (5%) of cases (ACS, 2012c). The risk factors for adenocarinoma in older women may be exposure to the human papillomavirus (HPV) and a history of abnormal cells in the cervix (ACS, 2012c).

  Clear cell adenocarcinoma is rare and occurs most often in women who are less than 30 years old who have a history of maternal diethylstilbestrol (DES) exposure (NCI, 2012). The incidence of clear cell adenocarcinoma peaked in the mid-70s, reflecting the use of DES in mothers during the 1950s (NCI, 2012). DES is an oral synthetic non-steriodal estrogen that was prescribed to pregnant women at risk for miscarriage between 1938 and 1971

(Schrager and Potter, 2004). The U.S. Food and Drug Administration issued a warning in 1971 against the use of DES based on new information relating to the association between in utero DES exposure and vaginal clear cell adenocarcinoma (Schrager and Potter, 2004).

Incidence and mortality

Vaginal cancers are rare and account for only about one-percent (1%) to three-percent (3%) of female genital tract malignancies (Creasman, 2005, Tewari, et al. 2001, Tjalma, et al. 2001). In 2011, there were approximately 2,640 new cases of vaginal cancers and 840 deaths reported (ACS, 2012b). The median age at diagnosis for cancer of the vagina is 68 years old (Howlader, et al. 2012). The mortality rate from 2005-2009 was 2 per 1,000,000 (Howlader, et al. 2012).

Demographic patterns

- *Age*

  According to the National Cancer Institute, most of the invasive vaginal cancers have been observed in older women (NCI, 2012) and the disease is seen most often in women between the ages of 60 and 79 (Creasman, 2005). However, clear cell adenocarcinoma resulting from in utero exposure to DES has usually been observed in adolescents after age 14 and has a peak incidence at age 19 (Bardawil, 2010).

- *Race*

  The 5-year survival rate was 47% for black females compared to 56% for white females 20-69 years of age (Kosary, 2007a). The 5-year relative survival was 39.1% for black females compared to 41.7% for white females 70+ years of age (Kosary, 2007a).

Histopathology and risk factors

The most common histological type of vaginal cancers reported to the SEER registries are squamous cell in origin (86%), followed by eight-percent (8%) adenocarcinoma, two-percent (2%) melanoma and four-percent (4%) other histologies (Madeleine and Daling, 2006).

Table 1 describes two models that suggest that vaginal cancer may exist as two separate types of cancer. Type 1 is related specifically to the exposure of DES, while Type 2 is squamous cell in origin. The exposure of DES in utero is a known risk factor for clear-cell adenocarcinoma that is typically found in younger women (Bardawil, 2010, Schrager and Potter, 2004). Offspring of pregnant women who took DES during pregnancy are at a higher risk of developing vaginal cancer, particularly clear cell adenocarcinoma (Schrager and Potter, 2004). Clear cell adenocarcinoma was most likely to develop in women with in utero DES exposure after age 14, and peak incidence is at age 19 (Bardawil, 2010). Since the focus of this study was on women who are over the age of 65, it is likely that there will be very few women with clear cell adenocarcinoma due to DES exposure in this study.

Table 1. Types of vaginal cancer

Characteristic	Type 1	Type 2
Age	Younger (after age 14 and peak incidence at age 19 years)	Older (Average ~68)
Cervical neoplasia	High association	High association
Cofactors	DES exposure	Increasing age
Histopathology of tumor	Clear cell adenocarcinoma	Squamous cell carcinoma
HPV DNA	No association	Frequent (> 60 percent)
Pre-existing lesion	CIN/VAIN/adenosis	CIN/VAIN
History of condyloma	Rare association	Strong association
History of sexually transmitted disease (STD)	Rare association	Strong association
Cigarette smoking	Low prevalence	High prevalence
Number of sexual partners	No association	Strong association
Previous abnormal Pap smear	Strong association	Strong association
Prior hysterectomy	No association	Strong association
Vaginal trauma (pessary use)	No association	Strong association
Vaginal adenosis	DES exposure	No association

The following are explanations of each of the risk factor characteristics as described in Table 1.

- *Cervical neoplasia*

  A history of prior dysplasia or invasive carcinoma of the cervix has been reported in approximately 30% of patients with vaginal carcinoma (Hellman, et al. 2004). Vaginal and cervical carcinomas have etiologies in common (Hellman, et al. 2004). The vagina and the cervix are lined with the same type of squamous cell epithelium and are embryologically

related (Hellman, et al., 2004). The major difference between vaginal and cervical carcinoma is that they occur in different age groups. Cervical carcinoma mainly occurs in women younger than 60, while vaginal carcinoma occurs mainly in older women (Hellman, et al. 2004).

- *HPV DNA*

  Oncogenic HPVs have been strongly associated in the development of squamous cell carcinoma of the vagina (Type 2) (Hellman, et al. 2004, Feng and Kiviat, 2005, Bardawil, 2010, Daling, et al. 2002, Hildesheim, et al. 1997b, Jamieson, et al. 2006). According to Bardawil (2010), the two types with the highest oncogenic potential are HPV subtypes 16 and 18, and infection with these subtypes can be linked to dyplastic changes in the female genital tract (Bardawil, 2010).

- *Number of sexual partners*

  Sex with multiple partners may be a risk factor for the disease since HPV is a sexually transmitted disease (Bardawil, 2010, Brinton, et al. 1990b).

- *Abnormal Pap smear*

  In general, an abnormal vaginal Pap smear in women who have not had a hysterectomy is usually vaginal neoplasia (Creasman, 2005). However, an abnormal Pap smear is usually an indication of possible neoplasia of the cervix rather than vagina, although studies have suggested CIN can extend to the vagina (Creasman, 2005). Vaginal intraepithelial neoplasia (VAIN) is usually located in the upper third of the vagina and more than half to two-thirds of all patients with VAIN have been treated for either cervical or vulvar neoplasia (Creasman, 2005). Furthermore, for patients who have been treated for cervical neoplasia, VAINs can appear many years later (Creasman, 2005). An increased risk for vaginal cancer

exists among women with two or more abnormal Pap smears (Brinton, et al. 1990b). A history of abnormal Pap smears was found among HIV-infected women with vulvar, vaginal or anal intraepithelial neoplasia (Jamieson, et al. 2006).

- *Smoking*

  Cigarette smoking places women at increased risk for vaginal cancer (Greene, et al. 2002).

- *Condyloma*

  There are more than 40 HPV types that affect the genital areas of both males and females. While most condyloma or genital warts are associated with HPV Types 6 and 11 that are associated with vaginal cancer, there may be other subtypes that contribute both condyloma and the development of vaginal cancer (such as high risk HPV types 16 and 18) (Nuovo, 2006).

- *Prior hysterectomy*

  The risk for vaginal carcinoma is highest in women who had a prior hysterectomy before the age of 40 (Brinton, et al. 1990b). The association between primary vaginal carcinoma and hysterectomy might be due to ambiguous surgical margins occurring with residual CIN or occult disease (Hellman, et al. 2004). In patients who have had a hysterectomy for benign disease, a subsequent Pap smear screening may not be beneficial based on the rare nature of vaginal cancer (Creasman, 2005). However, primary vaginal neoplasia does occur more frequently among women with prior hysterectomy for benign disease and is more common today than several decades ago (Creasman, 2005).

- *Vaginal trauma (pessaries use)*

  Pelvic organ prolapse affects 50% of parous women over the age of 50 (Fernando, et al. 2006). The treatment for pelvic organ prolapse has included non-surgical procedures such as

pelvic floor exercises and vaginal pessaries (Fernando, et al. 2006). One study of cancer and pessary use conducted by Schraub, et al. (1992) found that pessaries had been used by 30% of vaginal carcinoma cases. Furthermore, long-term pessary use and chronic irritation of vaginal mucosa in women with procidentia (complete failure of genital supports) has been associated with vaginal cancer (Bardawil, 2010).

- *Vaginal adenosis*

  Vaginal adenosis is a specific abnormality of the vagina (ACS, 2012c). Women affected are those who mothers took diethylstilbestrol (DES) during pregnancy. DES was a hormone used to prevent miscarriage in the U.S. from the years 1950 until 1971 (ACS, 2012c).

Symptoms and treatment

The most common signs and symptoms of invasive vaginal cancer include:

- *vaginal discharge* (often bloody) which is the most frequent symptom (Stehman, 1997)
- *irregular or postmenopausal vaginal bleeding* (Stehman, 1997)
- *gross lesion* (detected via pelvic examination) (Stehman, 1997)
- *urinary symptoms* (vaginal cancer can result in compression of the bladder, usually during the early stages of disease) (Stehman, 1997)

The elasticity of the upper vaginal area allows for large lesions to grow, which may not be detected, especially in women who are not sexually active (Stehman, 1997). These lesions are usually detected during late stages of the disease possibly because many patients are older women, sexually inactive and less likely to have routine pelvic examinations. In addition, the diagnoses may be delayed by virtue of the rare nature of the disease, as well as a possible delay in relating symptoms to vaginal cancer (Bardawil, 2010).

The treatment of invasive vaginal cancer depends on the histologic type, stage, location of the lesion, presence or absence of the uterus and history of previous radiation therapy (Bardawil, 2010, Stehman, 1997). Treatment consists of radiation therapy, surgery, chemotherapy or a combination of these treatments (Bardawil, 2010). In general, however, stage IVa treatment consists of both radiation therapy and pelvic exenteration (radical surgery that removes all organs from the pelvic cavity) (Bardawil, 2010). Pelvic exenteration is performed if a rectovaginal (abnormal connection between the rectum and vagina) or vesicovaginal (abnormal connection between the urinary tract and the vagina) fistula is present (Bardawil, 2010). If surgery for stage IVb cancer is not recommended, then radiation therapy is recommended for the palliative purposes only (relief of symptoms) (Bardawil, 2010).

Case-control studies

The purpose of Brinton, et al. (1990b)'s study was to investigate a pattern of risk for those cases with *in situ* and invasive vaginal carcinoma and shared etiology with cervical cancer. The cervical cancer risk factors included reproductive and sexual factors, selected hygiene factors, Pap smear screening history, selected medical conditions (sexually transmitted diseases and previous cervical cancer diagnosis), menopause status, oral contraceptive use and smoking status.

The study consisted of 41 pathologically confirmed cases diagnosed with *in situ* or invasive vaginal cancer and 97 controls. The cases ranged in age from 20 to 79 years, while the controls ranged in age from 20 to 69 years. Efforts were made to match at least two controls of the same age (within 5 years), race and area of residence to one case.

All of the cases reported having a Pap smear at least one year before diagnosis and all but four controls reported a previous Pap smear. Of particular interest to this study, the findings did

not suggest whether the presence of screening was effective in reducing vaginal cancer (i.e., all the cases had a previous Pap smear). However, a significant increased risk was found among subjects with two or more abnormal Pap smears (RR 6.7, 95% CI 1.8-25.9) even after cases with a history of cervical cancer were eliminated and risks were adjusted for type of cancer and age at menopause.

The low response rate (48.2% of cases and 57.1% of controls agreed to participate in the study) may not have allowed the researchers to stratify on age. Another important aspect would have been the examination of the relationship of *in situ* and invasive vaginal cancer to specific risk factors such as Pap smear history.

The purpose of Daling, et al. (2002)'s population-based, case-control study was to investigate the etiology of *in situ* or invasive squamous cell cancer of the vagina and the potential relationship to HPV. The study included 156 cases and 2,041 controls between the ages of 18 and 74 years. Interviews of cases and controls were conducted that included demographic, reproductive, contraceptive, medical, sexual and smoking histories. In addition, blood samples were requested at the end of the interview and 94.2% of cases and 89.5% of controls consented. Tumor blocks were also requested of cases for HPV testing; 67.9% cases consented to testing.

The results of the study suggest that HPV negative cases were found more frequently among somewhat older women, further supporting the hypothesis that HPV DNA may not be a critical risk factor in the development of invasive vaginal cancer among older women (Table 1). Furthermore, *in situ* tumors were more common among younger women; while invasive vaginal cancer was more common among older women. During the interview process, subjects were asked about abnormal Pap smear history. Among women who had a previous hysterectomy, but

no history of anogenital cancer, 75.5% had an abnormal Pap smear history compared to 18.1% of similar controls.

The limitations of the study include the low participation rate among both cases and controls. Of the 256 potential cases, 156 were interviewed for a 58.9% response rate (51 refused, 30 physicians refused and 28 women died). Of the 2,784 potential controls, 2,041 (67.7%) agreed to participate in the study. In addition, the measure of HPV exposure was limited to HPV 16 and HPV 18 subtypes only. There were other oncogenic HPV subtypes there were not investigated. Another limitation of interest to this study is that, while some Pap smear histories were taken, they were restricted to women who had previous hysterectomies. The study was not able to perform stratified analyses by age due to the small number of cases.

The study conducted by Hildesheim, et al. (1997b) tested the serologic response to HPV16 VLPs, HSV2 and *c. trachomatis* and risk of carcinoma of the vagina. The case-control study included 23 histologically confirmed cases of *in situ* or invasive vaginal cancer and 28 controls. Both cases and controls ranged in age from 20 to 79 years. In-person interviews were also conducted to collect data on risk factors such as socioeconomic status, a history of an abnormal Pap smear and a previous diagnosis of cervical cancer.

The results of the Hildesheim, et al. (1997b)'s study suggest that the greatest risk was among subjects with high levels of antibodies against HPV16 VLP (RR 33.0, 95% CI 2.5-430) and for those positive for evidence of infection with all three antibody sexually transmitted agents (RR 17.0, 95% CI 1.3-220). After adjustment for HSV2 and *c.trachomatis*, the increased HPV16 VLP associated risk was not reduced (RR 3.4. 95% CI 0.79-15). However, risk was reduced for HSV2 and *c. trachomatis* after adjusting for the two other sexually transmitted agents (RR 2.1, 95% CI 0.31-14 and RR 1.7, 95% CI 0.34-8.4, respectively).

Even though the results were statistically significant, this study was limited by the small sample size (23 cases and 28 controls). Risk in different age strata was not described, possibly due to the small sample size. Furthermore, Pap smear and pelvic examination histories were not reported.

Summary of case-control studies

The case-control studies described above were conducted primarily to investigate the etiology of vaginal cancer (Table 2). Overall, the conclusions suggest that the risk of invasive vaginal cancer is increased among women who report a history of abnormal Pap smears (Brinton, et al. 1990b, Daling, et al. 2002). In addition, both Daling, et al. (2002) and Hildesheim (1997b) found oncogenic HPV DNA to be a risk factor among women with invasive vaginal cancers; however, Daling et al. (2002), suggests that the risk is increased only among young women and that HPV negative cases are found primarily among older women. Hildesheim (1997b) was unable to report stratified data by age due to the very small sample, thereby the findings do not provide this study with similar results as the Daling, et al. (2002) study. Furthermore, these studies also had small sample sizes and the prevention measures such as Pap smears and pelvic examination histories were not reported in all of the studies.

Table 2. Vaginal cancer: case-control studies

	Diagnosis year	Study	Cases	Controls	Purpose	Age
Brinton, Nasca, Mallin, Schairer, Rosenthal, Rothenberg, Yordan and Richart (1989)	1986	Case-control	41	97	Types of vaginal cancer	20-79
Daling, Madeleine, Schwartz, Shera, Carter, McKnight, Porter, Galloway, McDougall, Tamimi (2002)	1991-1998	Case-control	156	2,041	Etiology of vaginal cancer	18-74
Hildesheim, Brinton, Nasca, Richarts, Jones, Ziegler and Schiller (1997b)	1985-1987	Case-control	23	28	Sexually transmitted agents	20-79

Vulvar cancer

Natural history

The etiology of vulvar cancer depends on the histologic subtype (squamous cell carcinoma and basal cell carcinoma) (Stehman and Look, 2006). The majority (90%) of vulvar cancer tumors are squamous cell carcinomas (Canavan and Cohen, 2002). Melanomas, sarcomas, basal cell carcinomas, Bartholin gland carcinomas, adenocarcinomas and undifferentiated histologies, are the other histological subtypes (Stehman, 1997).

- *Squamous cell carcinoma*

  There are different subtypes of squamous cell carcinoma of the vulva, one that is associated with HPV and one that is not (Stehman and Look, 2006). The vulvar intraepithelial neoplasia (VIN) that arises from HPV exposure predisposes women to invasive disease (Canavan and Cohen, 2002). This type most frequently occurs among younger women (Canavan and Cohen, 2002). Conversely, the second type that is not HPV related is associated with vulvar non-neoplastic epithelial disorders (VNED) and occurs at older ages leading to cellular atypia and cancer (Canavan and Cohen, 2002).

- *Basal cell carcinoma*

  Most of the vulvar cancers that appear in younger women arise in a field of warty or baseloid VIN and approximately 80% of those with warty VIN develop invasive disease (Canavan and Cohen, 2002).

- *Paget disease*

  Paget disease is primarily a disease of older post-menopausal women and most prevalent in whites (Wilkinson and Stone, 2008).

Incidence and mortality

Vulvar cancers are not as rare as vaginal cancers and account for approximately five-percent (5%) to eight-percent (8%) of all gynecological malignancies (Stehman and Look, 2006). There are estimated to be 4,490 new cases, and 950 deaths for the year 2012 from vulvar cancer (ACS, 2012a). The median age at diagnosis for vulvar cancer is 68 years (Howlader, et al., 2012).

The mortality rate 2005-2009 was 5 per 1,000,000 (Howlader, et al. 2012). However, mortality rates increase as age increases. For patients younger than 20, none of the patients died from vulvar cancer (Howlader, et al. 2012). Deaths for patients between the ages of 20 and 34 was 0.6%, ages 35 and 44, 2.4%, ages 45 and 54, 12.0%, ages 55 and 64, 17%, between 65 and 74, 30.8% and 85 and over 29.8% (Howlader, et al. 2012).

Demographic patterns

- *Age*

  While vulvar cancer has been observed in young women (approximately 15%) it is most commonly observed among women who are in their seventies (approximately 30%) (Stehman and Look, 2006), and the rate increases with age, reaching a peak of 20 per 100,000 women by 75 years of age (Canavan and Cohen, 2002).

- *Race*

  The 5-year relative survival rate was 81.6% for black females compared to 81.4% for white females 20-69 years of age (Kosary, 2007b). The 5-year relative survival rate was 59.9% for black females compared to 66.5% for white females 70+ years of age (Kosary, 2007b).

Histopathology and risk factors

The SEER registries report that most vulvar cancers are 92% squamous cell followed by two-percent (2%) basal cell, two-percent (2%) melanoma, two-percent (2%) Paget's disease and two-percent (2%) "other" histologies (Madeleine and Daling, 2006).

Canavan and Cohen (2002), suggest that squamous cell vulvar cancer may be two separate types of cancer as illustrated in Table 3. Warty, basaloid or keratinizing patterns characterize squamous cell vulvar cancer (Madeleine and Daling, 2006). Type 1 is warty or basaloid and tends to be due to infection with oncogenic HPV (Madeleine and Daling, 2006, Canavan and Cohen, 2002). An estimated 80% of younger women with warty or basaloid vulvar intraepithelial neoplasia (VIN) who remain untreated will develop invasive disease (Canavan and Cohen 2002).

Type 2, keratinizing vulvar cancer, on the other hand, has an undifferentiated morphology (Canavan and Cohen 2002). This type includes vulvar non-neoplastic epithelial disorders (VNED) and is observed at an advanced age (Canavan and Cohen, 2002). This type is not associated with HPV infection and often appears with lichen sclerosus or epithelial hyperplasia leading to cellular atypia and cancer (Madeleine and Daling, 2006, Canavan and Cohen, 2002).

Table 3 describes the etiology of the two types of vulvar cancer.

Table 3. Types of vulvar cancer

Characteristic	Type 1	Type 2
Age	Younger (35 to 65 years old)	Older (55 to 85 years old)
Cervical neoplasia	High association	Low association
Cofactors	Age, immune status, viral integration	Vulvar atypia, possibly mutated host genes
Histopathology of tumor	Intraepitelial-like (baseloid)	Keratinizing; squamous cell carcinoma
HPV DNA	Frequent (> 60 percent)	Seldom (< 15 percent)
Pre-existing lesion	VIN	Vulvar inflammation, lichen sclerosus, squamous cell hyperplasia
History of condyloma	Strong association	Rare association
History of sexually transmitted disease (STD)	Strong association	Rare association
Cigarette smoking	High incidence	Low incidence
Number of sexual partners	Strong association	Low association
Previous abnormal Pap smear	Strong association	Strong association

- *Prior history of cervical cancer*

  Jones and Rowland (2009) suggest that women who have previously been treated for pre-invasive or invasive disease in the cervix or vagina have an increased risk of developing invasive vulvar cancer.

- *Human papillomavirus (HPV)*

  HPV has been strongly associated in the development of squamous cell carcinoma of the vulva (Madeleine, et al. 1997, Jones and Rowland, 2009). There are etiologic pathways leading to the development of vulvar cancer that do not involve HPV, especially among older women (Madeleine, et al. 1997). Judson, et al. (2006) suggest that there are different age distributions

for invasive vulvar and cervical cancers, particularly in combination with patterns of *in situ* disease, which suggests that factors other than HPV are related to the development of invasive vulvar cancer especially in older women. The Basta, et al. (1999) study finds statistically significant results in women under the age of 45 with respect to HPV and non-significant findings among women over age 45 years.

- *Number of sexual partners*

  Brinton, et al. (1990a) suggests that an increasing number of sexual partners increase the risk of invasive vulvar carcinoma.

- *History of abnormal Pap smear*

  Patients with a history of abnormal cervical cytology have an increased risk of invasive vulvar carcinoma (Stehman and Look 2006, Jones and Rowland 2006).

- *Smoking*

  Cigarette smoking is associated with increased risk of vulvar carcinoma (Stehman and Look, 2006, Madeleine, et al. 1997, Brinton, et al. 1990a). Mabuchi, et al. (1985), conducted a case-control study of the epidemiology of vulvar cancer and ascertained smoking habits and found that among current smokers, a significantly increased OR (2.46, $p<0.05$) was obtained for individuals smoking ten (10) to 20 cigarettes per day.

- *Condyloma*

  Women with a history of condyloma, gonorrhea and HSV have an increased risk of both carcinoma *in situ* and invasive vulvar carcinoma (Stehman and Look, 2006, Jones and Rowland, 2006). A case-control study, conducted by Mabuchi, et al. (1985) with 149 cases with histologically confirmed vulvar carcinoma and the same number of patient controls without vulvar cancer that were matched for age, race, marital status and hospital from five (5) U.S.

metropolitan areas, suggested that condyloma or genital warts was present in five-percent (5%) to 10% of vulvar cancer cases.

Symptoms and treatment

The most common symptoms of invasive vulvar cancer are:

- *chronic, persistent itching* (ACS, 2012a)
- *distinct tumor on the vulva*
- *painful urination, bleeding and discharge not associated with normal menstruation*
- *ulcer that persists for more than a month* (ACS, 2012a, Stehman, 1997)

Many of these symptoms can occur with other conditions; therefore, sometimes practitioners fail to recognize the presence of invasive vulvar carcinoma (ACS, 2012a).

The type of treatment depends on histology, stage and location of the lesion (e.g., whether bowel or bladder involvement exists) (ACS, 2012a). Early stage disease treatment options include laser surgery, wide local excision or a skinning vulvectomy (a little thicker amount of skin is excised) (ACS, 2012a). However, even in stages I and II vulvar cancer treatment options include a partial radical vulvectomy, which includes the removal of superficial and deep groin lymph nodes or sentinel node biopsy (sentinel nodes are the lymph nodes to which cancer cells are likely to spread from the primary tumor) (ACS, 2012a). Stage III includes a radical vulvectomy with removal of lymph nodes (ACS, 2012a). However, recently, therapeutic options also include combination therapies, such as chemotherapy and radiation therapy, followed by surgery (ACS, 2012a).

Later stage disease (stage IV) includes a radical vulvectomy and other surgery (dependent on the metastases to other organs), such as pelvic exenteration that includes a vulvectomy and removal of the pelvic lymph nodes and one or more organs (lower colon, rectum, bladder, uterus, cervix and vagina) (Higgins, 2011). Chemotherapy may be required pre-surgery and radiation therapy may be required post-surgery (Higgins, 2011). Surgery may not be advised (based on the size of the tumor

and organ involvement) and radiation and chemotherapy may be the preferred treatment option (Higgins, 2011). In this case, chemotherapy and radiation therapy may be prescribed to treat symptoms (palliative care), not for curative purposes (Higgins, 2011). Women with late stage (stage IV) vulvar cancer are encouraged to enter clinical trials where they may receive new therapies that may be beneficial (ACS, 2012a). The five-year survival rate for women with late stage (stage IV) vulvar cancer is only 20% (Higgins, 2011).

Case-control studies

The case-control study by Basta, et al. (1999), collected Pap smears to obtain specimens from the vulva and performed a colposcopic examination of the cervix, vagina and vulva in all cases of vulvar intraepithelial neoplasia (VIN) and early stage vulvar cancer. The study investigated the role of HPV types 6, 11, 16, 18, 25, 31, and 33 in the development of VIN and early stage vulvar cancer (Basta, et al. 1999). Pap smears were also used to obtain specimens from 178 cases (68 women under the age of 45 and 110 women over the age of 45) from the vulva and a colposcopic examination of the cervix, vagina and vulva was also performed. The 115 controls (between the ages of 24 and 76) were both colposcopically and cytologically negative.

However, in accordance with the vulvar cancer model presented in this study (Table 3), the relative risk (RR) for VIN and VIN1 showed a statistically significant increased risk in women under 45 years old associated with HPV infection (RR 11.34, $p<0.001$), and non-significant results for women over 45 years (RR 1.43). HPV infection is less strongly associated with vulvar cancer in older women than in younger women. While the study utilized Pap smears and other evaluation techniques, neither histories of previous Pap smears nor pelvic examination histories was investigated.

The Brinton, et al. (1990a), Parazzini, et al. (1993) and Sherman, et al. (1994), studies collected information relative to Pap smear histories via interview to test their hypotheses. The

Brinton, et al. (1990a)'s study was designed to investigate the etiology of carcinoma of the vulva. Risk factors investigated included measures of sexual behavior, menstrual, reproductive and hygiene factors, smoking history, contraceptive methods, history of sexually transmitted diseases and selected risk factors such as number of sexual partners, Pap smear history, genital wart history and current smoking status. The study group consisted of 209 pathologically confirmed cases of women with *in situ* or invasive vulvar cancer and 348 controls, matched on age (within 5 years), race and residence. The ages of the cases ranged from 20 to 79 years, while the control ages ranged from 20 to 69 years.

Of particular interest to this study (Osterbur's), Brinton, et al. (1990a) further examined the relationship of *in situ* and invasive disease to specific risk factors such as number of sexual partners, Pap smear history, genital wart history and smoking status. The relative risk of *in situ* vulvar cancer was greatest for cases who had between five to nine sexual partners (RR 5.08, 95% CI 1.7-14.8), ever had genital warts (RR 18.50, 95% CI 5.5-62.5) and current smoker (RR 4.65, 95% CI 2.2-10.0) (Brinton, et al. 1990a). The relative risk of invasive vulvar cancer was greatest for cases that had between three and four sexual partners (RR 3.32, 95% CI 1.6-7.1), no previous Pap smear (RR 2.46, 95% CI 0.9-6.7) and ever had genital warts (RR 14.55, 95% CI 1.7-125.6).

While this study found an association between the absence of previous Pap smears (RR 2.46, 95% CI 0.9-6.7) and invasive vulvar cancer, the small sample size of the study population may not have allowed researchers to report on age strata or the frequency of Pap smear screening.

The purpose of Parazzini, et al. (1993)'s study was to evaluate the risk factors for invasive vulvar cancer. The study included 73 cases with histologically confirmed invasive vulvar cancer and 572 hospital controls in Milan, Italy. The cases ages ranged from 41 to 74 years old and controls ranged in age from 38 to 74 years old. Both cases and controls provided information such as

demographic variables, lifestyle habits, gynecological and obstetric data, related medical history, sexual habits and lifetime histories of Pap smears.

The main findings of the study include the inverse relationship of education level and invasive vulvar cancer (RR 0.6 and RR 0.4, respectively for subjects reporting seven (7) to 11 and 12 years or more of education). A higher risk existed among overweight women, but the trend was not statistically significant after taking into account confounding factors. There was a 70 to 80 percent lower risk of invasive vulvar cancer among women reporting ever having a Pap smear than in women reporting never having a Pap smear.

This study also stresses, from a public health perspective, the importance of Pap smear screening. Furthermore, the study suggested that Pap smear screening is largely associated with pelvic examination and has preventive implications regarding the importance of cervical screening programs for older women. This is of particular interest to this study, since some studies take into account the Pap smear status, while the pelvic examination status is often ignored even though these procedures generally occur together. The major limitation to this study is the small sample size. Of value is its provision of data for comparison with the American studies.

The purpose of Sherman, et al. (1994)'s case-control study was to determine if the reproductive history, menstrual history, exogenous estrogen use and body mass may play a role in the etiology of vulvar cancer. The study sought to determine the relationship with hormonal factors in vulvar cancer and utilized an interview process but did not obtain Pap smear or pelvic examination histories.

The study included 330 cases and 1,010 controls aged 18 to 79 years old (Sherman, et al. 1994). The results suggested that women diagnosed with vulvar cancer were at slightly higher risk due to early menarche [(before age 12) (OR 1.8, 95% CI 1.2-2.7), *in situ* cancer (OR 1.6, 95% CI 0.8-3.1)], excess weight (invasive cancer only, OR 2.9, 95% CI 1.5-5.8 for highest tertile of

Quetelet's index (body mass index)) and among pregnant women who have had their first pregnancy after age 24 (*in situ* only, OR 1.5, 95% CI 0.9-2.5). These findings suggest that *in situ* and invasive vulvar cancers are not strongly hormone related.

Limited information was provided concerning Pap smear history (results were not reported) which would have been of interest to this study. In addition, age strata were not provided that might have suggested the impact of invasive vulvar cancer on older women.

Madeleine, et al. (1997)'s study collected tissue samples from tumor blocks and sera to determine risk factors in the etiology of vulvar cancer. The purpose of the Madeleine, et al. (1997)'s matched case-control study was to determine the association of HPV, cigarette smoking and/or HSV2 with vulvar cancer. The study included 510 cases of *in situ* and invasive vulvar cancers with 1,403 controls of women between the ages of 18 and 79 years.

Interviews of cases and controls were conducted to collect demographic information, reproductive, birth control, sexual and smoking histories. The controls were frequency matched to the age distribution of cases in 5-year intervals. Furthermore, blood samples were requested from all subjects to which 479 (93.9%) cases and 1,215 (86.6%) controls consented. Tumor blocks were also requested from case subjects. HPV seropositivity to HPV 6, 16 and 18 was determined by the use of an ELISA test of all study samples. Antibody response to HSV2 was determined by the use of the Western Blot on all study samples. Vulvar tumor tissue was classified with respect to the presence or absence of HPV positivity through the use of polymerase chain reaction (PCR) to amplify HPV DNA. A board-certified pathologist reviewed the histological slides of 34 cases of invasive vulvar cancer.

The results of the study indicate that over half (51.8%) of cases who had invasive vulvar cancer were age 60 or over. Furthermore, the findings suggest that *in situ* tumors were more

common among younger women. The subjects who had two or more sexual partners or first intercourse before age 17 were more common among cases than controls.

Additional results suggested by Madeleine, et al. (1997) show the OR associated with HPV16 positivity for *in situ* tumors was 3.6 (95% CI 2.6-4.8) and for invasive vulvar cancer was 2.8 (95% CI 1.7-4.7). Smoking for *in situ* was 6.4 (95% CI 4.4-9.3) and for invasive cancers it was 3.0 (95% CI 1.7-5.3). The OR associated with HPV16 positivity and never smoking was 2.9 (95% CI 1.7-5.0); current smoking and HPV16 negativity was 4.9 (95% CI 3.3-7.5) and current smoking and HPV16 positivity was 18.8 (95% CI 11.9-29.8).

The OR associated with HSV2 positivity and HPV16 negativity was 1.9 (95% CI 1.3-2.7); HSV2 negativity and HPV16 positivity was 3.2 (95% CI 2.2-4.9) and HSV2 and HPV16 positivity was 5.7 (95% CI 3.8-8.4). In addition, among 34 case subjects registered as having invasive squamous cell tumors, histological slides were obtained. Of the 34 cases, 76.5% (26) were classified as keratinizing squamous cell carcinoma and 23.5% (8) were classified as basaloid or warty carcinoma. In 75% of the basaloid or warty carcinomas and 22.7% of keratinizing squamous cell carcinoma HPV 16 DNA was found.

The limitations of the study include the small sample size for both cases and controls (Madeleine, et al. 1997). Another limitation was that in the subset of invasive cancers, only 34 of the 110 were reviewed by a pathologist. There was also a lack of HPV DNA tissue testing among controls suggesting that the prevalence of HPV DNA may be underestimated. There may be other oncogenic HPV types not investigated in this study (the study tested HPV 6, 16 and 18) that are important in the natural history of vulvar carcinoma.

Other limitations are that pelvic examination and Pap smear histories were not investigated and the analyses were not stratified by age or the presence of HPV DNA. Other studies have hypothesized that invasive cancers in older women are not HPV related.

The matched case-control study conducted by Trimble, et al. (1996) collected abnormal Pap smear histories via interview as part of the study to estimate risk factors in the etiology of squamous carcinoma of the vulva. The study included 123 cases histologically confirmed squamous carcinomas of the vulva between the ages of 20 and 70 years and 246 controls. Two (2) controls were matched to one (1) case on age, race and residence.

The purpose of the study was to evaluate the risk factors, histological types and presence of HPV in squamous carcinoma of the vulva. Interview data was available from 71 of the 123 cases. Both cases and controls responded to a detailed questionnaire to obtain information on risk factors for vulvar cancer such as number of sexual partners, ever having an abnormal Pap smear, sexually transmitted disease, smoking and parity.

The results of the study suggest significance ($p<0.001$) in the prevalence of HPV in cases with high-grade VIN (48 of 54 or 88.9%), basaloid-warty carcinoma (BWC) (18 of 21 or 85.6%) and keratinizing squamous carcinoma (KSC) (3 of 48 or 6.3%) compared to controls. However, when risk factors for BWC were compared to KSC, BWC was significantly associated with cervical cancer risk factors such as number of sexual partners, age at first intercourse, abnormal Pap smears, venereal warts, low socioeconomic status and smoking, while KSC was less strongly linked to these factors (Trimble, et al. 1996). Furthermore, KSC was found primarily in older women (mean age 65.1 years) and was less related to being HPV DNA positive (6.3%), which suggests that there are two etiologies of vulvar cancer. This finding is of particular interest to the present study (Table 3) in supporting the suggestion that vulvar cancer in older women is less related to HPV DNA than vulvar cancer in younger women.

The limitations to the Trimble, et al. (1996) study include the small study size. Another limitation, with respect to the present one, is that the questionnaire asked respondents if they ever had an abnormal Pap smear, but did not provide information regarding if respondents had ever had a

Pap smear. It is conceivable that respondents may not have ever had an abnormal Pap smear simply because they never had a Pap smear.

Sera were collected in Heim, et al. (2005)'s study to perform various tests for the detection of specific HPV antibodies in subjects with vulvar precancerous and invasive lesions. The Heim, et al. (2005) study was conducted to suggest the best HPV serology test for the detection of specific antibodies in patients with vulvar cancer. The study also sought to determine whether populations exposed to specific HPV types are at greater risk of precancerous and invasive lesions of the vulva (i.e., vulvar lichen sclerosus (LS), VIN1, VIN2, VIN3, verrucous carcinoma (VC) and giant condyloma Buschke Lowenstein tumor). The study utilized 97 cases diagnosed with lichen sclerosus with and without squamous hyperplasia, 78 cases diagnosed with VIN and 16 cases with verrucous carcinoma and 126 healthy controls ranging in age from 16 to 81 years.

The results of the study indicate that in lichen sclerosus/squamous hyperplasia with atypia immunoglobulins G and A, antibody positivity rates to high-risk HPV types 16, 18 and 31 were significantly higher in cases than in the control group and the lichen sclerosus/squamous hyperplasia group without atypia. In cases with VIN1, increased immunoglobulin G antibody prevalence with both high-risk and low-risk (types 6 and 11) HPV particles were detected. In cases with VIN2 and VIN3, increased immunoglobulin G was detected with only HPV high-risk types.

The study suggests that high-risk HPV types, such as HPV16 play a role in the pathogenesis of precancerous and invasive vulvar lesions. However, the conclusions of this study should be perceived with caution. First, all subjects were Caucasian. Second, controls were chosen from women who visited the outpatient clinic for treatment for non-HPV related diseases. Third, the population sample used for the study was small and segmented into numerous types of vulvar anomalies (97 with lichen sclerosus with and without squamous hyperplasia, 78 with VIN and 16 with verrucous carcinoma) making it difficult to suggest with any certainty where HPV plays a role

in the development of precancerous and invasive lesions among older women. Analysis of age strata and how the sera were collected might have been useful. Furthermore, the study was not population based, which reduces the ability to generalize to a larger, more diverse population.

Hildesheim, et al. (1997a)'s study also collected sera to determine association with HPV types and risk of VIN3 and invasive vulvar cancer. The purpose of the study was to investigate whether a causal relationship between HPV16 and other risk factors were related to vulvar carcinoma, including contraceptive use, reproductive history, cigarette smoking and sexual behavior. The study included 142 cases histologically confirmed with VIN3 or invasive vulvar cancer and 126 controls matched on age, race and residence. The cases and controls ranged in age from 20 to 79 years.

The results of the study suggest that cases that tested positive for HPV16 had an adjusted 5.3 fold excess risk of vulvar cancer (adjusted OR 5.3, 95% CI 2.5-11.1). Subjects with high antibody levels have a 20 fold risk of vulvar cancer relative to those who tested negative (adjusted OR 20.1, 95% CI 5.4-76.7). Furthermore, a strong association was observed between HPV16 positivity and VIN3 (adjusted OR 13.4, 95% CI 3.9-46.5). A two-fold risk for HPV 16 positivity was observed among subjects with invasive vulvar cancer (adjusted OR 2.9, 95% CI 0.94-8.7).

The study also suggested other significant risk factors such as greater than two sexual partners (adjusted OR 2.8 and adjusted OR 2.4, 95% CI 0.93-6.0); greater than three sexual partners (adjusted OR 4.7 and adjusted OR 3.4, 95% CI 1.5-7.7); herpes simplex virus (HSV 1) (adjusted OR 2.7 and adjusted OR 2.5, 95% CI 1.1-6.0); and HSV2 (adjusted OR 3.6 and adjusted OR 3.2, 95% CI 1.0-10). For cases who tested HPV16 positive the risk of vulvar cancer was more than twice that observed among smokers than those who never smoked (OR 8.5 and 3.4); greater risk was observed among women who tested positive for *c. trachomatis* than those who tested negative (OR 7.6 and

6.2), and slightly greater risk among those who used oral contraceptives than those who never used them (OR 8.3 and OR 7.2).

The small study size did not allow the researchers to report on age strata which would have been of interest to this study. Furthermore, the study did not collect information regarding pelvic examination and Pap smear screening histories.

The study by Mabuchi, et al. (1985) utilized a matched case-control design that used hospital data and interviews that collected gynecologic history, but did not include Pap smear or pelvic examination histories to estimate the risk of vulvar cancer. The study included 149 cases histologically confirmed vulvar carcinoma and 149 controls that are matched on race, age, marital status and geographic area. Participants ranged in age from 30 to over 80 years old.

Cases and controls were interviewed to obtain demographic information, occupation, hazardous exposures (e.g., metals, dyes, radioactive materials, chemicals, sawdust, cement dust, coal and/or other dust, paints, dry cleaning/dying materials, gasoline/grease, textile machinery and cutlery machinery), habits, marital status, coital status, reproductive and menstrual history, medications, cigarette smoking status, coffee drinking status, religious affiliation, education and medical history. For each case interviewed, a control was matched based on the results of the interviews to determine hospital, sex, race, age (plus or minus 3 years) and marital status. The interviewers were blinded to the case/control status of the participants interviewed.

The statistically significant results suggested by Mabuchi, et al. (1985), include associations with employment as private household maids and servants (24 cases/12 controls, OR 2.19, $p<0.05$); in laundry, cleaning and other garment services (13 cases/3 controls, OR 3.81, $p<0.05$); and age (average 30) at first marriage (27 cases/17 controls, OR 3.29, $p<0.05$); cigarette smoking of 10 to 20 cigarettes per day (28 cases/13 controls, OR 2.46, $p<0.05$); coffee consumption of 3-4 cups (44

cases/28 controls, OR 2.99, $p<0.05$); coffee consumption of 5 or more cups per day (42 cases/33 controls, OR 2.42, $p<0.05$).

The study also found that a history of leukoplakia (13 cases/0 controls, $p<0.005$) and inflammation of the vulva or vagina (17 cases/2 controls, $p<0.005$) was reported (Mabuchi, et al. 1985). The frequency of prior cervical cancer was borderline significant ($p<0.10$) (five (5) of the six (6) cases who reported prior cancer had cervical cancer between 6 and 20 years before vulvar cancer).

The limitations of the study include a small sample size. Furthermore, the majority of both cases and controls were white (90%) and between the ages of 50 and 79 years (72%) with similar socioeconomic backgrounds. In addition, the controls were hospital controls making it difficult to generalize to the population. However, for the benefit of the present study (Osterbur's), the majority of patients with vulvar carcinoma were between the ages of 50 and 79 years which shows that vulvar carcinoma occurs more frequently among this age group. Age stratification for type and risk factors associated with vulvar cancer would have been useful, but because of the sample size this was not possible. Furthermore, while information was collected via interview for both cases and controls regarding various health prevention measures, history of pelvic examinations and Pap smears was not reported.

Summary of case-control studies

The primary purpose of the above case-control studies was to determine the etiology of vulvar cancer. Basta, et al. (1999) obtained both Pap smears and colposcopies to determine the role of HPV in the development of VIN1 and early stage vulvar cancer; while Trimble, et al. (1996) collected information on abnormal Pap smear histories. Both studies suggest that the role of HPV is a significant risk factor among younger women and a non-significant risk in older women, in accordance with other literature. These case-control studies also collected Pap smear histories and

found that women with no previous Pap smears were at greater risk than those who did have a previous Pap smear (Brinton, et al. 1990a, Parazzini, et al. 1993).

The Madeleine, et al. (1997), Sherman, et al. (1994), Heim, et al. (2005), Hildesheim, et al. (1997a), and Mabuchi, et al. (1985), studies did not collect information on previous pelvic examinations or Pap smear histories. However, the Madeleine, et al. (1997) and Mabuchi, et al. (1985) studies suggest that vulvar carcinoma is more common among older women. Madeleine, et al. (1997) found over half of cases that had invasive disease were over age 60 and Mabuchi, et al. (1985) between the ages of 50 and 79. Hildesheim, et al. (1997a) suggested that HPV was a risk factor in the development of invasive vulvar cancer.

While several studies took into account both pelvic examinations and Pap smears, they did not take into account specifically the potential lower use associated with gynecological screening. The present study serves to fill this gap in the literature. The following Table 4 summarizes the above-mentioned case-control studies.

Table 4. Vulvar cancer: case-control studies

	Diagnosis year	Study	Cases	Controls	Purpose	Age
Basta, Adamed and Pitynski (1999)	1982-1996	Case-control	178	115	Risk factors	
Brinton, Nasca, Mallin, Baptiste, Wilbanks and Richart (1980)	1986	Matched case-control	209	348	Risk factors	20-79
Heim, Widschwendter, Szedenik, Greir, Christensen, Bergant, Concin and Hopfl (2005)	1991-1994	Case-control			Serologic response	
		Group 1	97 (LS w/wo SH)		to HPV	28-80
		Group 2	17 (VIN 1)			19-37
		Group 3	61 (VIN 1 or 111)			18-77
		Group 4	16 (VC of the vulva)			39-79
		Group 5	126 (chosen randomly for TX of non-HPV)			16-81
Hildesheim, Han, Brinton, Kurman and Schiller (1997)	1985-1987	Case-control	142	126	HPV	20-79
Mabuchi, Bross and Kessler (1985)	1972-1975	Matched case-control	149	149	Risk factors	30-80
Madeleine, Daling, Carter, Wipf, Schwartz, McKnight, Kurman, Beckmann, Hagensee, Galloway (1997)	1980-1994	Matched case-control	510	1,403	Cofactors with HPV	19-79
Parazzini, La Vecchi, Garsia, Negri, Sideri, Rognoni and Origoni (1993)	1987-1990	Case-control	73	572	Risk factors	38-74
Sherman, Daling, McKnight and Chu (1994)	1980-1990	Case-control	330	1,010	Hormonal factors	18-79
Trimble, Hildesheim, Brinton, Shah and Kurman (1996)	One year retrospective and 18 months prospective	Case-control	123	246	Role of HPV	20-70

Prior research of vaginal and vulvar cancers

Case-control study

The Jamieson, et al. (2006)'s study performed both Pap smears and physical (pelvic) examinations to determine HPV status, as well as colposcopy to determine precancer status and human immunodeficiency virus (HIV) screening (cluster of differentiation (CD) 4 counts)) to test their hypotheses that HIV is a risk factor in the etiology of vulvar, vaginal and perianal intraepithelial neoplasia. It should be noted the study, while collecting data relative to HPV and HIV, also collected (via interview) data relative to risk factors such as sexual behaviors and injection drug use among women between the ages of 16 and 55. Antiretroviral therapy use was also accessed via self-report by HIV infected cases.

The study included 189 cases that were HIV-infected women and 88 controls who were at high-risk for HIV. Two participants (who were not diagnosed with vulvar, vaginal or anal intraepithelial neoplasia) in the study seroconverted -- status changed from HIV negative to HIV positive -- and were included in the study until the event of seroconversion. There were 16 HIV-infected cases with vulvar, vaginal or anal intraepithelial neoplasia and only one had a normal Pap smear. Conversely, only one of the HIV-uninfected controls, while having a normal Pap smear, also had VIN (visible lesions were noted on physical examination). Furthermore, 10 cases diagnosed with vulvar, vaginal or anal intraepithelial neoplasia were also diagnosed with cervical intraepithelial neoplasia (CIN).

The study suggests that significant risk factors for development of vulvar, vaginal and perianal intraepithelial neoplasia among HIV-infected cases include CD4 counts (cells/μL) less than 200 (unadjusted Hazard Ratio (HR) 6.6, 95% CI 1.2-36.4); CD4 counts (cells/μL) between 200 and 500 (unadjusted HR 3.5, 95% CI 0.8-15.8); HPV PCR positive, any type (unadjusted HR 5.0, 95% CI 1.1-22.0); HPV PCR positive, high/intermediate risk type (unadjusted HR 3.1, 95% CI 1.1-8.8);

cervical, vaginal or vulvar condyloma noted at baseline physical exam (unadjusted HR 2.0, 95% CI 0.7-6.2) and antiretroviral use at baseline (unadjusted HR 3.9, 95% CI 1.3-11.1).

Summary of case-control study

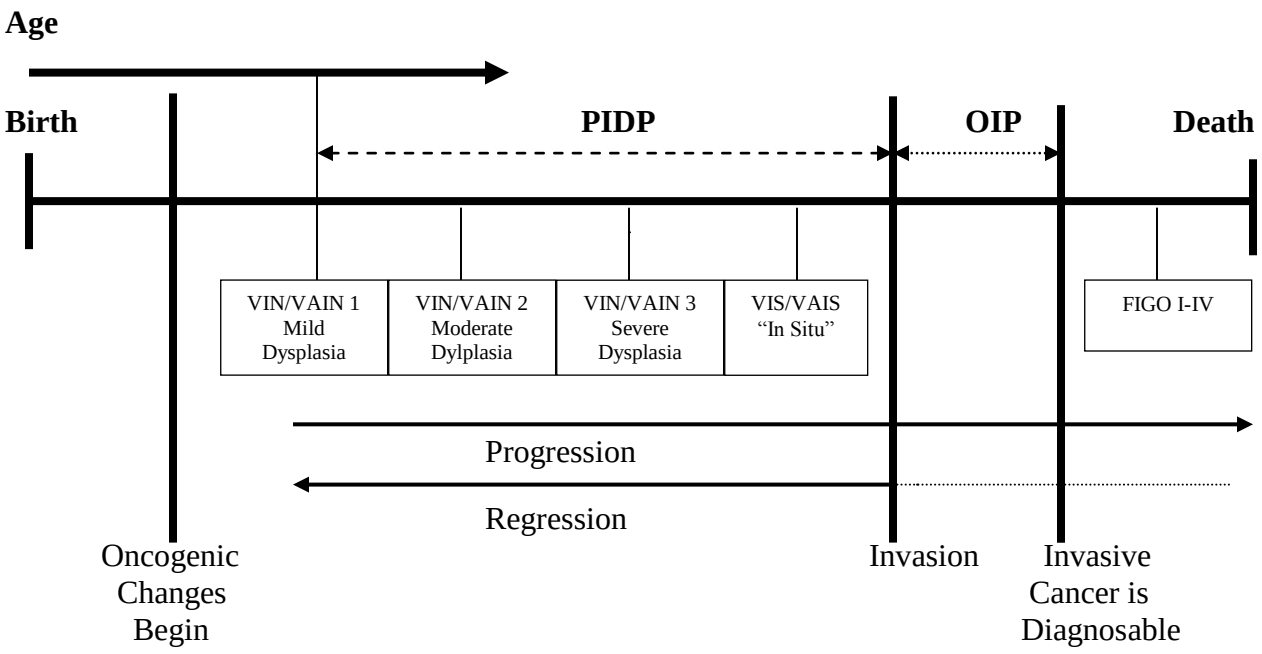
Jamieson, et al. (2006) suggested that HIV-infected women have a higher risk of lower genital tract intraepithelial neoplasia that is not limited to the cervix and recommended that the vulvar, vaginal and perianal regions be inspected during gynecologic exams. This study utilized both Pap smears and pelvic examinations; however, the study focus was on younger women (16-55 years) who tested positive for HIV.

Screening

Definition and rationale for screening

According to Sankankaranayanan, et al. (2005), the purpose of population screening policies is to divide the population into two groups: those with a low risk of disease and those with a high risk of disease who may warrant further diagnostic testing or examinations. Screening is applied to people who are asymptomatic and who meet the eligibility requirements for the screen. The purpose is to identify individuals whose disease is pre-invasive so that it can be effectively treated before becoming invasive. The disease screened must have a detectable preclinical stage for which effective treatment is available. The justification for any screening program is that early diagnosis will lead to a cost-effective and measurable reduction in invasive or late stage cancer.

Weiss (1999) suggested there is a natural history of cancer development wherein, during the pre-invasive detectable phase (PIDP) "changes occur in a particular tissue that pre-dispose to the development of cancer." It is during this time frame when screening tests are effective for determining precursor cancer lesions (i.e., vulvar intraepithelial neoplasia or vaginal intraepithelial neoplasia) (Figure 1). These changes may be present for a specific time period (i.e., years in the case of vaginal and vulvar cancers). The following Figure 1 illustrates this concept.



Adapted from David Maduram MD/PhD, University of Illinois,
"An analysis of the efficacy of cervical cancer screening in elderly women", 2009

Figure 1: Pre-invasive detectable phase (PIDP) and occult invasive phase (OIP)

Current policy recommendations for screening

Policy recommendations such as when to start and stop screening and screening frequency intervals for cervical lesions differ across professional and governmental organizations. The intervals for performing pelvic examinations and Pap smears in older women have been strongly debated among researchers and policymakers. The following Table 5 illustrates these differences.

Table 5. Cervical cancer screening guidelines, 1988, 1996, 2002, 2003, 2012

	1988 Consensus	1996 American Academy of Family Physicians (AAFP)	2002 American Cancer Society (ACS)	2003 American Congress of Obstetrics and Gynecology (ACOG)	2003 United States Preventive Services Task Force (USPSTF)	2012 USPSTF
When to start screening	Age 18 or with onset of sexual intercourse	Every 3 years after onset of sexual intercourse and have a cervix	Age 21 or about 3 years after onset of sexual intercourse	Age 21 or about 3 years after onset of sexual intercourse	Age 21 or about 3 years after onset of vaginal intercourse	Age 21, recommends against screening with HPV testing, alone or in combination with cytology in women younger than 30
Screening interval	Annually until 3 consecutive, satisfactory negatives, then interval may be extended at discretion of provider	Every 3 years	Annually until age 30. Every 2 years if liquid-based cytology or age 30 or older after 3 consecutive satisfactory negatives may screen every 2-3 years	Annually until age 30 using either conventional or liquid-based cytology or age 30 or older after 3 consecutive satisfactory negatives and no history of CIN2 or 3, may screen every 3 years	Every 3 years	Every 3 years with cytology, or women age 30-65 who want to lengthen screening interval, screening with combination of cytology and HPV testing every 5 years
When to stop screening	No upper limit	No recommendation	Age 70 in well-screened, low-risk women	Evidence inclusive to set upper age	Age 65 in well-screened low-risk women	Age 65 in well-screened low-risk women who are not otherwise at high-risk for cervical cancer
Posthysterectomy	No recommendation	Discontinue after hysterectomy if cervix removed	Discontinue after hysterectomy for benign disease if cervix removed, if no prior CIN2 or 3	Discontinue after hysterectomy for benign disease if cervix removed, if no prior CIN2 or 3	Discontinue after hysterectomy if no evidence of cervical neoplasia or cancer	Discontinue after hysterectomy with removal of cervix, if no prior CIN2 or 3

The 1988 consensus statement (Table 5) recommended that starting at age 18 or with the onset of sexual activity, all women should have an annual pelvic examination, including a Pap test (Waxman, 2005). The 1988 consensus statement was upheld by professional and governmental organizations and supported by practitioners until 1995, when the American Congress of Obstetrics and Gynecology (ACOG) issued a committee opinion that listed risk-based exceptions to the extended screening interval including a list of social and demographic risk factors, as well as items related to risk including sexually transmitted diseases, multiple partners and low socio-economic status (SES). Since then, medical research and technology have increased our understanding of the pathogenesis of cervical cancer and the role of HPV in the development of cervical and vaginal cancers. Furthermore, since new screening methods are available to practitioners, more studies that deal with screening efficacy and cost-effectiveness have all led to differences in screening recommendations among professional and governmental organizations.

In 2001, the American Geriatrics Society issued a position statement on the screening for cervical carcinoma in older women (AGS, 2001). It suggests that the recommendations by such professional organizations as the ACS and ACOG do not take into account the risk factors for the development of cervical carcinoma in older women. Taking account of risk factors such as multiple sex partners, history of HPV, HIV, cervical dysplasia, smoking and immunosuppression may suggest that the frequency of cervical cancer may increase in older women. Further, the AGS guidelines suggest that the present recommendations assume that women younger than 60 have frequent screenings when studies reveal that between 28% and 64% of women age 65 and older have never had a Pap smear or have not had one performed within the past within three

years. The AGS suggests that this may account for the high rate of invasive disease in older women.

The National Cancer Institute at the National Institutes of Health (NIH) Cervical Cancer Screening PDQ® last updated in 2012, suggests that cervical cancer mortality increases with age, especially among women who have never been screened. These unscreened populations include older women, a higher population of the uninsured, ethnic minorities, especially elderly Hispanic and black women and poor women, particularly those who live in rural areas.

Conversely, there are authors who suggest that cervical cancer screening should stop at age 50 for women who have had regular Pap tests prior to age 50 with negative results (Cruickshank, et al. 1997). Similarly, other authors suggest that stopping Pap smears at age 50 may be more appropriate provided that such women had at least three consecutive Pap smears with negative results (Van Wijngaarden and Duncan, 1993, Flannelly, et al. 2004). Flannelly, et al. (2004) further suggested that women with a positive Pap smear result history should continue screening after 50 years of age.

The U.S. Preventive Service Task Force (USPSTF) has suggested that routine Pap smears are unnecessary for women who have had a hysterectomy with removal of the cervix for benign disease (Sirovich and Welch, 2004b). Furthermore, Fetters, et al. (2003) suggests that vaginal Pap smears in women with a prior hysterectomy for benign disease is not worthwhile.

Medicare screening policies

The USPSTF was formed in 1984 to address the inconsistencies among clinicians regarding the effectiveness of preventive interventions (Richardson, 2006). The USPSTF consists of experts from various fields to evaluate the effectiveness of these interventions.

Medicare coverage for preventive services adheres closely to the recommendations of the USPSTF.

Prior to July 1990, Medicare coverage for Pap smears was extended only to beneficiaries who were being treated for an existing gynecological cancer or for those at risk for disease, but did not cover routine screening (CMS, 1990). After July 1990, Medicare coverage for Pap smear screening was extended to beneficiaries of Medicare Part B after a study conducted by the congressional Office of Technology Assessment (OTA begun in 1972 and defunded in 1995) found that about 25% of new cases of invasive cervical cancer occur in women age 65 and older. The OTA also suggested that about half of older women have had a Pap smear within the past three years and one out of every four women have never had a Pap smear. The OTA estimated that screening older women would save approximately 21,400 life years per one million women screened.

To encourage screening in older women, Medicare provides funding for gynecological screenings. As such, from July 1990 until July 2001, Pap smears were reimbursed by Medicare every three years for low-risk women and every two years for high-risk women (CMS, 2004). This policy covers my study observation period, which includes the years from 1991 to 1999. (However this policy, updated in July 2001, currently reimburses screening Pap smears every two (2) years for low-risk women (CMS, 2004). This policy update does not affect my study population.) Furthermore, since January 1998, pelvic examination and Pap smear screenings were reimbursed annually for high-risk women. Medicare coverage of pelvic examinations without Pap smears was recommended to all female beneficiaries as of January 1998, affecting only two (2) years of this study population (the years 1998 and 1999).

The following Tables 6 and 7 illustrate Medicare Part B coverage for both pelvic examinations and Pap smears

Table 6. Medicare Part B coverage 2005-2010

Service	What Medicare covers	What beneficiaries pay
Pap test	One Pap test every 24 months, unless in high risk group, Medicare will pay for a Pap test once every 12 months	20% of the Medicare approved amount for the part of the exam when the doctor/health care provider collects the specimen. Beneficiaries pay nothing for lab Pap test. No Part B deductible for this service
Pelvic examination/clinical breast examination	One pelvic/clinical breast examination every 24 months, unless in high risk group, Medicare will help pay for a pelvic examination once every 12 months	20% of the Medicare-approved amount. No Part B deductible for this service

Adapted from Women with Medicare: Visiting your doctor for a Pap test, pelvic exam, and clinical breast exam, U.S. Department of Health and Human Services (DHHS), Centers for Medicare and Medicaid Services (CMS). Rev. July 2005.

Table 7. Pelvic examination procedures according to Medicare Part B 1990-2010

Years	Pelvic examination procedures
1990-1997	Preventive services for cervical or vaginal screening were not covered by Medicare during these years unless treated for pre-existing condition
1998-2010	Screening pelvic examination (of the following procedures at least 7 must be performed) • Inspection and palpation of breasts for masses or lumps, tenderness, symmetry or nipple discharge • Digital rectal examination including sphincter tone, presence of hemorrhoids and rectal masses • Pelvic examination, with or without specimen collection for smears and cultures, including: o Inspection of external genitalia for general appearance, hair distribution or lesions o Inspection of urethral meatus for size, location, lesions or prolapse o Inspection of the bladder for fullness, masses or tenderness o Inspection of the vagina for general appearance, estrogen effect, discharge, lesions, pelvis support, cystocele or rectocele o Inspection of the cervix for general appearance, lesions or discharge o Inspection of the uterus for size, contour, position, mobility, tenderness, consistency, descent, or support o Inspection of the adnexa/parametria for masses, tenderness, organomegaly or nodularity o Inspection of the anus and perineum

Payment for screening pelvic examinations performed on asymptomatic women occurred only if a previous screening had not been performed or paid for by Medicare within three years in which the last Medicare-covered screening was performed (CMS, 2006).

The Patient Protection and Affordable Care Act (May 2010), makes it possible for beneficiaries of original Medicare to qualify for a yearly wellness visit and many preventive services for free. As of January 1, 2011, cervical cancer screening, including Pap smear and pelvic examination is available without the need for Medicare Part B deductible or copayment (DHHS, 2012).

Definition and mechanisms of screening pelvic examination and Pap smears (gynecologic)

A Pap smear is a microscopic examination of cells scraped from the cervix. Vaginal cancer can be detected by routine Pap smear and pelvic examination in 20% of cases (Averette,

et al. 1993). However, vaginal cancer often presents symptoms such as postmenopausal spotting, bleeding, foul discharge and pain. After an abnormal Pap smear or presentation of symptoms, a colposcopic investigation is required of the vaginal walls.

Vulvar cancer too, can be detected via routine Pap smear and pelvic examination, but the majority of patients present with symptoms such as a long history of itching or burning (Kagie and Ansink, 2000, Canavan and Cohen, 2002, Averette, et al. 1993). Since the vulva is an external organ, early detection can be readily achieved via routine pelvic examination (Averette, et al. 1993).

For purposes of this study, while there are other screening methods, the study analyzes the efficacy of pelvic examinations performed at the time of Pap smear alone. Following are terminology to describe pelvic examination and Pap smear cytology.

- *Pap smear cytology*

  The conventional Pap smear, developed by Dr. George N. Papanicolaou, has been used in screening for cervical cancer since its inception in 1950. Exfoliated cells in body tissues and fluid are examined to determine the specific types of cells present (Fischbach, 2004). Gynecologic specimens are smeared and fixed in 95% alcohol. A spray fixative is also used to preserve the sample. All specimens are examined for the number of cells, cell distribution, surface modification, size, shape, appearance and staining properties. The cell nucleus is also examined. Abnormal cells can be identified to determine malignant and premalignant conditions. This method did not change until 1988 with the implementation of the Bethesda System that allows for the standardization of cervical cytology and reporting terminology. Plus, new advances in smear technology such as the ThinPrep, a liquid-based technique that collects smears in a special preservative solution (Fischbach, 2004) allows for

more accurate interpretations of cancer (cervical, vaginal and vulvar) precursors. A more recent advancement in gynecological cancer screening is HPV co-testing that serves to detect high-risk HPV types. In practice, results of cytologic studies are commonly reported as:

- Inflammatory
- Benign
- Atypical
- Suspicious for malignancy
- Positive for malignancy (invasive versus *in situ*)

- *Pelvic examination*

  A pelvic examination is a physical examination of the uterus, vagina, vulva, ovaries, fallopian tubes, bladder and rectum (Bates, et al. 2011). The vulva and introitus (opening of the vagina) are inspected for hair pattern over lower abdomen, groin and mons publis. The skin is inspected for changes, concerning nevi (moles) and lesions and the labia major and minora are also inspected along with the size of the clitoris, urethra, introitus and hymen. Careful inspection is important for lesions of the vulva and is the most productive diagnostic technique. It utilizes a speculum to examine the cervix and vagina for any anomalies.

Screening and diagnosis of vaginal cancer

In the beginning phase of disease, generally there are no symptoms (Greene, et al. 2002, Creasman, 2005, Bardawil, 2010). However, once invasive vaginal cancer reaches advanced stages symptoms begin to manifest themselves. Many symptoms may be similar to other medical conditions experienced by older women (Greene, et al. 2002).

The most common symptom of vaginal cancer is abnormal vaginal bleeding (Greene, et al. 2002, Stern, 2002, Creasman, 2005, Tewari, et al. 2001, Bardawil, 2010) and even during menopause abnormal vaginal bleeding is a sign of a problem (Greene, et al. 2002). Other symptoms include abnormal vaginal discharge, difficulty or pain when urinating, pain during sexual intercourse, pelvic pain (lower part of the abdomen between the hip bones), pain in the back of the legs and edema (Greene, et al. 2002, Stern, 2002, Bardawil, 2010).

When a diagnosis is made, several factors such as age and medical condition of the patient, the type of cancer, severity of symptoms and any previous test results are considered for follow-up and treatment. The following Table 8 illustrates the various types of diagnostic and screening tools that are useful in screening and diagnosing vaginal cancer (The College Faculty of the University of Washington, 2005).

Table 8. Diagnostic tools to screen and diagnose vaginal cancer

Test	Vaginal
Pelvic examination	Yes
Pap smear	Yes
Colposcopy	Yes
Biopsy	Yes
X-ray	Yes
CT/CAT scan	Yes
MRI/PET scan	No
Cystoscopy	Yes
Proctoscopy	Yes
Pelvic examination (anesthesia)	Yes

Tewari, et al. (2001) studied 71 patients with primary vaginal carcinoma. Half of the study population presented with vaginal bleeding, 26% presented with vaginal pain or dysparunia and 20% with asymptomatic who were diagnosed via vaginal biopsy of a lesion found during a routine pelvic examination. Similarly, Bardawil (2010) recommends that during a routine pelvic examination there should be not only visual examination of the vagina, but also

the palpation of the entire vagina in order to feel any hardened or raised areas that may indicate a residual tumor. A routine Pap smear may indicate an abnormality in a patient with carcinoma *in situ* or in a patient with very early invasive disease who is asymptomatic. Further, VAIN tends to be multi-focal and, as such, if a lesion is identified the entire vagina needs to be inspected for multiple lesions (Sillman, 2000).

Sillman (2000), however, suggested that in about 90% of cases, an abnormal Pap smear (cervical or vaginal) precedes diagnosis. Sillman (2000) suggested that the remaining 10% of cases are found through colposcopic survey of high-risk patients (such as those with HPV, other anogenital neoplasm or immunosuppression) or in women who have been exposed to DES (Stern, 2002).

ACS (2012d) has suggested that both a routine pelvic examination and Pap test, where a sample of cervical or vaginal cells is collected for laboratory analysis, are necessary for a diagnosis of vaginal cancer. A colposcope may be used to view the vagina. If any abnormalities are detected, a tissue biopsy may also be taken to aid in the diagnosis. If metastases are suspected, an endoscopic examination of the bladder (cystoscopy) and/or rectum (proctoscopy) may also be performed.

Staging vaginal cancer

Staging, according to the International Federation of Gynecology and Obstetrics (FIGO), is clinical and not surgical (Stehman, 1997). Staging is utilized to describe where the cancer is located, if and to where it has spread and if the cancer is invading other organs in the body (FIGO, 2000). Staging is useful for identifying prognosis and determining the choice of treatment (FIGO, 2000). Different cancers typically have their own staging criteria (FIGO, 2000).

Table 9 provides the explanation of the FIGO staging of invasive cancer of the vagina. TNM is the abbreviation for tumor (T) which indicates how large and where the primary tumor is located; node (N) indicates if the tumor has spread to adjacent lymph nodes, and metastasis (M) indicates if the cancer has metastasized to other parts of the body (AJCC, 2002).

Table 9. FIGO staging of invasive cancer of the vagina

Stage 0			
Tis	N0	M0	Carcinoma *in situ*, intraepithelial carcinoma
Stage I			
T1	N0	M0	Carcinoma is limited to the vaginal wall
Stage II			
T2	N0	M0	Carcinoma has involved the subvaginal tissue but has not extended to the pelvic wall
Stage III			Carcinoma has extended to the pelvic wall
T1	N1	M0	
T2	N1	M0	
T3	N0	M0	
T3	N1	M0	
Stage IV			Carcinoma has extended beyond the true pelvis or has involved the mucosa of the bladder or rectum; bullous edema as such does not permit a case to be allotted to Stage IV
Stage IVa			Spread of the growth to the adjacent organs and/or direct extension beyond the true pelvis.
T1	N2	M0	
T2	N2	M0	
T3	N2	M0	
T4	Any N	M0	
Stage IVb			Spread to distant organs
Any T	Any N	M1	

Adapted from Stehman, 1997, p. 599.

The five-year survival rates of vaginal cancer vary according to the various stages of disease. Table 10 of squamous cell carcinoma of the vagina survival rates by stage and age illustrates the premise that as stage of disease increases, five-year survival rate decreases.

Table 10: Squamous cell carcinoma of the vagina: survival rates by stage and age 1988-2001*

Stage	Relative 5-Year Survival Rate (%)	
	20-60	70+
I	72.9	61.9
II	61.7	43.3
III	33.0	37.0
IV	23.6	17.4

*AJCC (SEER modified, 3rd edition)

Screening and diagnosis of vulvar cancer

Vulvar cancer has different symptoms than vaginal carcinoma. The most common is pruritus (severe chronic itching) (Kagie and Ansink, 2000, Canavan and Cohen, 2002). Burning pain of the vulvar area, dysparunia (painful sexual intercourse), changes in the color of the vulva, bleeding or discharge not related to menstruation or the vulvar skin that appears white and feels rough are symptoms of vulvar cancer (Kagie and Ansink, 2000, Jones and Rowland, 2009). Similar to vaginal cancer, vulvar cancer symptoms often resemble other conditions or medical problems (Greene, et al. 2002).

Vulvar cancer is a disease which is characterized by delayed diagnosis where diagnosis, even when symptoms such as pruritus and irritation are present. Symptoms are often ignored by both patients and practitioners based on their non-specific nature (ACS, 2012a).

When VIN is diagnosed histologically, the vagina and the cervix should be fully examined as well to determine if there are any co-morbid conditions since there is a high incidence of the concurrence of vaginal and cervical cancers (Kagie and Ansink, 2000). The following Table 11 illustrates the various types of screening and diagnostic tools to identify vulvar cancer.

Table 11. Diagnostic tools to screen and diagnose vulvar cancer

Test	Vulvar
Pelvic examination	Yes
Pap smear	Yes
Colposcopy	Yes
Biopsy	Yes
X-ray	Yes
CT/CAT scan	Yes
MRI/PET scan	Yes
Cystoscopy	Yes
Proctoscopy	Yes
Pelvic examination (anesthesia)	Yes

This is no specific screening procedure for vulvar cancer (Homesley, 1995, Stehman, 1997). According to Stehman (1997), careful visual inspection of the vulva during routine physical examination is the most useful technique in diagnosis. Furthermore, a history of prior Pap smears has been associated with a decreased risk of vulvar cancer (Sturgeon and Sherman, 2000). Sturgeon and Sherman (2000) further suggested that patients who participate in Pap smear programs are more likely to also undergo a routine pelvic examination which allows for early detection and treatment of vulvar cancer.

However, patients who have had a history of cervical or vaginal cancer should have the vulva inspected with or without coloposcopic examination **(**Benedet, et al. 2000). Colposcopic examination is more reliable for ruling out vaginal or cervical cancer than it is for ruling out invasive carcinoma of the vulva; patients should undergo colposcopy of the cervix, vagina and vulva before treatment is prescribed (Homesley, 1995).

Both colposcopic examination and biopsies are essential in diagnosing vulvar lesions (Kagie and Ansink, 2000). However, the value of a detailed vulvoscopy is debatable based on the keratinized, squamous, hair bearing tissues of the vulva (Sideri, et al. 2009) where lesions occur. Multiple biopsies may be necessary in the evaluation of suspicious lesions (Homesley,

1995, Stehman, 1997). A punch biopsy, best accomplished under local anesthesia, should be performed because it provides full-thickness skin specimens (Stehman, 1997, Kagie and Ansink, 2000, Sideri, et al. 2009).

While palpation of the groin is part of the assessment of vulvar carcinoma it is not reliable -- creating false-negative rates of 23% and false-positive rates of 60% (Sideri, et al. 2009). Furthermore, radiology, including computed tomography (CT) and magnetic resonance imaging (MRI) are also not reliable instruments for the diagnosis of vulvar carcinoma.

The initial diagnosis should be established based on histology, because other methods, such as gross appearance or cytology, are unreliable (Kagie and Ansink, 2000). Because of the high incidence of the coexistence of VAIN and/or CIN, the vagina and cervix should both be fully assessed.

Staging vulvar cancer

Table 12 below illustrates the five-year survival rates for squamous cell carcinoma of the vulva. The later the stage of disease and the older the age, the relative five-year survival rate decreases. However, at early stages of disease, there are higher rates of survival.

Table 12: Squamous cell carcinoma of the vulva, by stage and age 1988-2001*

	Relative 5-Year Survival Rate (%)	
Stage	20-60	70+
I	94.0	92.9
II	86.0	73.1
III	70.0	39.7
IV	40.6	16.9
*AJCC (SEER modified, 5th edition)		

The staging for vulvar cancer is also staged according to the FIGO. The following table illustrates the FIGO stage of invasive cancer of the vulva.

Table 13. FIGO staging of invasive vulvar cancer

Stage 0			
Tis	N0	M0	Carcinoma *in situ*, intraepithelial carcinoma
Stage I			
T1	N0	M0	Tumor confined to the vulva and/or perineum – 2 cm or less in greatest dimension (no modal metastasis)
			Stage Ia Lesions 2 cm or less in size confined to the vulva or perineum and with stromal invasion no greater than 1.0 mm* (no modal metastasis)
			Stage Ib Lesions 2 cm or less in size confined to the vulva or perineum and with stromal invasion greater than 1.0 mm (no modal metastasis)
Stage II			
T2	N0	M0	Tumor confined to the vulva and/or perineum – more than 2 cm in greatest dimension (no modal metastasis)
Stage III			Tumor any size with
T3	N0	M0	(1) Adjacent spread to the lower urethra and/or vagina, or the anus and/or,
T3	N1	M0	(2) Unilateral regional lymph node metastasis
T1	N1	M0	
T2	N1	M0	
Stage IVa			
T1	N2	M0	Tumor invades any of the following: upper urethra, bladder, mucosa, rectal mucosa, pelvic bone and/or bilateral regional node metastasis
T2	N2	M0	
T3	N2	M0	
T4	Any N	M0	
Stage IVb			
Any T	Any N	M1	Any distant metastasis including pelvic lymph nodes

*The depth of invasion is defined as the measurement of the tumor from the epithelial-stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion. Adapted from Stehman, 1997, p. 209.

This chapter covered in detail the natural history of both vaginal and vulvar cancers, as well as other details that include prior research. The highlights of the history of screening protocols by professionals and governmental organizations illustrate the experience that has resulted in current screening recommendations.

CHAPTER 3: METHODOLOGY

Overview of study methodology

This research project included four major steps in the analysis of data as illustrated in Figure 2 below. First, the data was obtained from the SEER-Medicare program, which included both SEER cancer registry data and the linked SEER-Medicare dataset. Both case and control data were formatted, cleaned and imported into a SAS compatible dataset. Second, cases and controls that did not fit the study criteria were excluded. Third, appropriate vaginal and vulvar cancer controls were matched with cases. Utilizing SAS, frequency tables were produced for both cases and controls. Finally, conditional logistic regression analysis was performed to estimate the effect of gynecologic cancer screenings and development of invasive vaginal and vulvar cancers utilizing STATA.

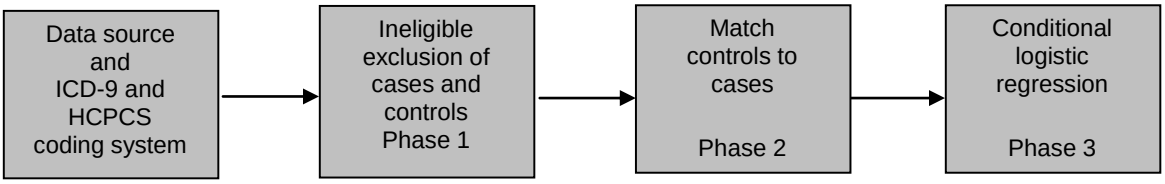


Figure 2: Overview of study methodology

The four major steps will be discussed further in the following sections.

Data source

The study was designed to perform analyses to determine whether both Pap smear and pelvic examination screenings decrease the risk of invasive vaginal and vulvar cancers in women aged 65 or older using a matched case-control design. These two case-control studies compared cases of persons diagnosed with invasive vaginal or vulvar cancers with matched controls enrolled in Medicare between the years 1991 through 1999 to determine whether they had a

history of screening during the estimated combined duration of the pre-invasive detectable phase (PIDP), which occurs prior to the occult invasive phase (OIP).

In an effort to study the efficacy of screening among adults age 65 and older, the Surveillance Epidemiology and End Results (SEER)-Medicate data set was utilized. This combined data set links the clinical information from the SEER cancer registries and claims data from the Medicare administrative database (Hewitt and Simone, 1999). The combined SEER-Medicare data set includes the files PEDSF, SUBDENOM, MEDPAR, NCH and OUTPT. The patient entitlement and diagnosis summary file (PEDSF) includes SEER cancer cases (Engles, et al. 2011). The summarized denominator (SUBDENOM) is the file that contains a five-percent (5%) random sample of Medicare recipients living in SEER areas, excluding SEER cancer cases. The medical provider analysis and review (MEDPAR) file contains Medicare Part A hospital claims. The national claims history (NCH) file contains Medicare carrier claims from physicians and other non-institutional Medicare providers. The last file that comprises the SEER-Medicare data set is the outpatient (OUTPT) file that contains Medicare claims from institutional outpatient providers.

Data for cases

The SEER-Medicare data set is two linked population-based sources that have been merged to provide detailed information about older adults (SEER-Medicare, 2003). The SEER data provided patient-specific information regarding the date of diagnosis, tumor location, grade and stage at diagnosis, histological type, as well as patient demographic characteristics such as age, gender, race and marital status (Fritz and Ries, 1998); while the Medicare data set provided information regarding specific healthcare services utilized by patients covered by Medicare. The SEER-Medicare merged data set provided the screening histories of each case and control prior

to diagnosis or reference date. These matched data sets provided the necessary information to perform the analyses for this study.

Controls were matched to cases on (1) SEER registry (metropolitan regions of Atlanta, Detroit, Seattle, San Francisco, Los Angeles; the San Jose-Monterey area; and the states of Connecticut, Iowa, New Mexico, Utah and Hawaii) (Warren, et al. 2002, Ries, et al. 2004)); (2) age and; (3) reference date (date of diagnosis of case). The SEER data included information on invasive cancer cases from hospitals, laboratories, autopsy reports and death certificates (Potosky, et al. 1993).

Data for controls

The pool of controls for this study was provided for by the National Cancer Institute and was a random five-percent (5%) sample of Medicare beneficiaries residing in the SEER areas who did not have cancer during the study time period. The case and control subjects were made up of Medicare beneficiaries enrolled in both Medicare Parts A and B (SEER-Medicare, 2003). Medicare Parts A and B are discussed in a subsequent section. The Medicare database used both standard ICD-9 (International Classification of Diseases) procedure coding and HCPCS (Healthcare Common Procedure Coding System) coding to record claims made by Medicare beneficiaries (Warren, et al. 2002).

ICD-9 and HCPCS coding system

ICD-9 and HCPCS coding systems were used to provide information regarding whether the case had received a Pap smear or pelvic examination screening during a specific year. While Medicare covered Pap smears every three (3) years for women over the age of 65, pelvic examinations were not covered during the study period until 1998. Until the Balanced Budget Act of 1997, pelvic examinations were not covered by Medicare except for patients who were

considered high-risk (see Table 14 for definition of high-risk patient) (Bagley and McVearry, 1998). The ICD-9 code V15.89 and HCPCS G0101 codes were amended in 1998 to include pelvic examinations (NCHS, 2008). Following is a description of the two coding systems.

ICD-9 codes

The ICD-9 is an international classification system for diseases and healthcare claims, and was originally developed by the World Health Organization (Clinical modification (ICD-9-CM 6th ed.) (NCHS, 2008). The Medicare Catastrophic Coverage Act of 1988 requires that health care professionals provide ICD-9 procedure codes on all Medicare claims (Legislative summary: the Family Support Act of 1988) (HCFA, 2012). The following Table 14 shows the ICD-9 codes used for Pap smear screening on Medicare claims (CMS, 1991):

Table 14. ICD-9 codes for Pap smear screenings

ICD-9 codes	Description
V76.2	Pap screening for malignant neoplasms of the cervix for low-risk patients
V76.47	Pap screening for malignant neoplasm, vagina
V76.49	Pap screening for malignant neoplasm, other sites
V72.31	Pap screening for malignant neoplasm of the cervix, exclusively in conjunction with a full gynecological examination (including pelvic examinations)
V15.89	Pap screening for malignant neoplasms of the cervix for high-risk patients. Medicare considers the following activities: 1. early onset of sexual activity (under age 16) 2. multiple sexual partners (> 5 in a lifetime) 3. history of sexually transmitted disease, including HIV 4. fewer than three negative Pap smears within the previous seven years 5. exposure to DES (diethylstilbestrol) while in utero (i.e., patient is a daughter of a mother who was exposed to DES)

HCPCS codes

Each carrier claim (services provided by health care professionals such as a pelvic examination) included a Healthcare Common Procedure Coding System (HCPCS) to describe the nature of the billed service (Buck, 2012). The HCPCS is composed primarily of Current Procedural Terminology (CPT) codes developed by the American Medical Association (AMA), with additional codes specific to the Health Care Financing Administration (HCFA) (now known as Centers for Medicare and Medicaid Services (CMS)). The HCPCS was developed in 1983, and used by healthcare professionals to bill Medicare for claims made on behalf of beneficiaries for services such as clinical procedures, supplies and other healthcare professionals. In order to distinguish between the ICD-9 codes and HCPCS codes, HCPCS describes the health care procedure in more detail. The following Table 15 shows the HCPCS codes used for Medicare claims for Pap smear screening:

Table 15. HCPCS codes for Pap smear screening tests

HCPCS code	Description
G0101	Pap cervical or vaginal cancer screening; unspecified (Balanced Budget of 1997, required that Medicare cover both pelvic examinations and breast examinations. G0101 coding was further defined to include both pelvic and breast examinations. This policy was instituted in January, 1998).
G0123	Pap screening cytopathology, cervical or vaginal (any reporting system), collected in preservative fluid, automated thin layer preparation; screening by cytotechnologist under physician supervision.
G0124	Pap screening cytopathology, cervical or vaginal (any reporting system, collected in preservative fluid, automated thin layer preparation; screening by cytotechnologist under physician supervision; requiring interpretation by physician.
G0141	Pap screening cytopathology smears, cervical or vaginal, performed by an automated system, with manual rescreening, requiring supervision by a physician.
G0143	Pap screening cytopathology smears, cervical or vaginal, (any reporting system), collected in preservative fluid, automated thin layer preparation; with manual screening and rescreening by cytotechnologist under supervision by a physician.
G0144	Pap screening cytopathology smears, cervical or vaginal, (any reporting system), collected in preservative fluid, automated thin layer preparation; with screening by automated system, under supervision by a physician.
G0145	Pap screening cytopathology smears, cervical or vaginal (any reporting system), collected in preservative fluid, automated thin layer preparation; with screening by automated system and manual rescreening under physician supervision.
G0147	Pap screening cytopathology smears, cervical or vaginal, performed by an automated system under physician supervision.
G0148	Pap screening cytopathology smears, cervical or vaginal performed by an automated system with manual rescreening.
P3000	Screening Papanicolaou smear, cervical or vaginal, up to three smears, by technician under physician supervision.
P3001	Screening Papanicolaou smear, cervical or vaginal, up to three smears, by technician under physician supervision, requiring interpretation by physician.
Q0091	Screening Papanicolaou smear; obtaining, preparing and conveyance of cervical or vaginal smear to laboratory.

A pelvic examination and Pap smear screening are used to screen for the detection of abnormal cancer cells. The ICD-9 and HCPCS codes were used to create dichotomous variables to determine whether cases and controls had received a Pap smear and/or pelvic examination screening during a particular year.

Data cleaning

Once the ICD-9 and HCPCS coding schemes were applied to both cases and controls, the data were cleaned. Typographical errors were corrected (such as the letter "O" where the number "0" should have been) and cross-checking zip code data with state data (as well as other demographic information).

Phase 1: Exclusion of ineligible cases and controls

Cases and controls that did not meet the study criteria were excluded. This study originally included 632 and 2,195 cases of vaginal and vulvar cancers, respectively identified from the SEER-Medicare data set. Thereafter, the data were cleaned to correct typographical errors, zip-code, state data and any other corrections that were deemed necessary. The rationale for exclusion is that in order to determine the efficacy of screening in older women, only those women age 65 and over were included.

Study criteria exclusion for cases included:

- *Age that was less than 65 years and greater than 100 years*
- *HMO coverage during the duration of the study period* (excluded because non-Medicare HMOs do not track claims/billing data)
- *Did not subscribe to both Medicare Parts A and B coverage during the duration the study period*
- *Cancers that were not histologically confirmed*

- *Diagnoses of in situ cancer*
- *Primary histological subtype was melanoma*

Study criteria exclusion for controls included:

- *Age that was less than 65 years and greater than 100 years*
- *Did not subscribe to both Medicare Parts A and B coverage during the duration of the study period*
- *Missing residential geographical information*

Since Medicare coverage extends to younger individuals who have a disability or end-stage renal disease, these younger women were excluded from this study. The study also excluded study subjects who did not subscribe to both Medicare Parts A and B. Medicare Part A provides coverage for both inpatient hospital care and skilled nursing facility care, while Medicare Part B provides coverage for private physician care and outpatient care.

Medicare Part A is provided to all qualified beneficiaries. Part A of Medicare provides coverage for inpatient care in short and long-term care facilities, skilled nursing facilities and home health or hospice care (Warren, et al. 2002). Medicare Part B is a voluntary option offered to all Part A eligible Medicare beneficiaries that provides coverage of physician services, outpatient care, durable medical equipment and some home health services (Warren, et al. 2002). It was important that study subjects subscribed to both Medicare Parts A and B based on the claims of services beyond that of Part A coverage of primarily inpatient care, in order to detect the history of previous Pap smear and pelvic examination screenings.

Since the aim of this study was to determine the efficacy of both pelvic examination and Pap smear screening in the reducing the risk of invasive vaginal and vulvar cancers, cases diagnosed with *in situ* cancers were excluded. The aim of screening is to detect *in situ* cancers

and additional dyplastic conditions. This study was designed to investigate the efficacy of preventive screenings in preventing the invasive disease rather than detecting pre-invasive disease.

Since both cases and controls were matched on population-based SEER registry, it was necessary to exclude those controls with missing residential geographical information.

Phase 2: Matching controls to cases

After excluding subjects that did not meet the study criteria, the controls were matched to cases. This study randomly matched eight or fewer controls with cases. It is important that case-control designs constitute a representative sample from the control population (McNeil, 1996). As mentioned in the data source section, there were four variables on which controls were matched to cases:

- *SEER registry*
- *Age*
- *Length of time in Medicare Part B coverage*
- *Date of diagnosis of the case/control*

The first variable is a categorical variable SEER registry which was matched to eliminate confounding by geographical location of residence.

The second covariate, age, is a continuous variable ranging from 65 through 100 years which is related to the incidence of vaginal and vulvar cancers. We utilized Kupper's caliper matching method. Since it would be difficult to match controls with an "exact" age match to cases, caliper matching allowed for cases and controls to be matched within a range of plus or minus two years (Kupper, 1998).

The third matching variable, reference date, is neither continuous nor categorical. This variable was used in matching to ensure that both cases and controls had a similar period of observation. Controls were matched to cases that had screening data over the same chronological period (cf. Weiss, 2006). This further ensures that cases and respective controls were followed for a similar number of years.

The matching procedures utilized the SAS statistical software package (SAS, 2005) to perform the data management to match controls to respective cases using algorithms and code to match controls to cases (Mounib and Satchi, 2000). The algorithms and code were used to construct the matched case/control data sets. The algorithms developed by Mounib and Satchi (2000) used the "without-replacement" technique to ensure that up to eight controls were matched to only one case.

Frequency tables

Once the data were cleaned and controls matched to cases, frequency tables were generated. Utilizing SAS, comparisons between cases and controls were made with respect to race, age, geographical location, income, and education. In order to classify income and education, they were changed into categorical variables so that analysis could be done. Each variable (income and education in the patient's zip code area) were divided into quartiles of 25%, 50%, 75% and 100% of the frequency in controls.

The SEER-Medicare data set has seven different race categories that include: white, black, Asian, Hispanic, North American Native, other and unknown. Since both vaginal and vulvar cancers are rare cancer sites, the race categories were combined even further by maintaining white and black races, while other races included Asian, Hispanic, North American Native, other and unknown races were included in the "other" race category.

Phase 3: Conditional logistic regression - analysis of association with screening tests

Conditional logistic regression was the third phase. The steps were as follows:

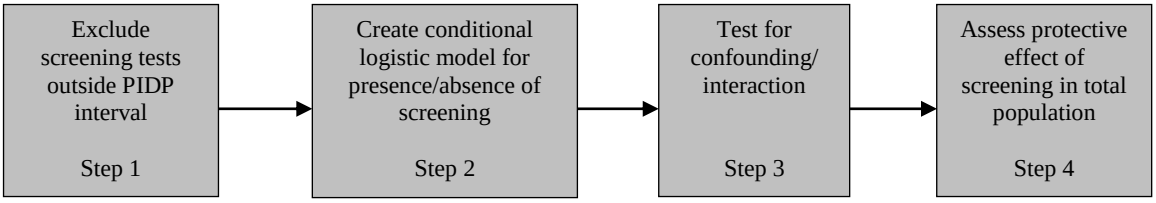
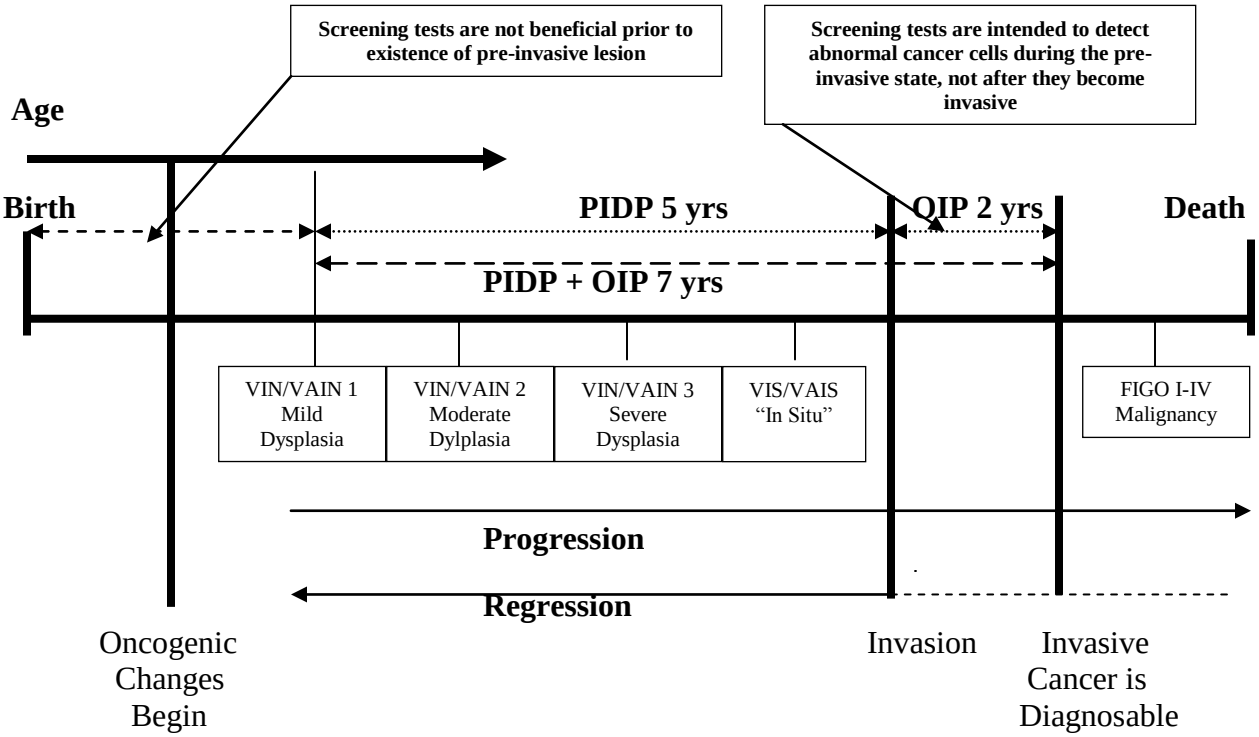


Figure 3: Overview of conditional logistic regression phase

Conditional logistic regression models were utilized to assess whether the presence of screening measures is effective in reducing invasive vaginal and vulvar cancer.

Step 1: Exclude screening tests outside PIDP interval

Once case-control matching was performed, screening histories of all subjects were assessed and screening tests that were in the pre-invasive detectable phase (PIDP) were classified as exposed. Weiss (1999) suggests there is a natural history of cancer development wherein, during the pre-invasive detectable phase (PIDP) "changes occur in a particular tissue that predispose to the development of cancer" (p. 102). It is during this time frame (PIDP) when screening tests are effective for determining a precursor cancer lesion (i.e., vulvar intraepithelial neoplasia or vaginal intraepithelial neoplasia). It is also necessary to exclude screening tests that were performed after an invasive cancer has occurred (OIP, the occult invasive phase) (Weiss, 1999). The rationale is that before the PIDP interval, the pre-cancerous lesion cannot be detected, thus the benefit of screening cannot be assessed. Similarly, screening tests performed after the lesion has become invasive cannot provide information about the benefit of screening (OIP). These changes may be present for a specific time period (i.e., years in the case of vaginal and vulvar cancers) (Figure 4). The nature of screening is to prevent invasive late stage disease.



Adapted from David Maduram MD/PhD, University of Illinois,
"An analysis of the efficacy of cervical cancer screening in elderly women", 2009

Figure 4: Exclusion of screening tests before PIDP and after OIP and screening tests that occurred between 2 and 7 years from date of diagnosis

Conditional logistic regression was used to analyze the protective effects of screening (Pap smears and pelvic examinations) and whether the presence of screening is effective in reducing the incidence of invasive vaginal and vulvar cancers. Figure 4 illustrates the practical implementation of screening test exclusion utilizing an OIP duration of two (2) years and PIDP duration of five (5) years. Population-based cervical cancer data were originally utilized by Weiss (1999) to calculate the OIP of two (2) years and PIDP of five (5) years for women of all ages. However, because the data utilized for this study was based solely on women in a Medicare population who were 65 years of age and older, it is possible that the durations of the OIP/PIDP may differ if older women are more likely than younger women to experience more

aggressive forms of vaginal and vulvar cancers. As such, to evaluate the effect of OIP/PIDP durations, this analysis examined various durations of the OIP and PIDP to assess difference in the estimated screening efficacy of pelvic examination and Pap smear screenings to determine the optimal estimated OIP and PIDP intervals.

The following Table 16 illustrates the combinations that were utilized for this analysis:

Table 16. Duration of occult invasive phase (OIP) and pre-invasive detectable phase (PIDP)

Duration of OIP (years)	Duration of PIDP (years)
1	4
1	5
1	6
2	4
2	5
2	6
3	4
3	5
3	6

Step 2: Create conditional logistic regression model for presence/absence of screening

The following regression model was used to test the hypothesis that the presence of screening is effective in reducing the incidence of invasive vaginal and vulvar cancers.

Regression model

The regression model was designed to assess whether Pap smear and pelvic examination screening reduces the risk of invasive vaginal and vulvar cancers. The following Table 17 illustrates the dependent and primarily independent variables in the model.

Table 17. Conditional logistic regression model: dependent and independent variables

Variable type	Variable	Coding
Dependent	Case-control status	1=case (i.e., disease present) 0=control (i.e., disease absent
Primary independent	Screening (during PIDP)	1=screened 0=not screened

As Table 17 indicates the first independent variable describes the screening status of the subject during the PIDP. This particular dichotomous variable score "1" indicates that the subject was screened during the PIDP, while "0" indicates that the subject was not screened during the PDIP. Table 18 illustrates the potential confounding variables.

Table 18. Potential confounding variables

Variable	Description	Coding
Race	White Black Other (Other, Asian, Hispanic, North American Native, Unknown)	Dummy variable coding (Table 6)
Income	Median household income of patient's zip code region	Dummy variable coding: 0=1st income quartile (0-24%) 1=2nd income quartile (25-49%) 2=3rd income quartile (50-74%) 3=4th income quartile (75-100%) Based on control values
Education	% individuals in patient's zip code region without high school or other education	Dummy variable coding: 0=1st education quartile (0-24%) 1=2nd education quartile (25-49%) 2=3rd education quartile (50-74%) 3=4th education quartile (75-100%) Based on control values

The above Table 18 illustrates the variable race as a categorical variable that is used to control for the potential confounding effects of race. The race "white" was used as the baseline for race and is dummy coded as follows:

Table 19. Coding for testing race as a potential confounder

	Race-based dummy variable	
Race	Race 1	Race 2
White	0	0
Black	1	0
Other	0	1

In addition to race, income and education are also potential confounders. Testing for the significance will add precision to the estimates if variables are statistically significant. The categorical variables income and education are based on quartiles of median household income and education levels present in the control population zip code areas.

Step 3: Test for confounding and interaction

Hosmer and Lemeshow (2000) suggest that the additional independent variables, discussed in the previous paragraph allow for statistical adjustment of potential differences in the distribution of the data. Further, Hosmer and Lemeshow (2000), suggest that epidemiologists use the term confounder to describe a covariate that is associated both with the outcome variable of interest (i.e., invasive disease) and the primary independent variable (i.e., absence/presence of screening). An interaction is described as the presence of a difference in an association between a risk factor and an outcome variable in different levels of a potential effect modifying variable (interaction).

Confounding

Case-control studies require some sort of statistical control in their design or analysis in order to strengthen the validity of conclusions (Breslow, 2005). "A confounder is an extraneous

factor(s) that may account for the observed effect of risk on disease." (Hosmer and Lemeshow, 2000, p. 70). In this study potential confounders such as income, education and race may need to be controlled for in order to make valid inferences on the exposure of interest (screening). In effect, potential confounders can have the potential to over or under estimate the primary independent variable and its association with the outcome variable (i.e., diagnosis of vaginal or vulvar cancer) (Rothman and Greenland, 2008).

Hosmer and Lemeshow (2000) suggest two ways of estimating the impact of a potential cofounder. The first is that the importance of the potential confounder can be assessed by determining whether there is an important change in the magnitude of the odds ratio for the primary independent variable (screening) between a logistic regression model fit without the potential confounder and a logistic regression model fit with the potential confounder (Hosmer and Lemeshow, 2000, Rothman and Greenland, 2008). The second step is to test the significance of the variable to see whether it affected the precision of the overall maximum likelihood estimate between a logistic regression model fit without the potential confounder and a logistic regression model fit with the potential confounder (Hosmer and Lemeshow, 2000). Both of these options were performed.

Confounding was first assessed by determining whether the inclusion of the potential confounder causes a substantial percentage change (> 5%) in the odds ratio of the primary independent variable. The odds ratio percentage change assessment does not determine statistical significance, but serves to determine whether a variable may be confounding. Next, the significance of the confounding variable was tested, utilizing the likelihood ratio test, and to assess the effect of the variable on the overall goodness of fit of the regression model. Each

potential confounder was incrementally added to the model, and tested for statistical significance to assess its role in increasing the precision of the estimate.

The CLOGIT procedures in the STATA statistical package were utilized to test the importance of the potential confounders.

Interaction

Once the confounders and significant variables were identified, the next step was to determine whether there is interaction among the variables. Epidemiologists use the term "effect modifier" to describe a covariate that interacts with a risk factor (Hosmer and Lemeshow, 2000). Effect modification occurs when association differs in different strata (e.g., age groups, education levels). It is important for the model to test for interactions that may potentially exist because interactions tend to significantly distort the parameter estimates of the independent variables (screening in the case of this study) in the model.

Effect modification or interaction is explored by creating an interaction variable equal to the product of the effect-modifying covariate and risk factor and by assessing the significance of the interaction when added to the full logistic model (Hosmer and Lemeshow, 2000). Effect modification can also be examined by stratification, but is not always practical in a matched study if the modifier has not been matched on (Kleinbaum, et al. 2003). The following Table 20 lists the potential model interaction variables.

Table 20. Model interaction variables

Interaction	Variable
Screening X	Income
Screening X	Race
Screening X	Education
Screening X	Age

This step in the model building process determined which interaction terms should be included in the model. Table 20 lists potential model interactions tested. Each interaction was added one at a time to the main effects model. The likelihood ratio test for the interactions terms was tested for significance to determine the most significant interaction term that should be included in the model. The difference between the two LR $\chi 2$ values is the difference of the $\chi 2$ and degree(s) of freedom using Excel's CHIDIST formula command to determine the LRT p-values.

The model interactions illustrated in Table 20 can be tested according to Hosmer and Lemeshow (2000) by testing the significance of the p-value of the interaction term at the alpha-level of 0.05. I tested for the multiplicative interaction among the covariates in the model. Based on earlier findings, potential interaction effects were tested (1) screening, race and income (vulvar cancer) and (2) screening, race and college education (vaginal cancer). As such, interaction variables were created between these variables utilizing STATA, and conditional logistic regression including these terms was executed.

Efficacy of screening

Once the final model was determined, whether the efficacy of screening remained constant within specific stratums of the population was investigated. Screening efficacy was studied with respect to age, race, cancer stage and histological type.

Step 4: Assess effect of screening in total population

Stratified regression analysis

The level of potential confounding and interactions in both cases and controls were tested, and the overall efficacy of screening was determined. Specific groups of cases (i.e., with localized, regional, distant cancers) were stratified to estimate the efficacy of screening

differences for stages of invasive disease. Stratified analysis was performed to test whether the stratified groups of cases and controls result in unique screening history patterns and if the efficacy of screening varies among the various case strata. Following (Table 21) are the variable strata for the stratified regression analysis.

Table 21. Variable strata for stratified regression analysis

Variable	Case strata	
Cancer stage	Localized Regional Distant Unstaged	
	Vaginal	Vulvar
Cancer histological types	Squamous cell carcinoma Adenocarcinoma Other	Squamous cell carcinoma Basal cell Paget Other

The CLOGIT procedure, included in the STATA statistical software package was used to perform the stratified regression analysis (StataCorp, 2005).

CHAPTER 4: RESULTS

The results of these analyses were performed in three phases as detailed in Chapter 3; (1) exclusion of ineligible cases and controls, (2) match controls to cases and (3) conditional logistic regression. The following are the results of these analyses.

Phase 1: Exclusion of ineligible cases and controls

The second step, or Phase 1 of the study, was to exclude those cases and controls that did not meet the study criteria. The following table illustrates the results of exclusionary data.

Table 22. Vaginal and vulvar cancers exclusion criteria for cases

Exclusion criteria	Cases in population after exclusion	
	Vaginal	Vulvar
Base population	632	2,195
Women younger than 65 years old and older than 100	632	2,186
Enrolled in an HMO during study period	560	1,966
Not covered by both Medicare Parts A and B	529	1,862
Diagnosed with intermediate behavior or *in-situ* disease	334	1,126
Cancers not histologically confirmed	328	1,108
Diagnosed "melanoma"	328	1,103

The base population included 632 vaginal cancer cases and 2,195 vulvar cancer cases. There were zero (0) vaginal cases excluded among women younger than 65 years and older than 100 years and nine (9) vulvar cases that were excluded from this category. There were 72 vaginal cancer cases and 220 vulvar cancer cases excluded who were enrolled in an HMO during the study period. There were 31 vaginal cancer cases and 104 vulvar cancer cases not covered by both Medicare Parts A and B. Among cases diagnosed with intermediate behavior or *in situ* disease, 195 vaginal cancer cases and 746 vulvar cancer cases were excluded. Of vaginal cancer

cases, six (6) and vulvar cancer cases, eight (8) were excluded whose cancers were not histologically confirmed. Since "melanoma" is not diagnosed among vaginal cancer cases, none (0) were excluded; however, there were five (5) vulvar cancer cases excluded. Finally, there were 328 vaginal cancer cases and 1,103 vulvar cancer cases included in this analysis (Table 22).

Phase 2: Match controls to cases

Once the data were cleaned and controls were matched to cases, frequency tables were generated. The following tables were generated based on (1) age, (2) geographic location, (3) race, (4) income, (5) education, (6) historic stage and (7) histology.

Age

Age was stratified into five-year age groups in order to generate appropriate frequency tables.

Table 23. Frequency tables for age in cases and controls, vaginal cancer

	Cases		Controls	
Age	Frequency	Percentage	Frequency	Percentage
65-70	20	6.1	160	6.1
71-75	52	15.9	416	15.9
76-80	90	27.4	720	27.4
81-85	74	22.6	592	22.6
86-90	53	16.2	424	16.2
91-95	32	9.8	256	9.8
96-100	7	2.1	56	2.1
All Ages	328	100.0	2,624	100.0

The majority of invasive vaginal cancer cases peaked around the age of 76-80 accounting for 27.4% of cases; while there are fewer cases at the youngest age category (6.1%) and the oldest age category (2.1%) (Table 23). Since the controls were matched to cases based on age and other variables, the distribution of cases and controls is evenly distributed.

Table 24. Frequency tables for age and cases, vulvar cancer

	Cases		Controls	
Age	Frequency	Percentage	Frequency	Percentage
65-70	26	2.4	208	2.4
71-75	144	13.1	1,152	13.1
76-80	232	21.0	1,856	21.0
81-85	276	25.0	2,208	25.0
86-90	237	21.5	1,896	21.5
91-95	141	12.8	1,129	12.8
96-100	47	4.3	376	4.3
All Ages	1,103	100.0	8,825	100.0

As illustrated in Table 24, the same strategy of matching controls to cases was applied to the vulvar cancer data set. For invasive vulvar cancer, cases peaked at the 81-85 year age group accounting for a quarter (25%) of cases. The fewest cases were found in the youngest (2.4%) and oldest (4.3%) age categories.

Geographic location

Both cases and controls were selected from the eleven geographic locations where SEER cancer registries are located. These areas include the states of Connecticut, Iowa, New Mexico, Utah, Hawaii and the metropolitan regions of Atlanta, Detroit, Seattle, San Jose, San Francisco and Los Angeles.

Table 25. Frequency tables for geographical location in cases and controls, vaginal cancer

Geographic location	Cases		Controls	
	Frequency	Percentage	Frequency	Percentage
Connecticut	34	10.4	272	10.4
Iowa	42	12.8	336	12.8
Detroit	72	22.0	576	22.0
Atlanta	22	6.7	176	6.7
New Mexico	18	5.5	144	5.5
Utah	11	3.4	88	3.4
Seattle	34	10.4	272	10.4
San Jose	8	2.4	64	2.4
San Francisco	24	7.3	192	7.3
Los Angeles	54	16.5	432	16.5
Hawaii	9	2.7	72	2.7
All Regions	328	100.0	2,624	100.0

The majority of both invasive vaginal cancer cases and controls are from the Detroit cancer registry (22.0%), followed by Los Angeles (16.5%), Iowa (12.8%), Connecticut and Seattle (both 10.4%), San Francisco (7.3%), Atlanta (6.7%), New Mexico (5.5%), Utah (3.4%), Hawaii (2.7%) and San Jose (2.4%) (Table 25). However, since the controls were matched on geographical location the distribution of cases and controls is evenly distributed.

Table 26. Frequency tables for geographical location in cases and controls, vulvar cancer

	Cases		Controls	
Geographic location	Frequency	Percentage	Frequency	Percentage
Connecticut	189	17.1	1,512	17.1
Iowa	208	18.0	1,664	18.9
Detroit	205	18.6	1,640	18.6
Atlanta	58	5.3	464	5.3
New Mexico	33	3.0	265	3.0
Utah	37	3.4	296	3.4
Seattle	114	10.3	912	10.3
San Jose	50	4.5	400	4.5
San Francisco	62	5.6	496	5.6
Los Angeles	135	12.2	1,080	12.2
Hawaii	12	1.1	96	1.1
All Regions	1,103	100.0	8,825	100.0

The majority of both invasive vaginal cancer cases and controls are from the Detroit cancer registry (18.6%), followed by Iowa (18.0%), Connecticut (17.1%), Los Angeles (12.1%), Seattle (10.3%), San Francisco (5.6%), Atlanta (5.3%), San Jose (4.5%), Utah (3.4%), New Mexico (3.0%) and Hawaii (1.1%) (Table 26). However, since the controls were matched on geographical location the distribution of cases and controls is evenly distributed.

Race

There were not enough cases and controls to analyze the data without the combining of race categories.

Table 27. Frequency tables for race in cases and controls, vaginal cancer

	Cases		Controls	
Race	Frequency	Percentage	Frequency	Percentage
White	261	79.6	2,164	82.5
Black	46	14.0	233	8.9
Other	21	6.4	227	8.7
All Races	328	100.0	2,624	100.0

The majority of invasive vaginal cancer cases (79.6%) are of the white race, followed by black (14.0%) and other (6.4%) races (Table 27). Since controls are matched to cases, similar results are found, the majority of controls are of white race (82.5%), black race (8.9%) and other (8.7%) races. There is a higher percent of black women with vaginal cancer (14.0%) than the percent of women without vaginal cancer among black women (8.9%).

Table 28. Frequency tables for race in cases and controls, vulvar cancer

	Cases		Controls	
Race	Frequency	Percentage	Frequency	Percentage
White	1,008	91.5	7,712	87.4
Black	48	4.4	632	7.2
Other	46	4.2	481	5.5
All Races	1,103	100.0	8,825	100.0

The majority of invasive vulvar cancer cases (91.5%) are of the white race, followed by black (4.4%) and other (4.2%) races (Table 28). Once again, since controls are matched to cases, similar results are found, the majority of controls are of white race (87.4%), black race (7.2%) and other (5.5%) races. There is a higher percent of white women with vulvar cancer (91.5%) than women without vulvar cancers (87.4%).

Income

The following are the frequency distributions of income for both vaginal and vulvar cancers based on quartile values.

Table 29. Frequency tables for median income in cases and controls, vaginal cancer

	Cases		Controls	
Income	Frequency	Percentage	Frequency	Percentage
$0-$36,330	109	33.0	656	25.0
$36,331-$46,757	93	28.0	658	25.0
$46,758-$59,719	63	19.0	655	25.0
$49-720-$200,001	63	19.0	655	25.0
All Income	328	100.0	2,624	100.0

The majority of invasive vaginal cancer cases are in the lowest median quartile (33.0%) suggesting that lower income is associated with invasive disease (Table 29). Further, invasive vaginal cases based on income are followed by the second lowest median quartile (28.0%), third median quartile (19.0%) and fourth median quartile (19.0%), illustrating that as income increases, invasive vaginal cancer decreases.

Table 30. Frequency tables for median income in cases and controls, vulvar cancer

	Cases		Controls	
Income	Frequency	Percentage	Frequency	Percentage
$0-$37,189	284	26.0	2,212	25.0
$37,190-$46,838	295	27.0	2,210	25.0
$46,839-$60,030	300	27.0	2,200	25.0
$60,031-$200,001	224	20.0	2,203	25.0
All Income	1,103	100.0	8,825	100.0

The majority of invasive vulvar cancer cases are found in the second and third median quartiles (27.0% and 27.0%, respectively), followed by the lowest median quartile (26.0%) and the highest median quartile (20.0%). Although the first three quartiles are very similar in number of cases, at the highest income invasive vulvar cancer frequency decreases indicating that as income rises, the frequency of invasive disease decreases.

Education

The following are the results of education for both vaginal and vulvar cancers based on these quartile values.

Table 31. Frequency tables for education, vaginal cancer

	Cases		Controls	
	Frequency	Percentage	Frequency	Percentage
Less than high school:				
0.0%-9.2%	56	17.0	657	25.0
9.3%-14.4%	67	20.0	656	25.0
14.5%-23.3%	85	26.0	655	25.0
23.4%-100.0%	120	37.0	656	25.0
High school:				
0.0%-18.5%	56	17.0	656	25.0
18.6%-25.4%	89	27.0	656	25.0
25.5%-32.4%	94	29.0	658	25.0
32.5%-100.0%	23	27.0	654	25.0
Some college:				
0.0%-25.0%	84	26.0	656	25.0
25.1%-28.9%	88	27.0	658	25.0
29.0%-32.8%	79	24.0	657	25.0
32.9%-100.0%	77	23.0	653	25.0
College:				
0.0%-15.0%	118	36.0	655	25.0
15.1%-24.1%	91	28.0	657	25.0
24.2%-38.1%	58	18.0	656	25.0
38.2%-100.0%	61	19.0	656	25.0

The results in Table 31 suggest that low educational level is associated with vaginal cancer. At the lowest education level, the “less than high school” category (23.4%-100.0% level), 37% of women had invasive vaginal cancer. However, it is also important to note, that in

the lowest level of four years or more of college education level there were 36% of women with invasive vaginal cancer.

Table 32. Frequency tables for education, vulvar cancer

	Cases		Controls	
	Frequency	Percentage	Frequency	Percentage
Less than high school:				
0.0%-9.3%	238	22.0	2,203	25.0
9.4%-13.9%	281	25.0	2,212	25.0
14.0%-20.3%	270	24.8	2,206	25.0
20.4%-100.0%	313	28.0	2,204	25.0
High school:				
0.0%-19.2%	263	24.0	2,204	25.0
19.3%-26.6%	259	23.0	2,213	25.0
26.7%-33.7%	291	26.0	2,206	25.0
33.8%-100.0%	290	26.0	2,202	25.0
Some college:				
0.0%-25.0%	282	26.0	2,227	25.0
25.1%-28.7%	280	25.0	2,212	25.0
28.8%-32.7%	274	25.0	2,197	25.0
32.8%-100.0%	267	24.0	2,189	25.0
College:				
0.0%-15.1%	311	28.0	2,214	25.0
15.2%-23.5%	269	24.0	2,207	25.0
23.6%-38.3%	278	25.0	2,202	25.0
38.4%-100.0%	245	22.0	2,202	25.0

As Table 32 suggests, invasive vulvar cancer frequency cases are fairly evenly distributed among all educational levels. However, in the lowest education level, the “less than high school” (20.4%-100.0%) category, 28% of women had invasive vulvar cancer. In the highest education category (four years or more of college), 28% of women were in the lowest quartile.

Cancer historic stage and histology

The SEER-Medicare dataset for vaginal and vulvar cancer cases provided several descriptive variables about the nature of the tumor, including cancer historic stage and histologic type. The following Tables 33 and 34 show the results of the frequency tables for both historic stage and histologic type in vaginal cancer.

Table 33. Frequency tables for historic stage in cases, vaginal cancer

Historic Stage	Frequency	Percentage
Localized	114	34.8
Regional	84	25.6
Distant	55	16.8
Unstaged	75	22.9

Table 33 suggests that invasive vaginal cancer is diagnosed more commonly among the localized historic stage of disease (34.8%), followed by regional (25.6%), unstaged (22.9%) and distant (16.8%) of invasive disease cases.

Table 34. Frequency tables for histological type in cases, vaginal cancer

Histological Type	Frequency	Percentage
Adenocarcinoma	29	8.8
Squamous cell carcinoma	242	73.8
Other histologies*	57	17.4
*Carcinomas, NOS, other specific carcinomas		

As the above Table 34 shows 73.8% of invasive vaginal cancer was of the squamous cell carcinoma histological type, with “other histologies” and adenocarcinoma accounting for 17.4% and 8.8% respectively.

The following Tables 35 and 36 present the results of the frequency tables for historic stage and histological type in cases for vulvar cancers.

Table 35. Frequency tables for historic stage in cases, vulvar cancer

Historic stage	Frequency	Percentage
Localized	680	61.7
Regional	303	27.5
Distant	45	4.1
Unstaged	75	6.8

The majority of cases in the study were diagnosed at the localized historic stage of vulvar cancer (61.7%), followed by regional (27.5%), distant (4.1%) and unstaged (6.8%) disease (Table 35).

Table 36. Frequency tables for histologic type in cases, vulvar cancer

Histological type	Frequency	Percentage
Squamous cell carcinoma	807	73.2
Basal cell carcinoma	129	11.7
Paget disease	127	11.5
Other histologies*	40	3.6
*Carcinoma, NOS, other specified types		

Table 36 shows that squamous cell carcinoma was by far the most common histological type for invasive vulvar cancer, followed by basal cell carcinoma (11.7%), Paget disease (11.5%) and "other histologies" (3.6%).

Phase 3: Conditional logistic regression

After generation of frequency tables, four steps were performed in phase 3 of the analysis: (1) exclusion of screening tests outside the PIDP interval; (2) creation of conditional logistic regression models for presence/absence of screening; (3) testing for confounding and interaction; and (4) assessing protective effect of screening in total population.

Step 1: Exclude screening tests outside the PIDP interval

Screening histories of both cases and controls were assessed. Screening tests that were in the pre-invasive detectable phase (PIDP) were included (see Figure 1, Chapter 3). Several combinations of OIP and PIDP were analyzed. The OIP of two (2) years and PIDP of five (5) was determined for both vaginal and vulvar cancers. The combination captures the majority of cases who have invasive vaginal or vulvar cancers and excludes screening histories that were likely to have been done for the purpose of diagnoses in response to symptoms or signs of disease. The combination includes only those histories that were done for screening purposes (Weiss, 1999).

Step 2: Create conditional logistic regression model for presence/absence of screening

First, the unadjusted estimates were analyzed along with a test for trends. The following Tables 37 and 38 show the results of this analysis.

Table 37. Vaginal cancer unadjusted estimates

		Cases		Controls			
Variable		Frequency	Percentage	Frequency	Percentage	OR	95% CI
Screening status	Screened	48	14.6	464	17.7	0.79	0.57-1.11
	Unscreened	280	85.4	2,160	82.3		
Race	White	261	79.6	2,164	82.5	1.00	
	Black	46	14.0	233	8.9	1.72	1.20-2.46
	Other	21	6.4	227	8.7	0.69	0.41-1.17
Income	$0-$36,330	109	33.0	656	25.0	1.00	
	$36,331-$46,757	93	28.0	658	25.0	0.84	0.62-1.13
	$46,758-$59,719	63	19.0	655	25.0	0.54	0.38-0.75
	$59,720-$200,001	63	19.0	655	25.0	0.50	0.35-0.72
						(p = 0.00001)	
Less than high school	0-0.0972	56	17.0	657	25.0	1.00	
	0.0973-0.14954	67	20.0	656	25.0	1.17	0.82-1.68
	0.14955-0.2298	85	26.0	655	25.0	1.38	0.97-1.97
	0.2299-1	120	37.0	656	25.0	2.18	1.56-3.04
						(p =0.0000001)	
High school	0-0.19	56	17.0	656	25.0	1.00	
	0.25226-0.2893	89	27.0	656	25.0	1.47	1.04-2.08
	0.2894-0.3286	94	29.0	658	25.0	1.99	1.34-2.94
	0.3287-1	23	27.0	654	25.0	1.92	1.24-2.96
						(p =0.001)	
Some college	0-0.25225	84	26.0	656	25.0	1.00	
	0.25226-0.2893	88	27.0	658	25.0	1.07	0.77-1.48
	0.2894-0.3286	79	24.0	657	25.0	0.95	0.67-1.34
	0.3299-1	77	23.0	653	25.0	0.91	0.63-1.31
						(p = 0.522)	
College	0-0.15161	118	36.0	655	25.0	1.00	
	0.15162-0.22675	91	28.0	657	25.0	0.78	0.57-1.06
	0.22676-0.37065	58	18.0	656	25.0	0.47	0.33-0.66
	0.37066-1	61	19.0	656	25.0	0.46	0.32-0.65
						(p = 0.00000002)	

The univariate or unadjusted estimates model allows analysis of a single variable. The above Table 37 (vaginal cancer) presents finding for the variables race, income, education (less than high school, high school, some college and college) for vaginal cancer cases and controls. The trends test suggests that income, less than high school education, high school education and college are statistically significant at the $p<0.05$ level.

The unadjusted estimates model suggests that overall screening status (everpap) decreases the risk of invasive vaginal cancer when screening is performed (OR 0.79, 95% CI 0.57-1.11), but these results are not statistically significant (Table 37). Regarding income, significant results are found in the third and fourth income quartiles (OR 0.54, 95% CI 0.38-0.75 and OR 0.50, 95% CI 0.35-0.72, respectively); test for trend is also significant at the $p<0.05$ level. Invasive disease is related to lower socio-economic status.

Significant results are also found among invasive vaginal cancer cases in the third and fourth quartiles of more than four years of college education (OR 0.47, 95% CI 0.33-0.66 and OR 0.46, 95% CI 0.32-0.65, respectively); test for trends is also significant at the $p<0.05$ level. Again, these findings, while unadjusted, suggest that invasive vaginal cancer is related to low socio-economic status.

Table 38. Vulvar cancer unadjusted estimates

Variable		Cases		Controls			
		Frequency	Percentage	Frequency	Percentage	OR	95% CI
Screening status	Screened	218	19.8	1,588	18.0	1.13	0.95-1.33
	Unscreened	885	80.2	7,236	82.0		
Race	White	1,008	91.5	7,712	87.4	1.00	
	Black	48	4.4	632	7.2	0.56	0.41-0.76
	Other	46	4.2	481	5.5	0.69	0.50-0.97
Income	$0-$37,075	284	26.0	2,212	25.0	1.00	
	$37,076-$46,467	295	27.0	2,210	25.0	1.06	0.89-1.27
	$46,468-$59,703	300	27.0	2,200	25.0	0.99	0.82-1.19
	$59,704-$200,001	224	20.0	2,203	25.0	0.76	0.62-0.93
							(p = 0.009)
Less than high school	0-0.09384	238	22.0	2,203	25.0	1.00	
	0.09385-0.14084	281	25.0	2,212	25.0	1.23	0.82-1.68
	0.14085-0.2071	270	24.8	2,206	25.0	1.17	0.97-1.97
	0.2072-1	313	28.0	2,204	25.0	1.33	1.56-3.04
							(p = 0.008)
High school	0-0.1927	263	24.0	2,204	25.0	1.00	
	0.1928-0.2670	259	23.3	2,213	25.0	1.02	0.58-1.24
	0.2671-0.3385	291	26.0	2,206	25.0	1.19	0.97-1.47
	0.3386-1	290	26.0	2,202	25.0	1.24	0.98-1.48
							(p = 0.035)
Some college	0-0.2507	282	26.0	2,227	25.0	1.00	
	0.2508-0.2875	280	25.0	2,212	25.0	1.00	0.84-1.19
	0.2876-0.3275	274	25.0	2,197	25.0	0.99	0.82-1.19
	0.3376-1	267	24.0	2,189	25.0	0.94	0.77-1.15
							(p = 0.571)
College	0-0.1515	311	28.0	2,214	25.0	1.00	
	0.1516-0.2350	269	24.0	2,207	25.0	0.88	0.74-1.05
	0.2351-0.3823	278	25.0	2,202	25.0	0.90	0.75-1.08
	0.3824-1	245	22.0	2,202	25.0	0.78	0.64-0.94
							(p = 0.017)

In the above Table 38 (vulvar cancer), analyses of the variables race, income, education (less than high school, high school, some college and college) for vulvar cancer cases and controls are presented. The test for trend shows that income and less than high school are statistically significant at the $p<0.05$ level which may relate to low income and low education and their association with greater disease risk. Furthermore, four or more years of college is also statistically significant at $p<0.05$ level, suggesting that at higher education categories the risk of disease is lower.

Furthermore, the unadjusted estimates model suggests that overall screening status does not decrease the risk of invasive vulvar cancer when screening is performed (OR 1.13, 95% CI 0.95-1.33) (Table 38). Significant findings are suggested in the race category, where black (OR 0.56, 95% CI 0.41-0.76) and "other" races (OR 0.69, 95% CI 0.50-0.97) are significant when compared to the reference category. Significant results are also found in the fourth quartiles of more than four years of college education (OR 0.78, 95% CI 0.64-0.94). These findings suggest that in these particular race and education categories, there is a decreased risk of invasive disease. However, these are unadjusted estimates and require further analysis.

In the third quartile level of income (OR 0.99, 95% CI 0.82-1.19) as well as in the third and fourth quartiles of the some college category (OR 0.99, 95% CI 0.82-1.19 and OR 0.94, 95% CI 0.77-1.15) there appears to be no association between the income categories and invasive disease. Findings for the second and third quartiles of four years or more of college (OR 0.88, 0.74-1.05 and OR 0.90, 95% CI 0.75-1.08, respectively) suggest that the higher the education, the lower the risk of invasive disease.

Step 3. Test for confounding and interaction

After testing the individual variables for significance, a forward selection approach to model building was used (Tables 39 and 40).

Table 39. Vaginal cancer forward selection models

Models	OR	% Δ OR	LRT p-value (one-sided) (everpap only)	LRT p-value (one sided) (everpap and race)
Everpap only model	0.79			
Everpap and race only model	0.80	-1.12	0.005017	
Everpap and race only model	0.80	-1.12		
Everpap, race and income only model	0.83	-4.11		0.00015
Everpap, race and < high school only model	0.84	-5.93		0.00012
Everpap, race and high school only model	0.81	-2.10		0.00914
Everpap, race and some college only model	0.80	-1.25		0.87085
Everpap, race and college only model	0.84	-5.14		0.00000

The likelihood ratio $\chi 2$ test for each parameter estimate was based on comparing two logistic models. The first model in Table 39 is the one with the individual variable included for testing and one without it. In this case the first model is the screening status only model and the second is the screening status and race model.

When comparing the everpap only model with the everpap and race only model the percentage change in odds ratio is calculated, along with the LRT p-value (one-sided) (everpap only). The resulting percentage change in odds ratio is less than five percent (5%) and the $p<0.05$ is significant. Since the result is significant, the other socio-economic variables with everpap and race were tested.

Next, income was added to the everpap and race model, then the other socio-economic status variables. The resulting percentage change in odds ratio for all the models is less than five percent (5%) and the LRT p-value is not significant for any of the other education variables. Therefore, the model with the most significant LRT $p<0.05$ is "everpap, race and college only model".

Table 40. Vulvar cancer forward selection models

Models	OR	% Δ OR	LRT p-value (one-sided) (everpap only)	LRT p-value (one sided) (everpap and race)
Everpap only model	1.13			
Everpap and race only model	1.11	1.90	0.000007	
Everpap and race only model	1.11	1.90		
Everpap, race and income only model	1.11	1.62		0.00000
Everpap, race and < high school only model	1.13	0.18		0.00013
Everpap, race and high school only model	1.12	1.08		0.07718
Everpap, race and some college only model	1.11	1.62		0.72626
Everpap, race and college only model	1.12	0.36		0.00224

For vulvar cancer, the first model tested (Table 40) is the one with the individual variable included for testing and one without. In this case the first model is the screening status only model and the second is the everpap and race model. The LRT and corresponding p-values were calculated the same way for vulvar cancer as for analyses of vaginal cancer.

The resulting percentage change in odds ratio is less than five percent (5%) for all models. However, for the "everpap, race and income only" and the "everpap, race and less than high school only" models are significant at the $p<0.05$. Since the result is significant, the other socio-economic variables with everpap and race were tested.

Next, income was added to the everpap and race model, then the other socio-economic variables. The resulting percentage change in odds ratio for all the models is less than five percent (5%) and the LRT p-value is not significant for any of the education variables. Therefore, the model with the most significant LRT p-value ($p<0.05$) is "everpap, race and income only model." For vulvar cancer, the model "everpap, race and income" was the most significant and thus, chosen to test for significance of interaction.

Table 41. Vaginal cancer test of significance of interactions

	Cases				Controls						
	Screened		Unscreened		Screened		Unscreened				LRT p-value
Variable	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage	OR	95% CI	(one-sided)
Age:											
65-74	6	1.3	53	11.6	40	8.8	356	72.5	1.02	0.40-2.64	
75-84	28	1.8	134	8.6	317	20.4	1,078	73.1	0.72	0.47-1.12	
85-100	14	1.5	93	9.9	104	11.1	729	80.6	1.11	0.59-2.05	0.43823
Race:											
White	42	1.7	219	9.0	405	16.7	1,759	72.5	0.84	0.60-1.17	
Black	2	0.7	44	15.8	29	10.4	204	73.1	0.41	0.90-1.83	
Other	4	1.6	17	6.9	27	10.9	200	80.6	2.18	0.64-7.46	0.18731
College:											
0.0%-15.1%	20	2.6	98	12.6	92	11.8	567	73.0	1.26	0.73-2.18	
15.2%-22.6%	9	1.4	74	11.2	94	14.3	481	73.1	0.65	0.31-1.34	
22.7%-37.0%	7	0.9	56	7.4	150	19.7	548	72.0	0.46	0.21-1.04	
37.1%-100.0%	12	1.6	52	6.9	125	16.5	567	75.0	1.04	0.53-2.03	0.02072

In the above Table 41, the variable “college” is significant at the $p<0.05$ level. Therefore, the analyses suggest a significant interaction between the variables “college” and “everpap”. There is no significant effect modification between screening status (everpap) and age ($p=0.44$), nor between screening status (everpap) and race ($p=0.19$).

The results in the above table suggest there is no pattern of association between age, race and screening status with four (4) years or more of college education and therefore age and race are not included in the final model.

Table 42: Vulvar cancer test of significance of interactions model

	Cases				Controls						
	Screened		Unscreened		Screened		Unscreened				LRT p-value
Variable	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage	OR	95% CI	(one-sided)
Age:											
65-74	15	1.5	119	11.7	155	15.3	725	71.5	0.57	0.31-1.00	
75-84	121	2.6	379	8.1	926	19.9	3,227	69.4	1.13	0.90-1.42	
85-100	82	1.9	387	9.1	511	13.0	3,281	77.0	1.38	1.06-1.80	0.01067
Race:											
White	207	2.4	802	9.2	1,461	16.8	6,251	71.7	1.11	0.94-1.32	
Black	7	1.0	41	6.0	73	10.7	559	82.2	1.30	0.56-3.03	
Other	4	0.8	42	8.0	58	11.0	423	80.3	0.72	0.25-2.09	0.65705
Income:											
$0-$37,075	55	2.3	221	9.1	335	13.8	1,814	74.8	1.33	0.96-1.84	
$37,076-$46,467	57	2.3	239	9.7	447	18.2	1,715	69.8	0.92	0.67-1.25	
$46,468-$59,703	63	2.4	236	9.2	414	16.1	1,860	72.3	1.20	0.88-1.62	
$59,704-$200,001	43	1.7	189	7.6	396	16.0	1,844	74.6	1.05	0.74-1.50	0.38247

The results in Table 42 shows the variable “age” to be significant at the $p<0.05$ level which indicates a significant interaction between the variable “age” and screening status (everpap). The negative effect of screening status is only seen at the youngest age category (65-74 years).

The results in the above table further suggest that even though there is no significant interaction between screening and race, the “other” race category suggests invasive vulvar cancer is decreased when screening is performed (OR 0.72, 95% CI 0.25-2.09). There is no significant interaction between screening status and race ($p=0.66$) or screening and income ($p=0.38$) (Table 42).

Table 43. Vaginal cancer final model

Variable		Cases		Controls		OR	95% CI	p-value
		Frequency	Percentage	Frequency	Percentage			
Screening status	Screened	48	14.6	461	17.6	0.84	0.60-1.17	0.297
	Unscreened	280	85.4	2,163	83.4			
Race	White	261	79.6	2,164	82.5	1.00		
	Black	46	14.0	233	8.9	1.37	0.94-1.99	0.098
	Other	21	6.4	227	8.7	0.81	0.34-1.00	0.049
College	0.0%-15.1%	118	36.0	655	25.0	1.00		
	15.2%-22.6%	91	28.0	657	25.0	0.81	0.59-1.10	0.175
	22.7%-37.0%	58	18.0	656	25.0	0.48	0.34-0.68	0.000
	37.1%-100%	61	19.0	656	25.0	0.48	0.34-0.68	0.000

The results in Table 43 suggest that the overall risk of invasive vaginal cancer is reduced by having pelvic examinations and Pap smear screenings (OR 0.84, 95% CI 0.60-1.17); however, these results are not statistically significant. Thus, our hypothesis that the use of pelvic examination and Pap smear screenings is effective in reducing the risk of vaginal cancers in women aged 65 and over is not supported. The results suggest there is no association between screening and the risk of invasive vaginal cancer.

For the the race category, black (OR 1.37, 95% CI 0.94-1.99) race has a positive association with invasive disease. In addition, older women who have had four (4) years of college (0.0%-15.1%) education have a decreased risk of vaginal cancer when compared to the reference group (OR 0.81, 95% CI 0.59-1.10; OR 0.48, 95% CI 0.34-0.68 and OR 0.48, 95% CI 0.34-0.68 respectively), thus indicating a negative association between high socio-economic status and invasive disease. Results are significant for the last two (2) quartiles of college education.

Table 44. Vulvar cancer final model

Variable		Cases		Controls		OR	95% CI	p-value
		Frequency	Percentage	Frequency	Percentage			
Screening status	Screened	218	19.8	1,592	18.0	1.11	0.94-1.31	0.215
	Unscreened	885	80.2	7,233	82.0			
Race	White	1,008	91.5	7,712	87.4	1.00		
	Black	48	4.4	632	7.2	0.47	0.34-0.65	>0.001
	Other	46	4.2	481	5.5	0.65	0.47-0.91	0.012
Income	$0-$37,075	284	26.0	2,212	25.0	1.00		
	$37,076-$46,467	295	27.0	2,210	25.0	0.95	0.79-1.14	0.587
	$46,468-$59,703	300	27.0	2,200	25.0	0.84	0.69-1.02	0.078
	$59,704-$200,001	224	20.0	2,203	25.0	0.63	0.51-0.78	<0.001

The results presented in Table 44 refer to the final model in the analysis. The results suggest that the overall risk of invasive vulvar cancer includes a slight positive association between disease and having pelvic examinations and Pap smear screenings (OR 1.11, 95% CI 0.94-1.31); however, the results are not significant. Thus, the hypothesis that use of pelvic examination and Pap smear screenings is effective in reducing the risk of vulvar cancers in women aged 65 and over is not confirmed. The results suggest there is no association between screening and the risk of invasive vaginal cancer.

For race, with white race as a baseline reference, there is a significant negative association between invasive disease and black race. For race, black (OR 0.47, 95% CI 0.34-0.65) compared whites presents an overall decrease in risk of invasive disease (Table 44).

All income category findings suggest that low income is related to the development of vulvar cancers. Compared to the baseline income category, at $37,076-$46,467 (OR 0.95, 95% CI 0.79-1.14), $46,468-$57,703 (OR 0.84, 95% CI 0.69-1.02) and the upper income category $59,704-$200,001 (OR 0.63, 95% CI 0.51-0.78), these findings show a reduced risk of disease with higher income.

Step 4: Assess effect of screening in total population

Assessing the association between screening and invasive vaginal cancer by age and college, involved testing for the interaction between age and college education (Table 45).

Table 45. Association between screening and invasive vaginal cancer by age, race and college education

	Screened				Unscreened					
	Cases		Controls		Cases		Controls			
Combinations	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage	OR	95% CI
Age:										
65-74 years	6	1.3	40	8.8	53	11.6	356	78.2	1.09	0.42-2.82
75-84 years	28	1.8	317	20.4	134	8.6	1,078	69.2	0.72	0.46-1.11
85-100 years	14	1.5	104	11.1	93	9.9	729	77.6	1.13	0.61-2.09
Race:										
White	42	1.7	405	16.7	219	9.0	1,759	72.5	0.86	0.60-1.22
Black	2	0.7	29	10.4	44	15.8	204	73.1	0.36	0.08-1.59
Other	4	1.6	27	10.9	17	6.9	200	80.7	0.54	0.55-5.85
College:										
0.0%-15.1%	20	2.6	92	11.8	98	12.6	567	73.0	1.29	0.75-2.23
15.2%-22.6%	9	1.4	94	14.3	74	11.2	481	73.1	0.65	0.31-1.34
22.7%-37.0%	7	0.9	150	19.7	56	7.4	548	72.0	0.46	0.20-1.05
37.1%-100%	12	1.6	125	16.5	52	6.9	567	75.0	1.03	0.53-2.03

The results of the conditional logistic regression analyses performed on age are shown in Table 45. Median age of cases and controls for vaginal cancer was 81.6 years. There was no significant interaction between screening and age. The results for race suggest that screening is effective in all race categories: white OR 0.86 (95% CI 0.60-1.22), black OR 0.36 (0.08-1.59) and other races OR 0.54 (0.55-5.85). However, these results are not significant.

The association between screening and invasive vaginal cancer among women with more than four (4) years of college education suggests the first (OR 1.29, 95% CI 0.75-2.23) and last (OR 1.03, 95% CI 0.53-2.03) tiers of individuals in zip code region are at a slight risk of invasive disease compared to the middle two tiers of women in those zip code regions with more than four (4) years of college education (OR 0.65, 95% CI 0.31-1.34 and OR 0.46, 95% CI 0.20-1.05, respectively) (Table 45). However, the results are not significant and there is not a pattern of interaction with college education..

Table 46. Association between screening and invasive vulvar cancer by age, race and income

	Screened				Unscreened					
	Cases		Controls		Cases		Controls			
Combinations	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage	OR	95% CI
Age:										
65-74 years	15	1.5	155	15.3	119	11.7	725	71.5	0.55	0.31-0.97
75-84 years	121	2.6	926	19.9	379	8.1	3,227	69.4	1.11	0.88-1.38
85-100 years	82	1.9	511	12.0	387	9.1	3,281	77.0	1.38	1.06-1.79
Race:										
White	207	2.4	1,461	16.8	802	9.2	6,251	71.7	1.13	0.95-1.33
Black	7	1.0	73	10.7	41	6.0	559	82.2	1.41	0.60-3.28
Other	4	0.8	58	11.0	42	8.0	423	80.3	0.67	0.23-1.95
Income:										
$0-$37,075	55	2.3	335	13.8	221	9.1	1,814	74.8	1.36	0.98-1.89
$37,076-$46,467	57	2.3	447	18.2	239	9.7	1,715	69.8	0.93	0.68-1.27
$46,468-$59,703	63	2.4	414	16.1	236	9.2	1,860	72.3	1.20	0.89-1.62
$59,704-$200,001	43	1.7	396	16.0	189	7.6	1,844	74.6	1.05	0.74-1.50

Among younger women, ages 65-74 years, who have been screened a slightly significant decreased risk of invasive vulvar cancer is indicated (OR 0.55, 95% CI 0.31-0.97) (Table 46). However, for women ages 75 and over there is no association between invasive disease and screening.

Regarding race, for white (OR 1.13 95% CI 0.95-1.33) and black (OR 1.41 95% CI 0.60-3.28) races there is no association between screening and invasive disease. However, for "other" (OR 0.67 95% CI 0.23-1.95) race category, there is a decreased risk of invasive disease but the findings are not significant.

In the income categories, the results suggest that there is no association between screening and invasive vulvar cancer.

Table 47. Vaginal cancer screening efficacy by stage

	Screened				Unscreened					
	Cases		Controls		Cases		Controls			
Historic Stage*	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage	OR	95% CI
Localized	22	2.1	161	15.7	92	9.0	751	73.2	1.09	0.65-1.83
Regional	12	1.6	132	17.5	72	9.5	540	71.4	0.78	0.40-1.51
Distant	3	0.6	67	13.5	52	10.5	373	75.4	0.31	0.09-1.03
Unstaged	11	1.6	101	15.0	64	9.5	499	73.9	0.86	0.43-1.70
**Adjusted for race , age and college*										

Stratified analyses suggested that Pap smear and pelvic examination screening had a stronger negative association with regional OR 0.78 (95% CI 0.40-1.51), distant OR 0.31 (95% CI 0.09-1.03) and unstaged OR 0.86 (95% CI 0.43-1.70). Historic stage vaginal cancer groups were found to show reduced risk as opposed to localized cancers OR 1.09 (95% CI 0.65-1.83) and were borderline significant for distant stage disease (Table 47).

The results indicate partial support for the hypothesis that specific subgroups of cases will have unique screening pelvic examination and Pap smear history relationships based on the progression of disease (i.e., localized, regional, distant and unstaged cancers); the more advanced the disease the more likely that the case has not had sufficient screening. The results suggest that screening tests are not effective in reducing the risk of early stage disease but are effective in reducing the risk of late stage disease.

Table 48. Vulvar cancer screening efficacy by stage

	Screened				Unscreened					
	Cases		Controls		Cases		Controls			
Historic Stage*	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage	OR	95% CI
Localized	156	2.5	951	15.5	524	8.6	4,490	73.4	1.42	1.16-1.73
Regional	46	1.7	480	17.6	257	9.4	1,944	71.3	0.71	0.51-1.00
Distant	6	1.5	65	16.0	39	9.6	295	72.8	0.68	0.27-1.70
Unstaged	10	1.5	96	14.2	65	9.6	504	74.7	0.77	0.37-1.59
**Adjusted for race , age and income*										

Similar findings were observed for vulvar cancers where stratified analyses suggested that Pap smear and pelvic examination screenings had a stronger negative association with regional OR 0.71 (95% CI 0.51-1.00), distant OR 0.68 (95% CI 0.27-1.70) and unstaged OR 0.77 (95% CI 0.37-1.59) invasive vulvar cancers as opposed to localized stage cancers OR 1.42 (95% CI 1.16-1.73). The findings suggested borderline significance for regional stage disease.

The findings indicate partial support for hypothesis that specific subgroups of cases will have unique screening pelvic examination and Pap smear history relationships based on the progression of disease (i.e., localized, regional, distant and unstaged cancers); the more advanced the disease the more likely that the case has not had sufficient screening. The results suggest that screening tests are not effective in the prevention of early stage disease but are effective in the prevention of late stage diseases.

Table 49. Vaginal cancer screening efficacy by histology

	Screened				Unscreened					
	Cases		Controls		Cases		Controls			
Histology*	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage	OR	95% CI
Adenocarcinoma	9	2.8	41	12.7	27	8.3	247	76.2	1.65	0.64-4.24
Squamous cell carcinoma	32	1.5	347	15.9	211	9.6	1,597	73.0	0.77	0.51-1.16
Other	7	1.6	73	16.6	42	9.5	319	72.3	0.70	0.33.1.47
**Adjusted for race , age and college*										

The results shown is Table 49 suggest that screening has a negative association among squamous cell carcinoma (0R 0.77, 95% CI 0.51-1.16) and other types of invasive vaginal cancer (0R 0.70, 95% CI 0.33-1.47) suggesting that screening may prevent the most common type of invasive vaginal cancer (squamous cell carcinoma) and other types of invasive disease. However, the findings are not significant.

Table 50. Vulvar cancer screening efficacy by histology

	Screened				Unscreened					
	Cases		Controls		Cases		Controls			
Histology*	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage	OR	95% CI
Squamous cell carcinoma	145	2.0	1,176	16.2	662	9.1	5,281	72.7	0.98	0.81-1.20
Basal cell carcinoma	31	2.7	155	13.4	98	8.4	877	75.5	1.84	1.17-2.90
Paget disease	33	2.9	198	17.3	94	8.2	818	71.6	1.53	0.97-2.41
Other	9	2.5	63	17.5	31	8.6	257	71.4	1.19	0.53-2.66
**Adjusted for race , age and income*										

The results presented in Table 50 suggest that screening has no association among squamous cell carcinoma (0R 0.98, 95% CI 0.81-1.20) and positive association among basal cell carcinoma (OR 1.84, 95% CI 1.17-2.90), Paget disease (OR 1.53, 95% CI 0.97-2.41) and other types of invasive vulvar cancer (OR 1.19, 95% CI 0.53-2.66) but the findings are not significant.

CHAPTER 5: DISCUSSION

This discussion chapter will summarize the study's significant findings and compare those findings with the previous literature. It will note the limitations of the study and offer conclusions the findings suggest.

Significant findings

Findings suggest that Pap smear and pelvic examination screenings reduce the risk of regional, distant and unstaged invasive vaginal cancer. Similar findings were observed for vulvar cancers suggesting that gynecological screenings reduce the risk of regional, distant and unstaged cancer stages. sdThese findings suggest that screening tests may be effective in the reducing the risk of later stages of disease of both vaginal and vulvar cancers.

Women aged 65-74 who have been screened have a moderately significant decreased risk of invasive vulvar cancer. This finding suggests that screening is most effective in reducing invasive vulvar cancer among women age 65-74 years.

Comparisons

Brinton, et al. (1990a)'s and Parazzini, et al. (1993)'s studies suggest that at least one or more Pap smear screenings decrease the risk of invasive vulvar cancer, which is consistent with this study's findings.

There are opinion articles and studies that suggest that cervical cancer screening should stop at age 50 for women who have had regular Pap tests prior to age 50 with negative results (Cruickshank, et al. 1997). Similarly, other studies suggest that stopping Pap smears screenings at age 50 may be more appropriate provided that such women had at least three consecutive Pap smears with negative results (Van Wijngaarden and Duncan, 1993, Flannelly, et al. 2004). Flannelly, et al. (2004) have further suggested that women with an abnormal Pap smear history

should continue screening after 50 years of age. The findings of this study suggest that gynecological screening decreases the risk of late-stage invasive vaginal and vulvar cancers among women ages 65 and older.

While older women tend to have lower gynecological cancer screening rates in general (Ostbye, et al. 2003), continued disagreement exists between professional organizations and government review boards with respect to the age related recommendations and guidelines for gynecological cancer screening (Sirovich and Welch, 2004a, USPSTF, 2012a). The findings of the present study support Ostbye, et al. (2003) in that women in a Medicare population tend not to have consistent screening histories. The study found that 1.6% of vaginal cancer cases, 15.7% of vaginal cancer controls, 2.2% of vulvar cancer cases and 16.0% of vulvar cancer controls were screened during the PIDP.

Walter, et al. (2004), suggest that based on a their study of 5,000 Medicare beneficiaries aged 70 and older, physicians may intend to consider health status in determining a patient's eligibility for screening yet screen patients equally regardless of health status. Older women rely on their primary care physician to make the suggestion for screening (Walter, et al. 2004, Blair, 1998, Sawaya, et al. 2009). However, while the Walter, et al. (2004) study concluded that even though physicians consider health status, they still provide the screen; conversely, other studies suggest that there are barriers to cancer screening by providers (Walter, et al. 2004, Blair, 1998). These barriers may include the lack of cancer screening guidelines knowledge, lack of acceptance of guidelines, patient's age, comorbidities of patient, time constraints or lack of patient compliance (Blair, 1998). This finding is contrary to the findings of this study which suggest that older women have low gynecological screening rates.

Another study conducted by Heflin, et al. (2006) surveyed physicians regarding their decision to offer screening to women between the ages of 70 and 90 years based on their perceived health status. According to the study, physicians were significantly less likely to offer a screening Pap smear to women who were either moderately ill or in frail health compared to women in good health (Heflin, et al. 2006). Older women aged 65 and older may have three or more chronic conditions or disabilities. The three most common include arthritis, cardiovascular disease and cancer (Blair, 1998). Furthermore, the Heflin study also suggests that a history of normal Pap smears was associated with a significantly lower likelihood of offering a screening Pap smear at an older age (Heflin, et al. 2006). The results of this study suggest that gynecological screening can be beneficial in the detection of early stage disease.

Limitations

This study has several methodological limitations that may introduce bias into the results. The first is the use of aggregate geographic data to estimate the income and educational levels of study subjects. The education and income data were obtained by geo-coding individual records contained in the SEER-Medicare database and then linked to socioeconomic characteristics of residential zip code areas obtained from census data. Historically, aggregate proxies have often been used to obtain socioeconomic data where the primary data has not been collected or the information is missing for the analysis of health outcomes (Brinton, et al. 1990a, Parazzini, et al. 1993, Madeleine, et al. 1997, Sherman, et al. 1994). The ability to utilize proxies to obtain socio-economic information may introduce misclassification into the study but it provides a method to control for potential confounding of missing information.

Second is the use of an OIP and PIDP framework to estimate the average durations of occult invasive and pre-invasive detectable phases of vaginal and vulvar cancers. The

OIP/PIDP model parameters were originally developed by utilizing a study population that included women from all age groups who were diagnosed with cervical cancer (Weiss, 1999). This study, however, exclusively focuses on a population of women at or over the age of 65 who were diagnosed with vaginal or vulvar cancers.

Third the data used for the study was obtained between the years 1991 and 1999 and needs to be updated.

Conclusion

The findings of this study suggest that Pap smear and pelvic examination screenings reduce the risk of late stage invasive vaginal and vulvar cancers. Gynecological screenings reduce the risk of vulvar cancer among women aged 65 to 74 years old and late stage vaginal and vulvar cancers in women aged 65 and over. Late stage vaginal and vulvar cancers have lower 5-year survival rates than early stage disease. The development of late stage disease has high disability rates (especially among older women with co-morbid conditions). Thus, continuation of gynecological screenings among Medicare recipients may reduce the risk of late stage disease from early detection of VIN and VAIN and early stage disease. Screening policy recommendations by professional and governmental organizations should support screening efforts in women over a lifetime from menarche.

The study recommends that older women be screened upon entering the Medicare system if they have not had sufficient previous screening history and subsequent to this if they have had three consecutive negative Pap smears. The Patient Protection and Affordable Care Act (May 2010), makes it possible for beneficiaries of original Medicare to qualify for a yearly wellness visit and many preventive services for free (Patient Protection and Affordable Care Act, 2010).

As of January 1, 2011, cervical cancer screening, including Pap smear and pelvic examination, is available without the need for Medicare Part B deductible or copayment (DHHS, 2012).

The study further recommends that future screening studies should also include the cost-effectiveness of screening policies that extend over a lifetime. Furthermore, the disabling effects of vaginal and vulvar cancer treatments can affect the quality-of-life for many women. Since women depend on their physicians for recommendation, physicians should be trained to counsel older women, especially those with co-morbid conditions. Future studies should also include the psycho-social and cultural aspects of cancer treatments in older women.

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