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HPV and Anal Dysplasia in Men Who Have Sex with Men:

An Indicator for Anal Papanicolaou Screening

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NURS 8000

May 2011

Introduction

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The human papillomavirus (HPV) is associated with several forms of cancer including anal, oral, penile and cervical (Gilbert, Brewer, Reiter, Ng, & Smith, 2010). The initiation of Papinicoau (Pap) screening over 30 years ago to detect cervical dysplasia (often caused by HPV) resulted in early detection and treatment and a dramatic decline in deaths from cervical cancer (Palefsky, 2009).

Nationally standardized cervical cancer screening exists for HPV related cervical cancer, however, universal screening protocols for HPV associated anal cancer is non-existent (Palefsky, 2009). In 1973, the rate of cervical cancer was 14.2 per 100,000, but with the advent of cervical Pap screening it has decreased to approximately 8 per 100,000 (Nanda, et al, 2000, Palefsky, 1999).

With the success of standardized cervical screening protocols, it is fair to suggest that similar screening protocols may be efficacious in the early detection of anal cancer. A screening protocol for early detection and treatment of anal cancer, aimed at high-risk groups, such as men who have sex with men (MSM), could theoretically demonstrate reductions similar to cervical cancer, in deaths and morbidity from anal cancer.

HPV and Anal Cancer

Epidemiology

Statistically, anal cancer is rare; however, incidence varies by risk group. In 2009, the American Cancer Society reported that there were 5290 new cases of anal cancer (3190 females and 2100 males). Seven hundred and ten deaths (450 females and 260 men) were caused by anal cancer (The American Cancer Society, 2009). Johnson, et al. (2004) found that among the general population diagnosis of anal cancer is 1.7 per 100,000 people, with women having a

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slightly higher incidence. Between 1998 through 2003, black men and women were diagnosed with anal cancer at a rate of 1.2 and 1.3, respectively (Centers for Disease Control [CDC], 2011).

Among HIV positive and negative men who have sex with men, statistics are drastically higher. The incidence of anal cancer among men who have sex with men is estimated at 35 per 100,000, statistics that are similar to the incidence of cervical cancer prior to the implementation of routine screening programs (Friedlander, et al., 2003; Arain, et al, 2005). Prior to the HIV epidemic, the incidence of anal cancer was 35 cases per 100,000; after HIV and AIDS became prevalent the incidence of anal cancer soared to 70 cases per 100,000 in men who have sex with men (Palefsky, 1999; Oon & Winter, 2010).

Individuals with compromised immune systems, as in HIV and AIDs, have a higher incidence of developing anal cancer. The likelihood of developing anal cancer in men with a co-morbid condition of HIV, increases thirty-five fold (Chaturvedi, 2010). The mean age of diagnosis of anal carcinoma in HIV positive males is 40.9 years, compared with the general population at around age 60 (Frisch, Biggar, & Goedert, 2000).

Pathophysiology, Histology, & Virology

The natural progression of anal cancer isn't clearly understood; however a correlation has been established between the human papillomavirus (HPV) and dysplastic effects, the precursor to anal cancer (Chaturvedi, 2010). It is believed that the etiology of anal squamous cell carcinoma is equivalent to cancer of the cervix. More than eighty genomes of HPV exist, and of those, nine types of genomes have been identified with anal dysplasia and cancer. The high risk genotypes HPV 16 and HPV 18 are most prevalently linked to various types of cancer, including cervical, oral, and anal (zur Hausen, 1999; Abbas, Yang, & Fakhri, 2010a, Palmer, et al, 1988).

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Eighty-eight to 91% of anal cancers are caused by HPV 16 and 18 (Oon & Winter, 2010). Of the 2100 males diagnosed with anal cancer in 2009, 80% of those cases were associated with HPV oncogenes 16 and 18 (Kim, 2010). Similar to cervical cancer, anal cancer typically develops in the transformation zone, where the change from columnar epithelium to squamous epithelium occurs (Palefsky, 1999). The progression of HPV related anal dysplasia and cancer is accelerated when immunosuppression coexists with the human papillomavirus (Panther, Schlect, & Dezube, 2005).

Risk Factors and Transmission

Multiple risk factors are associated with anal cancer, including HPV infection, receptive anal intercourse, number of lifetime partners, cigarette smoking, and history of genital warts (Abbas, et al, 2010a). Daling, et al. (1987) found that history of anal receptive intercourse, genital warts, gonorrhea, and cigarette smoking were associated with an increased incidence of anal cancer. Individuals with HIV who have lower CD4 counts, syphilis, anal warts, or hepatitis also pose a greater risk for developing anal cancer (Palefsky, 1999; Frisch, et al, 1997). Giuliano, et al, (2011) reports that the immune response to the human papillomavirus in men is lower than in women causing higher rates of HPV infection in the male population.

Clinical Presentation

HPV related anal carcinoma presents with a wide array of symptoms. The range of symptoms in anal carcinoma include being asymptomatic to weight loss, rectal bleeding, abdominal pain, change in bowel habits, and pain with anal receptive sex (Dyson & Draganov, 2009; Panther, et al, 2005). Nearly fifty percent of patients present with rectal bleeding, while thirty percent present with feelings of a mass or pain, and twenty percent are asymptomatic

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(Abbas, et al, 2010a; Lindsey, et al, 2009). Fifty percent of all anal cancer cases extend into the rectum or perineal skin, while in 10% of females, anal cancer proliferates into the anovaginal septum (Abbas, et al, 2010a)

Literature Review

Several studies have examined the utility of using anal Pap screening as first line detection of anal dysplasia. Examining the reliability of anal Pap screening is the first step in determining its utility in screening anal dysplasia.

Diagnostic Tool

Table 1 provides a comparison of seven randomized controlled trial, examining the sensitivity and specificity of anal Papanicolaou screening. Examination of the sensitivity and specificity of any tests provides the predictive value of correct positives and correct negative results that lends to the utility of the test. Anal cytology provides screening with a high sensitivity ranging from 81-98%, assuring a high number of correct positive results.

One may argue that the low rate of specificity or false negatives of anal pap testing is too low, averaging fifty percent of the seven randomized control trials. However, literature reveals that anal Pap testing has a similar variable sensitivity and specificity to that of cervical Pap testing. Nanda, et al (2000), found that in a review of twelve studies, the conventional Pap test for cervical screening had a sensitivity range from 30%-87% and a specificity from 86%-100%. Even though cervical dysplasia screening has a variable sensitivity and specificity, its use as a screening tool has significantly decreased mortality as a result of early detection and screening. Theoretically, anal dysplasia screening could demonstrate the same reductions in morbidity and mortality from anal cancer.

Table 1: Summary of Studies Using Pap test as a Diagnostic Screening Tool for Anal Dysplasia

Author/Title/Year	N/Type of Study	Findings
Arain, et al. The Anal Pap Smear: Cytomorphology of squamous intraepithelial lesions, 2005	198 Males Retrospective Design	High sensitivity (98%) for detection of ASIL, low specificity (50%) for predicting severity
Cranston, et al. The prevalence and predictive value of abnormal anal cytology to diagnose anal dysplasia in a population of HIV-positive men who have sex with men, 2007	244 MSM and HIV + Cross Sectional Design	Findings reported that anal cytology has positive predictive value with up to 95.7% accuracy for any cytological abnormality and to predict high-grade dysplasia at 55.9% accuracy
De Ruiter, et al. A comparison between cytology and histology to detect anal intraepithelial neoplasia, 1994	215 MSM Cross Sectional Design	High sensitivity 88% with low specificity 16%
Fox, et al. The value of anal cytology and human papillomavirus typing in the detection of anal intraepithelial neoplasia: a review of cases from an anoscopy clinic, 2005	99 Males Cross Sectional Design	Sensitivity 83% Specificity 38%
Friedlander, et al. Anorectal cytology as a screening tool for anal squamous lesions, 2003	51 Cross Sectional Design	Sensitivity 92% and specificity 50%
Palefsky, et al. Anal cytology as a screening tool for anal squamous intraepithelial lesions, 1997	658 MSM Cross Sectional Design	A total of 2958 anal cytology samples were collected from 648 subjects. Initial cytology sensitivity was 69% in HIV + and 47% in HIV -. Subsequent anal cytology samples had a sensitivity of 81% and 50% respectively.
Panther, et al. High resolution anoscopy findings for men who have sex with men: Inaccuracy of anal cytology as a predictor of histologic high-grade anal intraepithelial neoplasia and the impact of HIV serostatus, 2004	153 Cross Sectional Design	Sensitivity 47% Specificity 90%

Continued Debate

There has been debate over the utility of anal cytology Pap screenings; as a result of early studies that suggested its predictive value was not a useful determinant of abnormal anal cytology. However, more recent studies indicate it may be a worthwhile screening tool. This could be due to the switch from conventional slides to Thin Prep (Sherman, 1995). In an examination of 117 conventional Pap smears and 191 Thin-Preps, satisfactory specimens were found to be 41% and 82.7% respectively (Sherman, 1995). Friedlander, et al. (2003), found that when compared with conventional Pap smears, Thin-Preps detected eight times more squamous intraepithelial lesions. While fecal matter, poor preservation, and air drying artifact tends to obscure conventional smears, Thin-Preps reduce these factors allowing for more satisfactory specimens for pathological evaluation (Friedlander, Stier, & Lin, 2003, Sherman, et al, 1995).

A Consideration for Self-Collected Anal Cytology Samples

Fear of testing may lead some MSM to avoid screening in the clinic setting. However, self-collected anal cytology samples provide a potential alternative to clinic testing. Table 2 provides a comparison of three randomized control trials examining the reliability of self-collected anal cytology samples compared to clinic collected anal cytology samples. Adequacy of specimens for pathologic review ranged from 80-91% of self-collected and 68-99% in clinician-collected anal cytology samples. Sensitivity of the samples was provided in two out of the three randomized control trials and ranged from 60-68% for self-collected and 68-70% in clinician-collected anal cytology samples. Empirical evidence supports that self-collected anal cytology samples may provide an alternative option for individuals who may not otherwise seek screening measures.

Table 2: Summary of RCTs Comparing Self- and Clinician-Collected Anal Cytology Samples

Author/Title/Year	N	Findings
Chin-Hong, et al. Comparison of patient- and clinician-collected anal cytology samples to screen for human papillomavirus-associated anal intraepithelial neoplasia in men who have sex with men. 2008.	125 MSM Cross Sectional Design	Adequacy of specimens was 91% for clinician-collected and 80% for self-collected specimens. Sensitivity of clinician-collected specimens was 68% and self-collected samples was 60%.
Cranston, et al. Self-collected versus clinician-collected anal cytology specimens to diagnose anal intraepithelial neoplasia in HIV-positive men. 2004.	102 MSM Cross Sectional Design	Adequacy of specimens for pathological review was 99% in clinician-collected and 91% in self-collected samples. Sensitivity of clinician-collected samples was 70% and self-collected was 68%.
Lampinen, et al. Randomized clinical evaluation of self-screening for anal cancer precursors in men who have sex with men. 2006.	222 MSM Cross Sectional Design	Adequacy of specimens for pathological review was 92% clinician-collected and 83% self-collected. Information on sensitivity not provided.

It must be clearly understood that the utility of anal Pap screening would not be used to stage dysplasia, but to determine whether dysplasia is present or absent, similar to that of a cervical pap smear. If dysplasia is determined, the necessity of high resolution anoscopy and biopsy would be required to stage the grade of dysplasia.

Recommended Screening

Currently no national guidelines exist and routine screening is not recommended for the general population, however, recommendations for high risk populations do exist. Initial screening is recommended for high risk individuals, including HIV-positive and HIV-negative

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men who have sex with men, women who partake in anal receptive intercourse and individuals who are immunocompromised; the resultant anal cytology is the determinant for future follow up.

A normal result requires a repeat screening every two years for HIV-negative MSM and annually for HIV-positive MSM (Panther, et al, 2005). If the anal cytology is read as anything other than normal, the patient is referred for high resolution anoscopy (HRA), if no lesion is found then a repeat anal pap is performed in six months (Panther, et al, 2005). If an anal intraepithelial neoplasia (AIN) grade 1 is found after the biopsy, a repeat pap and HRA after six months is recommended; if AIN grade 2 or AIN grade 3 is found, the recommendation is to ablate the dysplastic cells and have a repeat pap and HRA in four to six months (Panther, et al, 2005). After anal cytology has been stable for two exams, screening can return to every twelve months (Panther, et al, 2005).

Performing Anal Pap Screening

Performing anal Pap screening takes little to no preparation on the patient's part, no bowel preparation is necessary, with the exception that the patient may need to evacuate their bowel prior to the procedure (Porche, 2006). The patient is placed in the left lateral position, and a Dacron swab that is lubricated with tap water is inserted 1.5 to 2 inches into the rectum. It is recommended that the swab be rotated 10-12 times while placing lateral pressure against the anal canal with the swab (Porche, 2006). The swab is then placed in a liquid medium, such as ThinPrep, and labeled with the patient's name, and other identifying information (Siekas & Aboulafia, 2009).

Staging and Prognosis

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Five year survival rates for anal cancer are 80.1% for localized or cancer confined to a primary site, 59.8% for regional spread to lymph nodes, and 30.5% for anal cancer with metastatic spread (National Cancer Institute, 2010). Prognosis and survival rates of anal cancer patients' worsens with the co-morbidity of HIV, one year mortality rates are 40% and five year mortality rates are 80% (Place, Gregorcyk, Huber, & Simmang, 2001).

Cost Effectiveness

Two Markov models were developed to assess the cost-effectiveness of screening for anal dysplasia and anal cancer among HIV-positive and HIV-negative men who have sex with men. The studies conducted found that screening HIV-positive MSM either annually or every two years and HIV-negative men every two to three years, will prolong quality adjusted life years while remaining cost effective (Goldie, et al, 1999; Goldie, et al, 2000). Both studies found that the most influential factor was the progression of the lesions, regardless screening annually for HIV-positive MSM and every two to three years for HIV-negative MSM provided a accurate screening modality while decreasing the economic burden (Goldie, et al, 1999; Goldie, Kuntz, Weinstein, Friedberg, & Palefsky, 2000).

Treatment

A broad spectrum of treatments exists and treatment type is determined by the degree of cellular dysplasia. High-grade anal intraepithelial lesions (the precursor to anal cancer) can be treated with trichloroacetic acid (either physician or patient applied), photodynamic surgery, electrocautery, or surgery (Abbas, et al., 2010b). Post surgical complications, include, but are not limited to bleeding, perianal bleeding, and anal sphincter dysfunction (Chang, Berry, Jay, Palefsky, & Welton, 2002). Recurrence rates twelve months post surgical was 79% for HIV-

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positive patients and zero recurrence for HIV-negative (Chang, et al, 2002). Anal cancer treatment typically involves a combination of chemotherapy and radiation (Goldstone, 2005). Typical treatment for anal cancer begins with a week of chemotherapy, followed by five weeks of radiation, followed up with another week of chemotherapy (Abbas, 2010b, Goldstone, 2005).

Billing

Careful coding is required to receive reimbursement for anal cytology screening. Two different billing codes exist for anal cytology, one for using liquid-based cytology, such as ThinPrep, and the other for conventional slides (Darragh & Winkler, 2004). Coding anal cytology as a gynecological specimen will lead to reimbursement failure (Darragh & Winkler, 2004).

Barriers to Receiving Screening

Reed, Reiter, Smith, Palefsky, and Brewer (2010), found the biggest barriers to receiving anal Pap screening among MSM were modifiable beliefs and lack of education. The most reported reasons for reluctance to testing was cost, lack of knowledge about the test, and embarrassment about getting the test (Reed, et al, 2010). Understanding that modifiable beliefs and fears, whether real or perceived, place the provider in a unique position to educate and inform clients about a necessary screening tool that could potentially save lives.

Education and Counseling

Several targeted interventions can be utilized in the prevention and screening of anal dysplasia. First, community based and individual education needs to focus on risk factors, transmission, screening, and vaccination. Community based education campaigns to educate the

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public that anal dysplasia and cancer is a sexually transmitted infection, resultant from having unprotected anal receptive intercourse with an HPV positive partner. Therefore, routine and correct condom use is recommended to prevent the spread of HPV.

Second, if a patient is identified as high risk for HPV related anal cancer, education on the necessity, process, and frequency of screening is warranted. Twenty-three percent of MSM have ever heard of an anal Pap and 14% had ever received an anal Pap (Reed, et al, 2010). With these staggering statistics, it is important to stress the necessity of screening. Fear of the procedure or anal cancer diagnosis can deter patients from asking about or being screened. To ameliorate potential or real anxiety and fear, careful explanation and sensitivity to individual concerns is required. Caring for the emotional and psychological aspect of the patient is crucial.

Vaccination

In October 2009, the FDA approved licensure for the use of Gardasil in males ages nine to twenty-six for the prophylactic role of HPV induced genital condyloma (genital warts), potential risk factors for the development of anal cancer (CDC, 2010). Yancey, et al (2010) data synthesis provides further supporting evidence that the quadrivalent vaccine Gardasil not only creates immunity from genital condyloma, it has the potential to decrease the incidence of HPV related anal dysplasia and cancer (Yancey, Pitlick, & Forinash, 2010). One obstacle to getting boys and young men vaccinated is a knowledge gap among this population. According to Gilbert, et al (2010), in a survey of 247 gay men only 21% thought that the HPV vaccine worked in men and 18% thought that the vaccination could be administered to males.

In 2011, results from a randomized, placebo-controlled, double-blind study was published regarding the use of the quadrivalent humanpapilloma vaccine to protect against HPV

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16 and 18, the precursors to anal cancer (Giuliano, et al, 2011). Giuliano, et al, (2011) found that receiving the three shot HPV regime significantly decreased the incidence of persistent infection caused by HPV 16, and 18 by 78.7% to 96.0%. Although this study provides concrete evidence that the quadrivalent HPV vaccine decreases the incidence of persistent HPV infection, further research needs to be conducted to determine its effects on decreasing the incidence of anal cancer, as well as oral, vaginal, and vulvar cancers.

Implications for Practice

Empirical data suggests that using anal cytology as a resource for surveillance programs is reliable and achievable; anal Papanicolaou screening should be considered a first line defense in early diagnoses. Identification of anal dysplasia prior to it turning into invasive anal cancer is the goal of any successful screening program. Primary care providers have a responsibility to serve at risk individuals and this begins with identifying individuals at a higher propensity for acquiring a disease or developing an illness. Providers' attitude and willingness to discuss sexual practices, prevention, screening options, and vaccinations is pivotal to the success of eliminating HPV related anal cancer in men who have sex with men.

Collecting complete health histories and risk taking behavior analysis is essential in determining high risk individuals. It is important as clinicians to remember to collect complete health history and a risk taking behavior analysis to determine at risk individuals. It is not only important to screen at risk groups, but to also identify other high risk individuals, such as heterosexual men and women who partake in anal receptive intercourse, are immune suppressed, and who partake in high-risk sexual behavior. Providers need to not shy away from asking individuals if they are not only sexually active, but if they participate in anal receptive

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intercourse either currently or in the past. Creating speaking points prior to a patient interview will assist in developing a comfort level when it comes to asking sometimes uncomfortable questions.

A critical question is how do we target prevention efforts towards high risk groups when no national guidelines exist? Of utmost importance, is screening and treating anal dysplasia prior to it turning into anal cancer through improved prevention and surveillance campaigns. Clinicians need to be educated on the importance of an anal dysplasia screening program and trained on how to effectively collect samples. Individuals providing anal cytology screening need to inform and educate clients about this option, become proficient at performing anal cytology, and explaining the procedure to clients. Clinicians also need to be aware of follow up for someone presenting with abnormal anal cytology.

Fear of discrimination can prevent patients from divulging the fact that they have partaken in high risk behavior/sexual encounters. Due to fear of discrimination, it is important to provide a welcoming, prejudice-free, safe environment.

Conclusion

HPV related anal dysplasia and cancer is a public health concern, just like other sexually transmitted infections. Certain individuals and groups have a higher prevalence, including men who have sex with men, immune compromised individuals, and women with a history of cervical and/or vulvular dysplasia and cancer. If this cancer is not caught early, it has disastrous effects. Due to the high rates in of anal dysplasia and cancer in MSM, it is logical to implement a screening program, similar to the cervical pap screening program. It is fair to estimate that the

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implementation of a universal surveillance program could provide the same epidemiological results for anal cancer in men who have sex with men.

Recommended Internet Sites

The internet sites listed below can serve as resources for information regarding anal dysplasia and cancer, and disease statistics. The gay and lesbian medical association website provides a database of medical providers and practitioners that support and provide a safe health care environment for gay, lesbian, and transsexual individuals.

The American Cancer Society <http://cancer.org>

The National Cancer Institute <http://www.cancer.gov>

The Center for Disease Control <http://www.cdc.gov>

American Social Health Association <http://www.ashastd.org>

World Health Organization <http://www.who.int>

Gay and Lesbian Medical Association <http://www.glma.org>

The Rainbow Health Initiative www.rainbowhealth.org

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