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Jillian Papa Date

Incidence, Mortality and Survival Patterns of Anal Cancer in the United States, 1975-2007: Results from the Surveillance, Epidemiology and End Results Program

By

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Epidemiology

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By

Jillian Papa

Bachelors of Arts
University of South Florida
2008

Thesis Faculty Advisor: Pamela Mink, PhD, MPH

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Abstract

Incidence, Mortality and Survival Patterns of Anal Cancer in the United States, 1975-2007: Results from the Surveillance, Epidemiology and End Results Program
By Jillian Papa

Background: Anal cancer is a rare malignancy of the anogenital tract. According to the American Cancer Society, there were approximately 5,260 new cases and 720 deaths from anal cancer in the United States in 2010. Studies have indicated that up to 93% of anal cancers are associated with the most common risk factor, HPV infection. Higher risk groups include persons with HIV-related immunosuppression, in particular men who have sex with men (MSM). The purpose of this descriptive epidemiology study was to investigate patterns of anal cancer incidence, mortality and survival in the United States between January 1, 1975 and December 31, 2007.

Methods: These publicly available data were obtained from the Surveillance, Epidemiology, and End Results (SEER) Program, a system of population-based tumor registries in the United States. SEER*Stat was used to generate age-adjusted incidence and mortality rates, age-specific incidence rates, and 5-year relative survival of anal cancer according to year of diagnosis, age group, sex, and race. Distributions of tumor histologic type and tumor stage were also generated.

Results: Incidence rates were generally higher among women than men (1.6 per 100,000 person-years and 1.3 per 100,000 person-years, respectively, during 2000-2007, the most recent period for which data were available). However, the incidence rates appeared to increase more rapidly among males. Mortality rates increased at the beginning of the study period for all groups regardless of race, sex, or year of diagnosis, but leveled off in recent years (approximately 0.02 per 100,000 person-years during 2000-2007). African Americans had similar incidence and mortality rates when compared to whites but their 5-year relative survival was lower (54.8% and 65.3 respectively). Squamous Cell Carcinoma (SCC) accounted for an increasing proportion of anal cancer cases in recent years, 47.2% from 1975-1984 and 70.1% from 1995-2007.

Conclusions: The incidence of anal cancer in the United States increased between 1975 and 2007 for both males and females, with males having a more pronounced increase. African Americans had similar incidence and mortality rates when compared to whites but their relative survival was lower. SCC became more common over the course of the study period.

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INTRODUCTION

According to the American Cancer Society, there were approximately 5,260 new cases and 720 deaths from anal cancer in the United States in 2010.[1] The age-adjusted incidence rate in the US, based on cases diagnosed during 2003-2007 from 17 Surveillance Epidemiology and End Results (SEER) geographic areas, was 1.6 per 100,000 person-years.[1] Anal cancer is found mainly in adults, with a median age at diagnosis of 60 years in the US.[2] The US age-adjusted mortality rate was 0.2 per 100,000 person-years from 2003-2007 estimated from 17 SEER geographic areas.[2] The disease is diagnosed more commonly among women than men, with incidence rates of 1.8 per 100,000 versus 1.4 per 100,000, respectively.[2] In recent years, both sexes have experienced increased incidence rates of anal cancer.[3]

Risk factors for anal cancer include a history of infection with high-risk genotypes of human papillomavirus (HPV) HPV16 and HPV18,[4] history of cervical dysplasia or cancer,[5] infection with human immunodeficiency virus (HIV),[5] and history of anal intercourse.[4] Studies have indicated that up to 93% of anal cancers are associated with the most common risk factor, HPV infection.[6] Anal cancer is relatively uncommon in the general population; however, there is increased risk in certain groups, including persons with HIV-related immunosuppression, in particular men who have sex with men (MSM).

Although anal cancer is a rare disease, it is possible that improved surveillance and targeting of high-risk groups will be beneficial in reducing morbidity and mortality associated with the disease. Recent studies suggest that changes in sexual behavior may have a significant impact on anal cancer incidence and survival.[3,4] In this descriptive epidemiology study, data from SEER were used to investigate patterns of anal cancer incidence, mortality and survival in

the United States between January 1, 1975 and December 31, 2007.

BACKGROUND

Anatomy

The anus is the body's opening at the lower end of the digestive tract. It is about an inch and a half long and connects the lower part of the large intestine to the outside of the body.[1] The anus' function is to open and allow the expulsion of feces during a bowel movement. Not all of the tumors that can grow in the anus are cancerous. Some are benign and others can eventually develop into dysplasia or precancerous conditions.[1] The anus is lined with squamous cells that are similar to the cells lining other organs in the body including the bladder, vagina, and urethra[1], which is why anal cancer is thought to be more similar etiologically to genital cancers than cancers of the gastrointestinal tract.[3] The most common type of anal cancer is squamous cell carcinoma. Colorectal cancers, on the other hand, are more likely to be adenocarcinomas.[7]

Occurrence

Anal Cancer is a rare disease. It accounts for only 1.5% of all gastrointestinal cancers and 4% of cancers involving the lower gastrointestinal tract.[8] The age-adjusted incidence rate, based on cases diagnosed during 2003-2007 from 17 SEER geographic areas, was 1.6 per 100,000 person-years.[2] Worldwide in 2002 there were an estimated 30,400 new cases of anal cancer.[9] World age-standardized incidence rates range between 0.2 per 100,000 for women in Osaka, Japan and 1.4 per 100 000 among white non-Hispanic men in San Francisco, USA.[10]

In the US, incidence rates amongst women during 2003-2007 were higher than men (1.8 per 100,000 versus 1.4 per 100,000, respectively), but the mortality rates were similar between men and women (0.2 per 100,000 person-years).[2] In analyses of temporal patterns in the US,

Johnson et al. reported increasing anal cancer incidence for both genders during 1973-2000, with the increase being more pronounced among men even though overall age-adjusted incidence rates were higher among females.[3] A 2004 study by Cook et al. evaluated sex differences in cancer incidences and reported that anal cancer, defined as cancer of the anus, anal canal, and anorectum, was one of just a few cancer sites that were more common in females than males at nearly all ages.[11] Cook also observed a 58% increase in anal cancer among men between the periods 1975 to 1984 and 1995 to 2004 compared to 41% in females.[11]

Few studies to date have described in detail the burden of anal cancer among racial and ethnic minorities. According to Johnson's results, black men had the sharpest increase in anal cancer rates between 1973 and 2000 based on data from 9 SEER registries.[3] According to the most recent report on anal cancer from the SEER program, 2003-2007, Asian/Pacific Islanders in the United States had the lowest incidence rates, 0.5 per 100,000 person-years,[2] which is consistent with the relatively low global rates observed in Japan as described above.[9]

Risk Factors

Human papillomavirus & HPV-associated cancers

HPV are small, double-stranded DNA viruses that infect skin or mucosal tissue, and are associated with a variety of clinical conditions including anogenital warts and cancer.[12] HPV infection is the most common sexually transmitted infection among sexually active couples. Approximately 20 million Americans are currently infected with HPV and another 6 million people become newly infected each year.[12]

HPV is the leading cause of invasive cervical cancer worldwide. The presence of HPV in almost all cervical cancer patients implies the highest worldwide attributable factor reported as a

specific cause for any human cancer.[12] In addition to cervical cancer, several other cancers are known to be associated with HPV. These include cancers of the penis, oropharynx, vulva, vagina, and anus.[13]

HPV is subdivided into types based on their genome sequences, with each type identified by a number. More than 100 HPV types have been identified to date, at least 23 of which have been shown to infect the anogenital mucosa.[7] HPV subtype 16 appears to be most frequently associated with anal cancer, detected in approximately 70% of cases in population-based studies.[3,4] Globally, approximately 90% of anal cancers (27,400) may be attributable to HPV.[9] In the United States, the proportion attributable to HPV is estimated to be about the same, 87.9%.[4]

Researchers have observed biologic similarity between the types of cells infected by HPV in the cervix and the anus[14]. The risk of anal cancer is elevated among women with cervical and vulvar cancers. Compared with the general population, survivors of cervical cancer had a 1.4-fold increased risk for a second malignancy.[15] For subsequent anal cancer, women with primary invasive cervical cancer had a relative risk of 4.6.[5] For subsequent cervical cancer, patients with a primary diagnosis of anal cancer had a relative risk of cervical cancer of 1.3.[5] Two other studies, one in Denmark and one in the United States, observed that the prevalence of anal HPV is actually higher than the prevalence of cervical HPV infection in some women.[16,17]

HIV & Immunosuppression

HIV is a retrovirus that infects cells of the immune system. As the infection progresses, these cells become impaired or destroyed and the immune system becomes weaker.[18] Thus, persons infected with HIV are more susceptible to infections including HPV. In 2006, the US

Centers for Disease Control and Prevention (CDC) estimated that about 56,000 people in the United States contracted HIV and about 1.1 million people were living with HIV.[11] In 2009, World Health Organization (WHO) estimated that about 2.6 million people were newly infected with HIV and there were 33.3 million people living with HIV.[18]

Prior to 1996, in the pre-highly active antiretroviral therapy (HAART) era, HIV patients generally did not live long enough to develop anal cancer, because of the complications of their infection. More recently, with the use of HAART therapy, patients are living longer and physicians are beginning to see a rise in anal cancer among HIV-positive patients.[19] Data since the introduction of HAART clearly indicate a growing risk of anal cancer among HIV-positive individuals, most notably among MSM.[9,19] In addition, the EXPLORE study, conducted in Boston, Denver, New York, and San Francisco, reported that HIV-positive MSM are more likely than HIV-negative MSM to test positive for anal HPV.[20]

Studies of HIV-positive MSM have reported elevated anal cancer incidence compared to the general population. For example, D'Souza et al. reported an incidence rate of 137 per 100,000 person-years for the years among HIV-positive MSM participating in the Multicenter AIDS Cohort Study.[21] Patel et al. observed an incidence rate of 78 per 100,000 person-years among HIV-positive MSM from a SEER Program-HIV registry match.[22] Potential associations between HIV and anal cancer have been difficult to elucidate because of strong associations between HIV infection and two potential confounding factors: HPV infection and anal intercourse. Coinfection with HPV is common amongst MSM populations. HPV infection is difficult to clear with a compromised immune system.[23] A compromised immune system increases the activity and duration of HPV infection, leading to an increase in anal carcinoma .[24,25] Therefore, HIV positive patients are likely to have persistent HPV infection in the anal

canal.

Anal intercourse & Other Sexual Practices

Increasing rates of anal cancer may be attributable to the increasing prevalence of anal intercourse.[26] Up to 10% of heterosexuals have reported at least one instance of anal intercourse in the previous year.[27] Recent studies have reported high prevalence of anal intercourse among heterosexual couples. A large-scale survey conducted in 2002 found that 40% of men between the ages of 25 and 44 and 35% of women aged 25 to 44 had engaged in heterosexual anal intercourse in their lifetime. In the 1992 National Health and Social Life Survey (NHSLS), about 25% of men and 20% of women reported lifetime heterosexual anal intercourse.[28] A prevention trial evaluating HIV counseling among STD clinic patients found the proportion of participants reporting anal intercourse in the previous three months was two times higher in the second trial, RESPECT II (1999–2000) than in the original, Project RESPECT (1993–1995). [29]

Condom use for anal intercourse among heterosexuals is typically low, with less use for anal intercourse than for vaginal intercourse.[27] In turn, women with anal cancer were more likely to be seropositive for sexually transmitted infections (STI) including Chlamydia trachomatis, genital warts and herpes simplex virus 2.[4] The risk for anal cancer was higher in men who were not exclusively heterosexual and in men who had ≥ 15 lifetime sexual partners.[4] Behaviors such as digital-penetration, manual stimulation, and oral–anal contact may have significant implications for the risk of STI transmission and consequently anal cancer. One study found that 51% of men and 43% of women had participated in at least one act of oral–anal sex, manual–anal sex, or anal sex toy use.[30]

Prevention

Vaccination

There are currently two HPV vaccines on the market, Gardisil® and Cervarix.®[11]Both vaccinations prevent against HPV16 and 18 infection, the two highest-risk HPV types. Approximately 85-90% of anal cancers are thought to be attributable to HPV16 and 18, however only 70-75% of cervical cancers are thought to be attributable to HPV 16 and 18.[31] Theoretically, the current vaccines could also prevent noncervical HPV-positive cancers such as anal cancer.

Vaccination strategies to reduce the incidence of cancer attributable to HPV infection in the United States should take into account that a substantial proportion (about 25%) of cancers caused by HPV infection arise in men.[31] In 2009, Gardisil® received Federal Food and Drug Administration (FDA) approval to expand to include males.[32] Vaccinating both sexes can possibly induce "herd immunity,"[33] in turn decreasing the incidence of HPV-associated cancers such as anal cancer.[34] A study evaluating the cost-effectiveness for 12-year-old females versus 12-year-old males in the US found that the cost per quality adjusted life year (QALY) for a 12-year-old girl was $40,310 and $20,990 for cervical cancer and all cancers, respectively.[35] When vaccination of 12-year-old males was added, the cost increased to $290,290 and $114,510 for cervical cancer and all cancers, respectively.[35] Although not cost effective now, research in regarding vaccination in males is ongoing and guidelines may change in the future.

Screening

Currently, there are no widely applied screening programs for noncervical HPV-associated cancers.[31] Screening for HPV infections is performed using an anal swab for HPV DNA, which can also be used for genotyping.[36] If the anal Pap results are abnormal, providers

may choose additional testing using tissue biopsy techniques or HPV typing in order to determine if a growth is cancer.[36] Digital rectal exams (DRE) can also be performed in order to detect lesions and masses.

Sensitivity of anal cytology is in the range of 50%–80%, with sensitivity being higher in HIV positive populations.[37] Studies of the potential cost-effectiveness of screening have found that screening HIV-positive and HIV-negative homosexual and bisexual men every 2–3 years would be cost-effective and have life-expectancy benefits.[37] Researchers have suggested that certain high-risk groups such as MSM, women with cervical cancer, and all HIV-positive men and women receive annual anal Pap smears.[20]

Diagnosis and Treatment

Diagnosis

Carcinomas in the anal canal usually produce symptoms early in their development. One would therefore expect that anal carcinomas are diagnosed at an early stage. The most common initial symptom of anal cancer is rectal bleeding. However, diagnosis can be delayed because this bleeding is often attributed to previous anal diseases such as hemorrhoids, fissures and abscess.[38] Other symptoms include rectal pain and/or mass sensation, which occur in approximately 30% of patients.[38] Twenty percent of patients report no symptoms at the time of diagnosis.[39]

Surgery

Prior to the mid-1980s, the standard treatment for anal cancer was abdominoperineal resection (APR), a procedure involving removal of the anus and rectum as well as their draining lymph nodes and resulting in a permanent colostomy.[7] The 5-year survival rate after APR for anal carcinoma is in the range of 40–70%, with worse outcomes for those with larger tumors and

nodal metastases.[39] Surgery is no longer the standard option for most people with anal cancer. APR is now reserved as salvage therapy for individuals with persistent disease after combined chemoradiation.[39]

Chemoradiotherapy

Today chemoradiotherapy is the main method of treatment for anal cancer.[40] When chemotherapy and radiotherapy are administered together, the chemotherapeutic agents can sensitize the cancer cells to the effects of radiation, leading to increased tumor-killing effects within the radiotherapy field.[41] The chemotherapy component can address any potential micrometastatic disease that, without therapy, could lead to an increased risk of the disease spreading.[41]

Treatment shifted significantly in the 1970s, when chemoradiation was found to cure patients with anal cancer without requiring APR. Nigro and colleagues were the first to discover the effectiveness of the combined-modality approach.[42] Three phase III randomized controlled trials were conducted to further evaluate the combination, and researchers concluded that combined chemoradiation therapy for anal carcinoma improved regional control and reduced the need for colostomy without increasing complications.[7] Treatment of HIV-positive patients requires careful monitoring, because the likelihood of toxicity is greater in patients with CD4 counts < 200/mm3.[7]

THESIS RATIONALE AND OBJECTIVE

In 2004, Johnson and colleagues published a descriptive analysis of anal cancer incidence and survival using data from 9 SEER registries from 1973-2000. Since then, there have been no

published analyses, to our knowledge, that include additional years of data. Results from a 2004 study by Cook and colleagues indicated that anal cancer, defined as cancers of the anus, anal canal, and anorectum, is just one of just a few cancers that were more common in females than males in nearly all age groups.[11] Cook also observed steep increases in male anal cancer incidence rates between the periods 1975 to 1984 and 1995 to 2004 of 58%.[11]

In this descriptive study, anal cancer incidence rates, mortality rates and relative survival in the United States were examined using data from 9 SEER registries from 1975 to 2007, to evaluate age-specific incidence rates, age-adjusted incidence rates over time, age-adjusted mortality rates over time, and 5-year relative survival. These patterns were examined according to race and sex. We also evaluated potential changes in the distributions of histology and stage at diagnosis over time.

METHODS

This study did not conduct human research. Institutional Review Board (IRB) submission was required but deemed exempt by Emory University IRB.

Data Source

The publicly available data used in this report is from the SEER Program of the National Cancer Institute (NCI), which is a system of population-based tumor registries in the United States. The SEER Program began in 1973 as a result of the National Cancer Act. SEER collected and published cancer incidence, mortality, and survival data from 5 state cancer registries (Connecticut, Hawaii, Iowa, New Mexico, Utah) and from 4 metropolitan population-based cancer registries (Atlanta, Detroit, San Francisco-Oakland, Seattle-Puget Sound), covering

approximately 10% of the US population.[2]

The 9 SEER registries listed above provided the data for this analysis.[2] Data is available for cases diagnosed from 1973 and later for these registries, but for this particular report, January 1, 1975 to December 31, 2007 was used. This is because a limited number of registries were included in 1973. The metropolitan area of Atlanta and the 13-county Seattle-Puget Sound area were added in 1974, in order to diversify the population represented by SEER. However, later registries, SEER 13 and SEER 17, were not used because they began collecting diagnosed cases after 1992, which makes it difficult for researchers to follow cancer trends over time.

By law, hospitals, outpatient clinics, radiology departments, doctors' offices, laboratories, surgical centers, or other providers who diagnose or treat cancer patients are required to report new cancer cases to a central cancer registry. [43] Incidence data was abstracted from medical records. US Mortality data is collected and maintained by the National Center for Health Statistics (NCHS).[2] SEER*Stat obtains mortality data from death certificates, in order to calculate mortality rates.

Cancer survival statistics are typically expressed as the proportion of patients alive at some point subsequent to the diagnosis of their cancer. Relative survival is defined as the ratio of the proportion of observed survivors (all causes of death) in a cohort of cancer patients to the proportion of expected survivors in a comparable cohort of cancer-free individuals.[43] Survival data was obtained from both incidence data from medical records and mortality data from death certificates, in order to track survival statistics.

Study Variables

Age of diagnosis refers to age (in years) at time of initial diagnosis for the reported cancer.[43] Age of diagnosis for age-specific incidence rates was categorized by SEER into five-year groups (0-4 years old, 5-9 years old, etc. to 85+ years old). For incidence rates over time and mortality rates, a variable was created called "five-level age of diagnosis," which grouped age of diagnosis as follows: 0-49, 50-59, 60-69, 70-79, and 80+.

Diagnosis date is defined as a record of the first diagnosis of anal cancer by a recognized medical practitioner.[43] A variable was created called "three-level year of diagnosis." This variable was used to evaluate age-specific incidence rates by year of diagnosis, and is grouped as follows: 1975-1984, 1985-1994, and 1995-2007. A separate variable was created called "six-level year of diagnosis," which was used to evaluate incidence rates and mortality rates over time. It is grouped as follows: 1975-1979, 1980-1984, 1985-1989, 1990-1994, 1995-1999, and 2000-2007.

For incidence and mortality rate calculations, SEER recoded detailed race information from medical records into four major categories in order to make them compatible with available annual population estimates used as denominators for the rates.[44] These categories are: White, Black, American Indian/Alaskan Native, and Asian or Pacific Islander. For purposes of this study, American Indian/Alaskan Native and Asian or Pacific Islander were combined into one variable called "other race."

SEER defines anal cancer primary site as cancer of the anus, anal canal or anorectum.[43] SEER identified anal cancer patients by the following International Classification of Diseases for Oncology (ICD-O-3) codes: C210, C211, C212, and C218, excluding lymphoma or leukemia (9590-9989), and Mesothelioma (9050-9055). The registry codes histologic types according to ICD-O codes. SEER then creates the histologic recode variable regardless of year of diagnosis

to the current version of ICD-O (i.e., ICD-O-3). For purposes of this study, the histologic recode variable used is called "histologic recode: broad groupings." The most commonly diagnosed histologic type groupings were squamous cell which was defined by ICD-O third edition histology codes 8010 and 8051–8081; adenomas and adenocarcinomas defined by 8140–8263 and 8480–8481; and transitional cell papillomas and carcinomas defined by 8120–8130. [43] The remaining histologic types diagnosed were collapsed into a new category called "other histologic types." Stage of disease at diagnosis was categorized using the SEER*Stat variable, "SEER historic stage A." This summary staging variable was created by SEER in order to standardize stages of cancer and apply it to all anatomic sites. Summary Staging uses all information available in the medical record, clinical, and pathological reports. "SEER historic stage A" is categorized into the following four categories: local, regional, distant, and unstaged. Local stage is defined as a malignancy limited to the organ of origin.[43] Regional stage is defined as a tumor extension beyond limits of organ of origin. [43] Distant stage is defined as tumor cells which have broken away from the primary tumor and have traveled to other parts of the body. [43] Unstaged can be defined as not having sufficient evidence to adequately assign stage to a cancer. [43]

Data Analysis

A dataset for analyses of incidence rates was created using SEER*Stat. This dataset was used to evaluate age-specific and temporal patterns of anal cancer by race, age, and sex.[45] Histology and stage distributions were generated separately using the incidence rate dataset and creating a cross-tabulation by the "three-level year of diagnosis variable." [45] A separate dataset was created for analysis of temporal patterns of anal cancer mortality rates by race, age, and sex.[46] Lastly, a survival dataset was created to evaluate 5-year relative survival by race, age, sex,

histology, stage, and "three-level year of diagnosis."

All incidence and mortality rates and generated in SEER*Stat software program with diagnosis dates from 1975 through 2007, and were calculated per 100,000 person-years. Incidence and mortality rates were age-adjusted to the 2000 United States standard population. Tables were generated using SEER*Stat showing age-specific incidence rates by five-year age group stratified by sex, race, and "three-level year of diagnosis."[45] SEER*Stat generated tables showing incidence rates and mortality over time using the "six-level year of diagnosis" variable. In addition, SEER*Stat was used to generate tables showing the distribution of anal cancer histology by the "three-level year of diagnosis" variable.[45] Similar tables for stage at diagnosis over time were also generated .[45]

Five-year relative survival and 95% confidence intervals was calculated using SEER*Stat software.[47] Survival analysis was restricted to patients whose cancer diagnoses were microscopically confirmed, had malignant behaviors, and who had known ages and were actively followed. Relative survival was used as the outcome variable. Relative survival takes into consideration other competing causes of death, which can account for age, gender, race, and calendar year. For purposes of this study, 5-year relative survival was analyzed according to age, race, sex, histologic type, stage of disease at diagnosis and year of diagnosis..

All incidence and mortality rates were plotted on a logarithmic scale[48] using Microsoft Excel with incidence and mortality rates on the y-axis and either age of diagnosis (5-year age groups) or "five-year time period year of diagnosis" on x-axis.

RESULTS

Incidence and Mortality

A total of 8,846 anus, anal canal, and anorectum cancers were reported to 9 SEER registries during January 1, 1975 and December 31, 2007. Age-adjusted incidence rates (per 100,000 person-years), between 1975 and 2007, for males and females were 1.1 and 1.3, respectively. Age-specific incidence rates were somewhat higher among men in younger age groups, but women had higher incidence rates after age 40 years (Fig. 1). Incidence rates over time were generally higher among women over the study period, but the increase in rates over time appeared somewhat more pronounced among males (Fig. 2). Mortality rates amongst both males and females were generally similar, particularly after 1989, and were 0.02 per 100,000 person-years during the most recent time period of 2000-2007 (Fig. 3).

During the study period (1975-2007) when observing the data by race, the age-adjusted incidence rate of anal cancer amongst African American age $\geq$ 25 years was 2.3 per 100,000 person-years. As age increased, incidence rates for whites and blacks became increasingly similar (Fig. 4). At younger ages, blacks had higher incidence rates than both whites and "other race" categories. For example, in the 35-39 years age group, the incidence rate was 1.0 per 100,000 person-years among blacks and 0.4 per 100,000 person-years among whites, whereas the incidence rates at age 65-69 years was 3.8 per 100,000 person-years among blacks and 3.9 per 100,000 person-years among whites. In recent years, incidence rates for blacks and whites have become increasingly similar (Fig. 5). The "other race" category, although having steadily increasing incidence rates up until the most recent year of diagnosis group, had much lower incidence rates of anal cancer overall (0.5 per 100,000 person-years in the 2000-2007 time period). Mortality rates amongst African Americans were slightly higher than whites and "other race" (Fig. 6). All three race categories showed a moderate increase in mortality rates from time period 1975-1979 to 1980-1984 and then leveled off, particularly amongst the white race

category.

The overall age-adjusted incidence rate of anal cancer among individuals ≥ 25 years was 1.9 per 100,000 person-years between 1975 and 2007 (data not shown). In younger age groups, the age-specific incidence rates increased after 1989, but age-specific incidence rates at older ages changed little since 1975 (Fig. 7). Age-adjusted incidence rates for persons age 50-59 years increased considerably from 1975-1979 (1.7 per 100,000 person-years) to 2000-2007 (3.7 per 100,000 person-years) (Fig. 8). Mortality rates from 1975-1979 to 1980-1984 increased substantially across all groups stratified by race, sex, and age. Some overlap was observed in the mortality rates amongst 50-59 year olds and 60-69 year olds. Figure 9 shows that the older populations have higher anal cancer mortality rates. The 80+ years age group had a mortality rate of 1.4 per 100,000 person-years from 2000-2007.

Histology and Stage

Figure 10 displays the changes in histologic types of anal cancer across "three-level year of diagnosis." From the 1975-1984 time period to the 1995-2007 time period, there was an increase in the proportion of squamous cell carcinomas and a decrease in the proportion of transitional cell papillomas and carcinomas. In the earliest decade of data from SEER 9 registries, 1975-1984, about 50% of anal cancer diagnoses were squamous cell carcinomas and 30% were transitional cell papillomas and carcinomas. In the most recent decade, 1995-2007, squamous cell carcinomas make up about 70% of all anal cancer diagnoses with transitional cell papillomas and carcinomas dropping down to about 11%. The proportion of cases that were adenocarcinomas also decreased over time. Over the course of three decades, the proportion of cases diagnosed at regional stages decreased, while the proportion diagnosed at localized stages increased from 1985-1994 (41% localized) to 1995-2007 (52% localized) (Fig. 11).

Survival

Table 1 shows 5-year relative survival and corresponding 95% confidence intervals of anal cancer reported by 9 SEER registries for sex, age, race, histology, stage and year of diagnosis. Between 1975 and 2007, men had poorer 5-year relative survival than women with anal cancer (59.1% and 67.1% respectively). Five-year relative survival decreased with age, with only 45.9% or cases diagnosed at ages 80 and older surviving for 5 years. The highest 5-year relative survival was observed among the 50-59 year age group, with approximately 70% of cases surviving for 5 years after diagnosis.. The 5-year relative survival was lower among blacks (54.8%) than whites (65.3%); survival for "other race" was generally similar to that of blacks (56.4%).

SCC, which accounted for the largest number of cases, also had the highest relative survival of 68.2%. The 5-year relative survival was considerably lower for adenocarcinomas (49.7%) and "other histologic types" (44.1%). Individuals with localized anal cancer had a 79.9% 5-year relative survival, whereas relative survival dropped to 20.1% for persons diagnosed at distant stages. The 5-year relative survival for unstaged anal cancer (n=696) was 56.0%.

DISCUSSION

Incidence Rates

Analysis of anal cancer reported by 9 SEER registries indicated that incidence rates have increased steadily for the past 25 years. Since 1990, both age-specific incidence rates and age-adjusted incidence rates have increased in all groups regardless of race and sex with the greatest increase observed amongst males, primarily at younger ages. In the 25-29 age group, incidence

rates were 0.08 per 100,000 person-years among males and 0.04 per 100,000 person-years among females (Fig. 1). The age-adjusted incidence rate for men increased from 0.7 per 100,000 person-years in 1975-1979 to 1.3 per 100,000 person-years in 2000-2007.

The overall increase in anal cancer incidence rates may be partially attributable to established risk factors including anal intercourse and condom usage,[3,4] HPV,[5] and immunosuppression as a result of HIV.[4] Increased incidence rates since 1990 may also be attributable to detection bias, particularly among subgroups such as HIV-infected MSM, due to increased surveillance. In certain areas of the United States, screening of HIV infected MSM became more common during the 1990s.[37] This could possibly explain the patterns of increase observed in males.

The rates of anal cancer incidence did not vary greatly between blacks and whites; however, the incidence rates were considerably lower among "other race," with the exception of the 85+ age group (Fig. 1). Age-adjusted mortality rates were slightly higher amongst African Americans. The gap between whites and blacks, however, became smaller in recent years (Fig.6).

Mortality Rates

Mortality rates increased substantially for all groups regardless of age and sex from 1975-1979 to 1980-1984. Although women had higher incidence rates than men during the entire time period, the mortality rates since 1990 for both sexes have remained similar (0.2 per 100,000 person-years). An overall increase in cases diagnosed in both males and females accompanied by little to no change in mortality rates comparing males to females in recent years may be because clinicians are treating anal cancer more successfully, thereby reducing mortality.

Stage and Histologic Type

Increased screening during the 1990s amongst HIV-infected MSM may have also caused a decrease in regional stage anal cancers in favor of localized stage cases. The distribution of stages of anal cancer was almost equal between localized and regional stages from 1975-1984 (Fig.11). Over time the proportion of anal cancers diagnosed at regional stage decreased, which could mean improvements in diagnostics. This caused the proportion of cases diagnosed at local stages, as shown in figure 11, to steadily increase over the course of three decades.

The distribution of histologic types of anal cancer changed substantially since 1975. There was a large increase in the proportion of SCC histologic types. Today the majority of SCC are associated with HPV infection.[51] During the 2000-2007 time period, 70% of all anal cancers were SCC compared to 47.2% from 1975-1984 and 51% from the previous decade, 1985-1994. Similar findings regarding increases in SCC types were observed in cancers such as vulvar, cervical, and vaginal.[51] We observed a two-fold decrease in transitional cell papillomas and carcinomas since 1974-1984. The proportion of transitional cell papillomas and carcinomas diagnosed went from 30% to 11%, from 1975-1984 to 1995-2007 respectively (Fig. 10).

Survival

Despite the similarities in incidence and mortality rates stratified by race, there was a disparity in relative survival. African Americans, when compared to whites, were very similar in terms of new anal cancer cases diagnosed, but African American 5-year relative survival was notably less than whites (54.8% and 65.3% respectively). Race health disparities could be one explanation for the differences among blacks and whites, including poor access to care, inequality of care, and poverty.

Relative survival for anal cancer patients was poorer in the oldest age group (45.9%). It also was poorer for men compared with women (59.1% and 67.1% respectively). The degree to which these differences may be related to etiologic differences and/or differences in access to care, receipt of health services and/or response to treatment is unknown. Relative survival of anal cancer amongst localized cases was good: 79.9% for localized cases versus 20.1% in distant staged cases, and 56% in unstaged cases. The 5-year relative survival has improved over the course of three decades, from 59.6% to 67.7%. This improvement could be attributed to the introduction and acceptance of combined chemotherapy and radiation for treatment of anal cancer. This approach has been shown to be more effective in reducing morbidity and mortality.[49]

Strengths and Limitations

SEER is a very useful resource for population based cancer research. The SEER Program is the only comprehensive source of population-based information in the United States that includes stage of cancer at the time of diagnosis and patient survival data. It represents one of the largest series of patients with anal cancers. It is publicly accessible and very helpful in conducting descriptive studies.

Limitations of this study must also be considered. Race was recoded from medical records into four major categories in order to make them compatible with annual population estimates used as denominators for the rates.[43] In the 2000 census, respondents had the option to choose more than one race category. This could have affected population estimates for racial groups and would therefore, affect race-specific incidence and mortality rates after 1990. It is unclear how the census and SEER data will be reconciled in regards to race. This has potential to skew results because races, such as Hispanic does not have its own race category which can

lead to misclassification bias and/or underreporting. Another limitation is that although SEER is the only comprehensive source of information on patient cancer survival, it has very limited variables, which made it difficult to explore the etiologic role of HPV status because the tumor registry does not record this information.

Future research

Because this was a descriptive study, the ability to examine possible risk factors of anal cancer was limited. Future investigation of the relationship between HPV and anal cancer is needed, particularly as it may be playing a role in the observed increased incidence. Also racial disparities in survival status versus incidence rates, particularly among African Americans, should be further examined. Further investigation of etiologic reasons for disparities among male and female incidence rates could also be explored, as well as explanations for the observed differences in 5-year survival by gender. As previous studies have suggested, further research can be conducted regarding the change in histology distributions of anal cancer, particularly as this may reflect changes in the prevalence of etiologic factors. Descriptive studies of other populations outside the US are also needed to determine whether similar patterns are evident elsewhere.

CONCLUSION

This descriptive epidemiology study analyzed data from SEER in order to investigate patterns of anal cancer incidence, mortality and survival in the United States between January 1, 1975 and December 31, 2007. Our study found that incidence rates were generally higher among women than men, but appeared to increase more rapidly among men over the course of the study period. Our study also found that overall African Americans had similar incidence

rates when compared to whites, but their relative survival was much lower than the other race categories. This could be due to differences in access to or quality of care. Finally, SCC accounted for a greater proportion of anal cancer cases in recent years, 47.2% from 1975-1984 and 70.1% from 1995-2007. Because of the relationship between SCC and human papillomavirus (HPV), this may indicate a rise in anal cancers related to HPV.

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LIST OF ABBREVIATIONS

SEER	Surveillance Epidemiology and End Results
HPV	Human Papillomavirus
HIV	Human Immunodeficiency Virus
MSM	Men who have sex with Men
CDC	US Centers for Disease Control and Prevention
WHO	World Health Organization
HAART	Highly Active Antiretroviral Therapy
NHSLS	National Health and Social Life Survey
STI	Sexually Transmitted Infections
FDA	Federal Food and Drug Administration
QALY	Quality Adjusted Life Year
DRE	Digital Rectal Exams
APR	Abdominoperineal Resection
NCI	National Cancer Institute
ICD	International Classification of Diseases for Oncology
SCC	Squamous Cell Carcinomas
NCHS	National Center for Health Statistics

TABLES

Table 1: 5-year Relative Survival of Anal Cancer reported by 9 SEER registries

SEER*STAT Variables		# of Anal Cancer Cases	5-year Relative Survival	95% Confidence Intervals
Sex	Male	2,912	59.1%	56.8-61.6%
	Female	4,223	67.1%	65.2-68.9%
Race	White	6,104	65.3%	63.7-66.8%
	Black	788	54.8%	50.5-59.0%
	Other race	243	56.4%	48.4-63.6%
Age (years)	0-49	1,509	67.1%	64.5-69.7%
	50-59	1,621	70.0%	67.3-72.5%
	60-69	1,688	62.7%	59.8-65.3%
	70-79	1,402	61.9%	58.4-65.2%
	80+	915	45.9%	40.3-51.4%
Histologic Type	Squamous Cell	4,351	68.2%	66.4-70.0%
	Transitional Cell	1,270	67.8%	64.5-70.9%
	Adenocarcinoma	964	49.7%	45.5-53.7%
	Other histologic type	550	44.1%	31.9-40.3%
Stage	Localized	3,326	79.9%	77.9-81.8%
	Regional	2,357	57.2%	54.7-59.6%
	Distant	775	20.1%	16.7-23.7%
	Unstaged	677	56.0%	51.3-60.5%
Year of Diagnosis	1975-1984	1,436	59.6%	56.4-62.6%
	1985-1994	1,913	61.2%	58.5-63.8%
	1995-2007	3,786	67.7%	65.6-69.7%

FIGURES

Figure 1

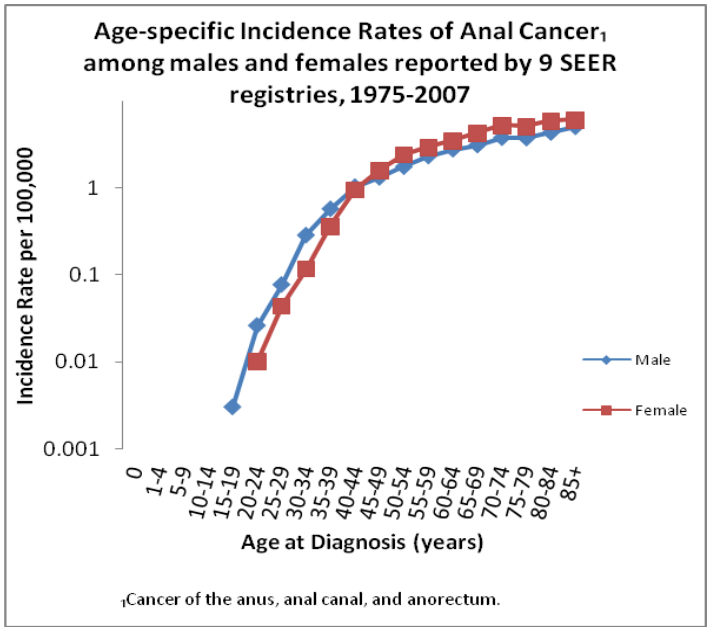
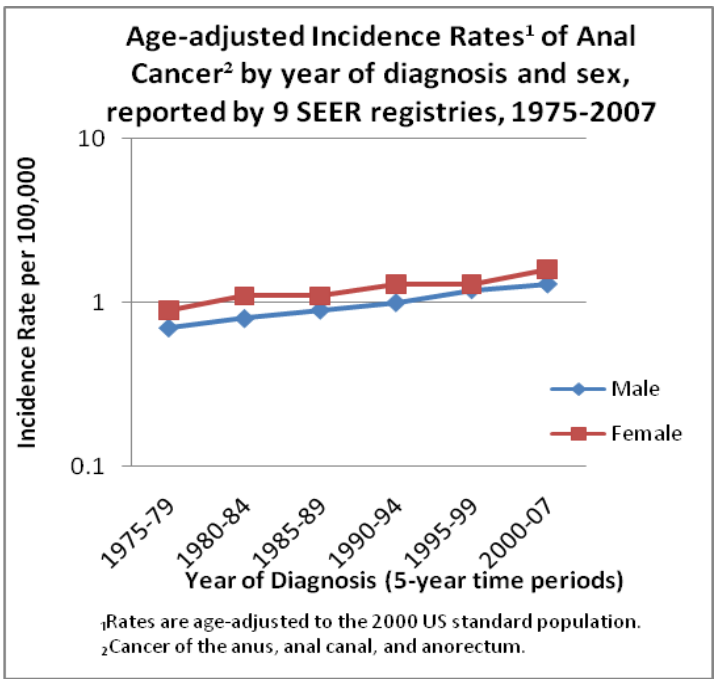


Figure 2



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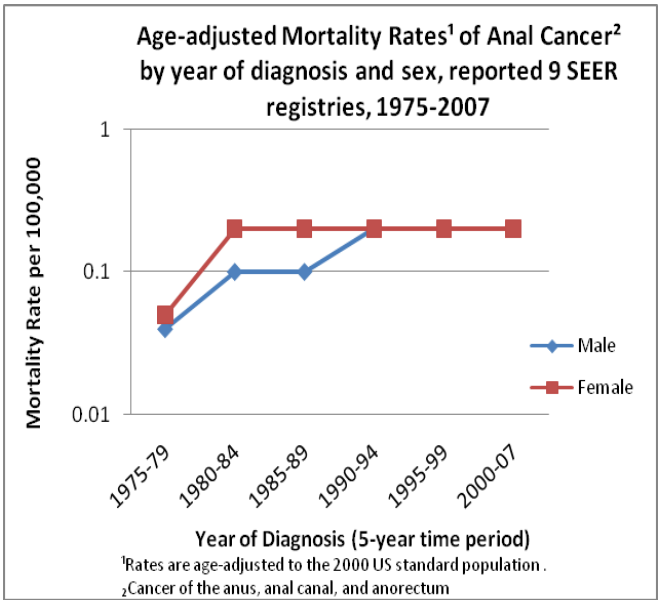


Figure 4

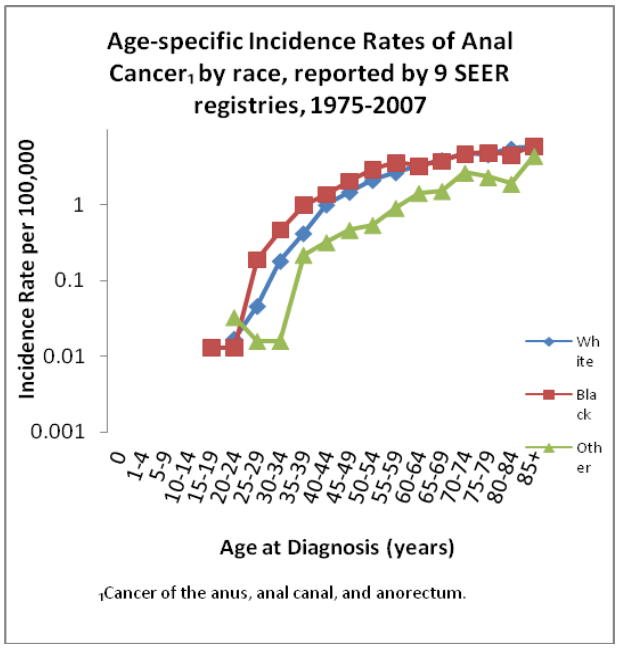
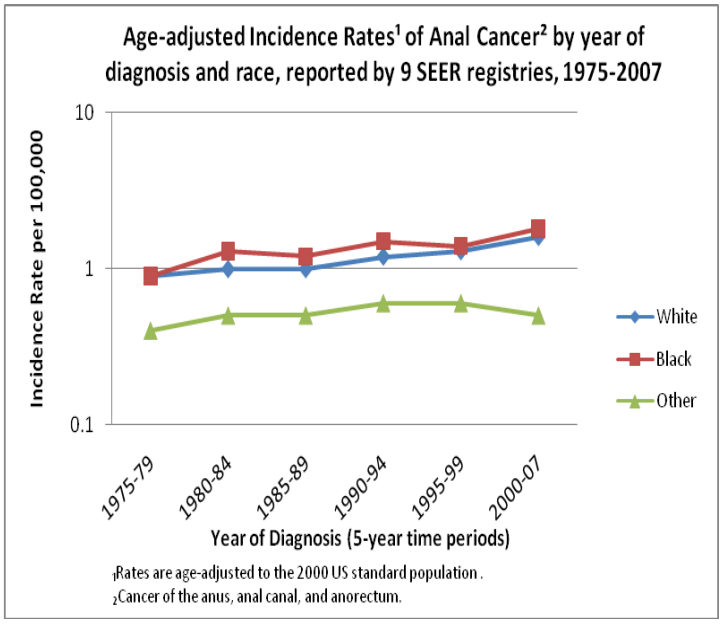


Figure 5



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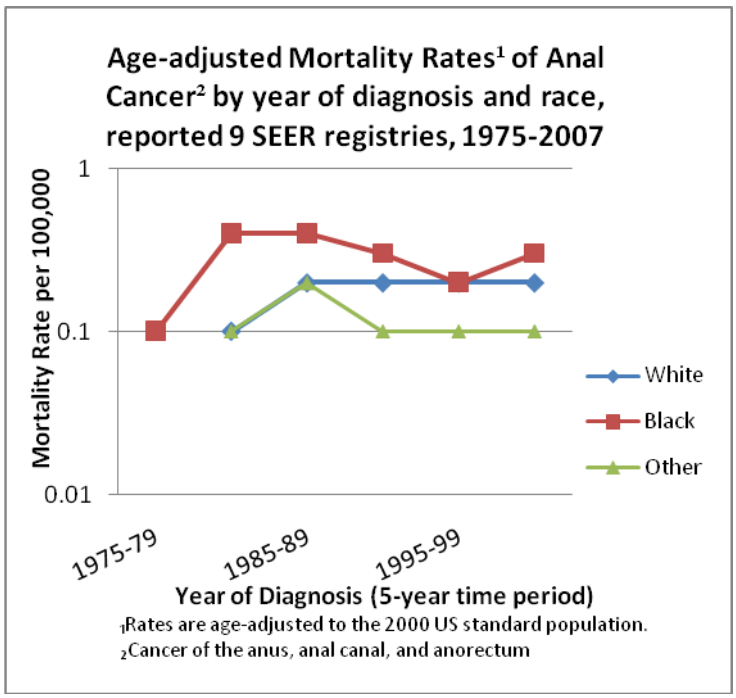


Figure 7

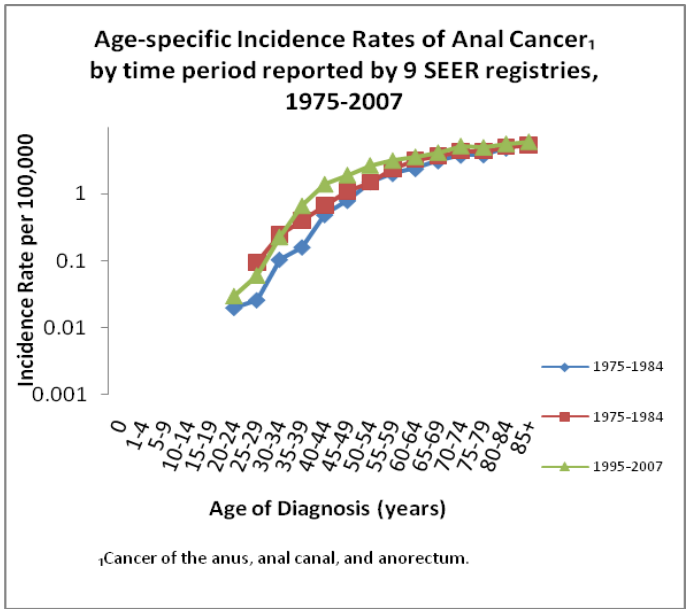


Figure 8

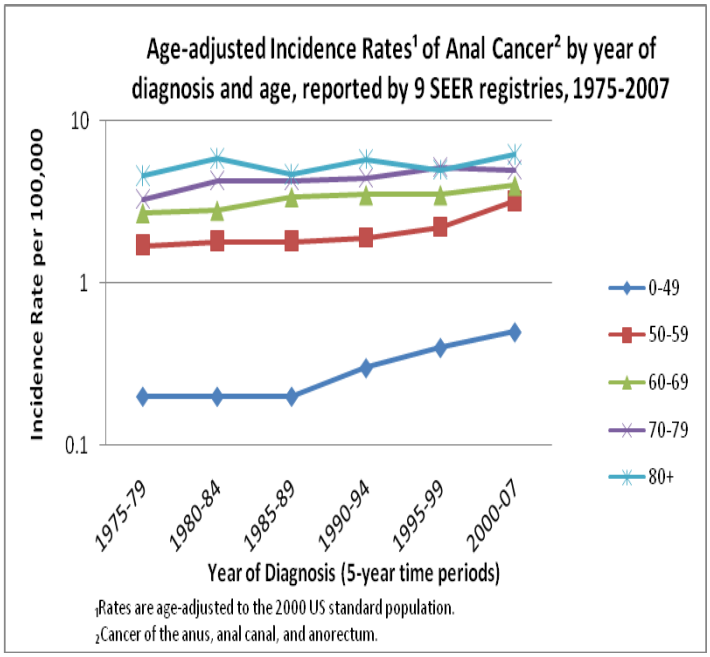


Figure 9

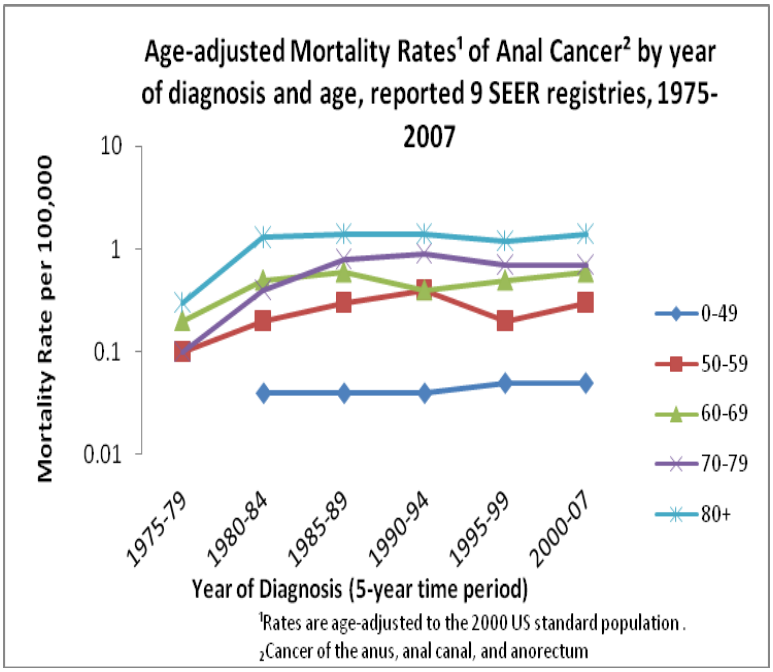


Figure 10

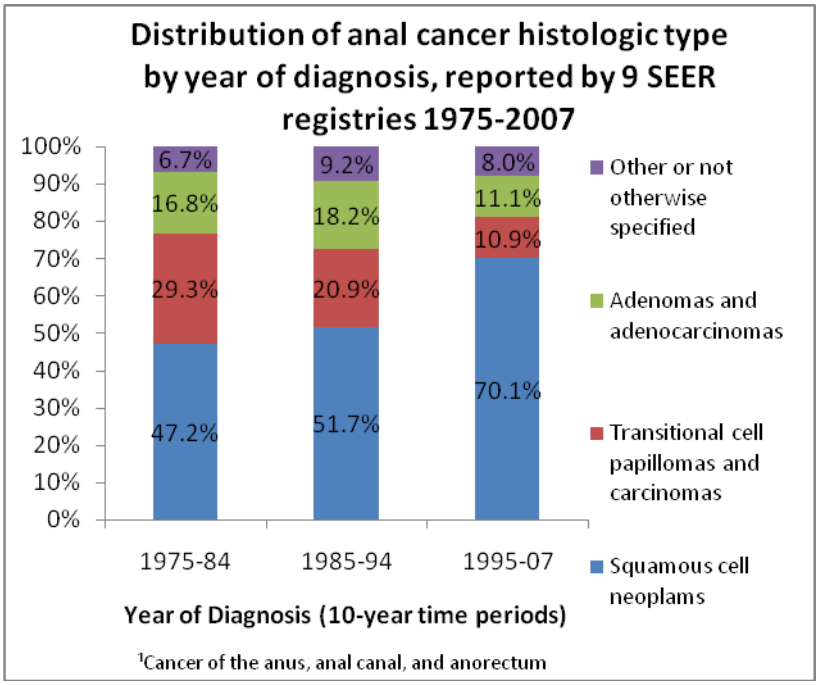
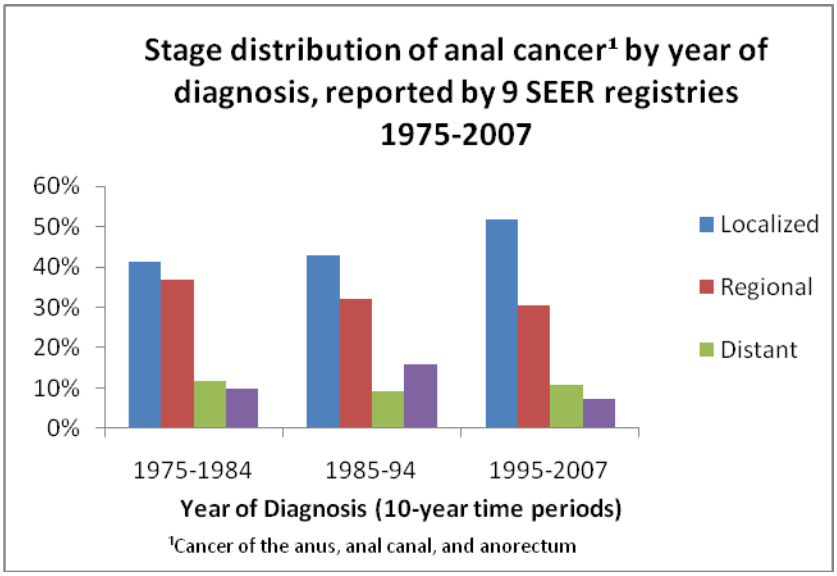


Figure 11


Stage distribution of anal cancer[1] by year of diagnosis, reported by 9 SEER registries 1975-2007
60%
50%
40%
30%
20%
10%
0%
1975-1984
1985-94
1995-2007
Year of Diagnosis (10-year time periods)
Localized
Regional
Distant
[1]Cancer of the anus, anal canal, and anorectum