Published in final edited form as:
J Acquir Immune Defic Syndr. 2008 August 1; 48(4): 491–499. doi:10.1097/QAI.0b013e31817aebfe.

Incidence and epidemiology of anal cancer in the Multicenter AIDS Cohort Study (MACS)

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Abstract

Objective—To examine the incidence and risk factors for anal cancer in a multicenter cohort of HIV-positive and negative men who have sex with men followed between 1984 and 2006 (MACS).

Methods—Prospective analysis using Poisson regression and Cox proportional hazard models, and a nested case-control study using conditional logistic regression.

Results—There were 28 cases of anal cancer among the 6,972 men who were evaluated. The incidence rate was significantly higher in HIV-positive men than in HIV-negative men (IR= 69 vs. 14 per 100,000 person-years). Among HIV-positive men, anal cancer incidence was higher in the HAART era than the pre-HAART era (IR=137 vs. 30 per 100,000 person-years). In multivariate analysis restricted to the HAART era, anal cancer risk increased significantly with HIV infection (RH=4.7, 95%CI=1.3–17), and increasing number of unprotected receptive anal sex partners at the first three study visits (p-trend=0.03). Among HIV-positive men, current HAART use did not decrease anal cancer risk.

Conclusion—HIV-positive men had increased risk of anal cancer. Improved survival of HIV-positive individuals following HAART initiation may allow for sufficient time for human papillomavirus (HPV) associated anal dysplasias to develop into malignancies, thus explaining the increased incidence of anal cancer in the HAART era.

Keywords

anal; rectal; cancer; incidence; MACS; sexual risk; HAART

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INTRODUCTION

The incidence of anal cancer has increased in the past decade[1], particularly in certain population subgroups. HIV-positive men and men who have sex with men (MSM) are at increased risk of anal cancer compared to the general population.[2–4] HIV-negative MSM have an estimated incidence rate of 35/100,000[5] which is comparable to the incidence of cervical cancer in the general female population before widespread cervical Pap screening was introduced (40–50 cases/100,000)[6] and greater than the current incidence of cervical cancer (~9 / 100,000)[7]. The incidence of anal cancer among HIV-positive MSM is thought to be even higher (~70–100 cases/100,000).[8] As HIV-positive men are living longer following the introduction of highly active antiretroviral therapy (HAART), cancer poses a larger problem for this population.

Recent evidence suggests that anal infection with human papillomavirus (HPV) is strongly associated with the subsequent development of anal cancer.[9–12] Anal HPV infection is believed to be sexually transmitted, and cross-sectional studies suggest that a higher number of sexual partners is associated with an increased odds of anal dysplasia[13] and anal cancer. [5, 10, 14] Sexual risk behaviors are known to serve as a surrogate for anogenital HPV infection[15], likely explaining the association of these behaviors with cancer risk. Longitudinal analysis to establish a temporal relationship between high-risk sexual behaviors and subsequent risk of anal cancer has not been reported.

The cancer subsites in the anus and rectum most likely to have an HPV etiology have not been thoroughly evaluated. Studies of anal cancer have used varying inclusion criteria for cancer site based on differing surgical and histological definitions of the boundaries of the anal canal. Most studies included rectal [2, 10, 16] and perianal skin [10, 16, 17] cancers in their "anal cancer" case definitions which could attenuate results by including etiologically heterogeneous cancers. Although HPV is known to infect squamous cells and the majority of anal cancers are squamous cell carcinomas (SCC), few studies[18] have focused exclusively on the epidemiology of anal SCC. Results from rectal cancer studies have varied, with some suggesting low[10] and others high[19, 20] HPV prevalence in rectal adenocarcinomas. HPV has been recently shown to be an important cause of cervical adenocarcinomas[12, 21] so it is possible that HPV may play a role in rectal adenocarcinomas as well.

The natural history of anal HPV infection and co-factors for persistence of anal HPV infection are not well understood. In addition, the effects of HIV-associated immunosuppression and HAART on anal cancer risk are not well described. Recent studies have suggested the incidence of anal cancer in HIV-positive individuals is higher in the HAART era than the pre-HAART era[3, 18] and that anal HPV persistence and progression of HPV-associated pre-cancers are not reduced in those on HAART. [22, 23]

This manuscript describes the incidence of, and risk factors for, anal cancer using longitudinal data from HIV-positive and negative men in the Multicenter AIDS Cohort Study (MACS). This is one of the first studies to evaluate incidence or risk factors for anal cancer using exposure information collected before the cancer diagnosis.

METHODS

Study Population

The study included all men in the Multicenter AIDS Cohort Study (MACS), a cohort that has been described elsewhere.[24–26] In brief, the MACS includes primarily HIV-positive and HIV-negative MSM and has study sites in Baltimore, Chicago, Los Angeles and Pittsburgh. The study began in 1984 and a total of 6,972 men have been enrolled over three separate enrollment periods (1984–85, 1987–91, and 2001–03). Anal cancer cases included only men with T1 invasive anal or rectal disease.

Outcomes

Subject self-report of cancer was verified by histology report or cancer registry. Histology reports and medical records were collected, reviewed and summarized by trained abstractors and centrally re-reviewed for this paper. Tumor specimens were not available for histological review, testing or adjudication for these analyses.

Incident anal (ICD-O=154.2–154.8 or ICD-O3=21.0–21.8), perianal (ICD-O3=44.5 with record noting perianal location) and rectal (ICD-O=154.0–154.1 or ICD-O3=19.9–20.9) ICD codes were classified together as anal cancer for these analyses. Cases were classified using documented pathology reports (n=23) or physician narrative indicating diagnosis of anal cancer (n=1). Where no medical documentation was available, self-report of anal cancer by study subject was accepted (n=4). Sub-analysis using only those cancers with anal tumor site and squamous cell morphology (ICD-O code 8052–8084 or ICD-03=8070.2–8078) was also performed and these cancers are referred to as anal squamous cell carcinomas (ASCC); only T1 invasive cancers confirmed by pathology report review were included in the ASCC sub-analysis. Data gathered between 1984 and March 2007 were included in these analyses.

Exposures

Detailed behavioral data were collected from participants every six months using interviewer-administered and/or audio computer assisted self interview format. Recent sexual behaviors assessed at each visit included the number of total, anal insertive, anal receptive, and unprotected anal receptive sexual partners in the past six months. The number of unprotected anal receptive partners *at baseline* was chosen for this analysis due to the long latency period between HPV infection and development of cancer and the expectation that more distant measures of sexual risk better represent current risk of malignancy. A summary measure of baseline sexual risk was created by adding the number of unprotected anal receptive partners reported at each of the initial three study visits. Recent tobacco use was also assessed at each visit as tobacco use has been associated with elevated anal HPV prevalence, viral load[27] and odds of anal cancer.[16]

Positive enzyme-linked immunosorbent assays (ELISA) with confirmatory Western blot tests were used to determine HIV seropositivity. Plasma HIV RNA levels were determined using the Roche Ultrasensitive RNA PCR assay (Hoffman-LaRoche, Nutley, NJ), with a

detection limit of 50 copies/mL. T-lymphocyte subset levels were quantified by each MACS center using standardized flow cytometry.[28]

Self-reported use of antiretroviral medications at each visit was summarized to define whether participants were using HAART. The definition of HAART was guided by the DHHS/Kaiser Panel[29] guidelines and defined as: (a) two or more nucleoside reverse transcriptase inhibitors (NRTI) in combination with at least one protease inhibitor (PI) or one non-nucleoside reverse transcriptase inhibitor (NNRTI) (89% of observations classified as HAART); (b) one NRTI in combination with at least one PI and at least one NNRTI (5%); (c) a regimen containing ritonavir and saquinavir in combination with one NRTI and no NNRTIs (1%); and (d) an abacavir or tenofovir containing regimen of three or more NRTIs in the absence of both PIs and NNRTIs (5%), except for the three-NRTI regimens consisting of: abacavir, tenofovir and lamivudine OR didanosine, tenofovir and lamivudine. Combinations of zidovudine and stavudine with either a PI or NNRTI were not considered HAART.

Semiannual visits also included standardized physical examinations, medical histories, and phlebotomy for laboratory measurements and storage of cells, serum and plasma in centralized repositories. Medical records were sought and reviewed for confirmation of all reported AIDS defining illnesses, cancers, and other specified conditions. Passive and active methods were used to ascertain deaths, and information on causes of death was captured by death certificate review.

Statistical Methods

Poisson regression models were used to calculate anal cancer incidence rates. Given the very long follow-up involved in this study, reasons for right-censoring (i.e. time when follow-up ended) varied between the original and more recently recruited participants in the MACS. More than two-thirds (69%) of men enrolled in 2001–03 remained in active follow-up as of September 2006 compared to only 27% of those whose baseline visit was prior to 2001. At time of analysis, death (64% vs. 4%, respectively) was much more common among HIV-positive men enrolled prior to 2001 than among similar men who were more recently enrolled.

Cox proportional hazard models were used to calculate the relative hazard for risk factors of interest. Study entry (baseline) was used as the time origin and men were at risk up to the date of anal cancer diagnosis or last date of contact or March 30, 2007, whichever came first. Tobacco use, current HAART use, nadir CD4 cell count and HIV viral load were evaluated as time-updated covariates in these models. Trends in risk were tested by modeling ordinal variables as single, continuous, independent variables.

Kaplan-Meier curves were generated using age as the time-scale and assuming anal cancer free time from study entry back to age 30. HIV-positive participants who contributed time before 1996 were included in a "HIV+, pre-HAART era" curve, with exit age at the date of anal cancer or last date of contact or December 31, 1995, whichever came first. HIV-positive participants who contributed time after 1996 were included in a "HIV+, HAART era" curve, with entry age at January 1, 1996. Thus, HIV-positive men who were enrolled

before 2001 and still enrolled and anal cancer free in 1996 contributed to both pre-HAART and HAART era curves.

Given the large proportion of men in the original MACS cohort who died before HAART became available, competing risks could affect interpretation of longitudinal analysis. Many men early in the epidemic died before having the "opportunity" to develop cancer but still contributed time to the longitudinal analysis. To address this concern, we performed a nested case-control study.

Case-control analysis was performed using conditional logistic regression. Each anal cancer case was individually matched to three controls using the following matching criteria: age at diagnosis (± 5 years), year of study enrollment, HIV serostatus, ever/never HAART use, and follow-up time (+2.5 years). Follow-up time was defined as the time from study entry until anal cancer diagnosis for HIV–negative and HIV-positive HAART-naïve participants. HIV-positive cases who used HAART before their cancer diagnosis were matched to controls on the time of HAART initiation (± 3 years) and time from first HAART use until diagnosis (± 2.5 years). Cases who were HIV seropositive at study entry were also matched by CD4 cell count at study entry (± 50 cells/μL) to account for duration of infection. Cases with incident HIV during the study were matched with HIV-prevalent participants with baseline CD4 counts >750 cells/ μL due to unavailability of seroconverters as matched controls. All analyses were performed using SAS 9.1 (Cary, NC). Graphical illustrations were generated by S-plus 6.2 (Insightful Corporation, Seattle, WA).

RESULTS

Description of cancers

Between 1984 and March 2007, 28 anal, perianal or rectal (hereafter referred to collectively as anal) cancers were observed among the 6,972 men in the MACS cohort. This included 21 anal cancers, of which 17 were SCC, one was neuroendocrine and three had unconfirmed morphology. Of the seven rectal cancers included, five were adenocarcinomas and two were SCC. Six anal cancers were diagnosed among HIV-negative men and 22 were diagnosed among HIV-positive men (Table 1). More than half (67%; 4 of 6) the anal cancers in HIV-negative men were rectal adenocarcinomas compared to only 14% (3 of 22) of anal cancers in HIV-positive men ($p<0.001$). Anal cancers in HIV-positive men were twice as likely to have squamous morphology (68% vs. 33%) as cancers in HIV-negative men ($p=0.034$). The median age at cancer diagnosis was 47.4 years in HIV-positive and 57.8 years in HIV-negative men. The median follow-up time for men enrolled between 1984–91 and 2001–03 was 10.5 and 3.9 years respectively. Participants enrolled earlier in the study were more likely to have died (34.2% vs. 2.7%, $p<0.001$) and equally likely to have been lost to follow-up (29.5% vs. 28.4%, $p=0.19$) than participants enrolled in 2001–03.

Cases occurred throughout the 22 year follow-up period including nine cases in the pre-HAART (1984–1995) and 19 in the post-HAART (1996–2006) era. Age, HIV viral load and CD4 cell count at diagnosis varied considerably (Table 1). HIV-positive anal cases included both men with suppressed HIV viral RNA and high CD4 cell count as well as severely immunocompromised men. Among HIV-positive cases, half were diagnosed with an AIDS-

defining condition at time of their anal cancer diagnosis (Table 1). This proportion was higher among HIV-positive cases in the pre-HAART (4 of 5) than the HAART era (7 of 17). When diagnosed with anal cancer, 27% of the HIV-positive cases were HAART-naïve. However, this included men who developed cancer in the pre-HAART era. Of the 16 cases which occurred in the HAART era, 15 (94%) started HAART before their cancer diagnosis.

Incidence

The overall incidence of anal cancer was 37 per 100,000 person-years (95% CI=25–53) and that of confirmed ASCC cases was 22 per 100,000 person-years (95%CI=14–36). Anal cancer incidence was five-fold higher among HIV-positive men (Incidence Rate [IR]=69 per 100,000 person-years, 95%CI=46–105) than among HIV-negative men (IR=14 per 100,000 person-years, 95%CI=6–30). Among HIV-positive men, the incidence of anal cancer more than fourfold higher in the HAART era (1996–2006; 137 per 100,000 person-years, 95%CI=84–224) than in the pre-HAART era (1984–1995; IR=30 per 100,000 person-years, 95%CI=13–66).

Time to event analysis

Risk factors for anal cancer were explored using time-to-event analysis. In univariate analysis, risk of anal cancer increased non-significantly with increasing age (p-trend=0.15). Men with seven or more unprotected anal receptive sexual partners at the first three study visits had significantly higher risk of anal cancer (Relative Hazard [RH]=2.7, 95%CI=1.08–6.5) compared to men with no unprotected receptive anal sex partners. Additionally, a dose-response trend was suggested by significantly increasing risk with increasing number of unprotected receptive anal sex partners (p-trend=0.03, Table 2). Consistent with this finding, the median number of unprotected receptive anal sex partners reported in the initial three study visits was significantly higher in anal cancer cases than in other study participants (p=0.018, Figure 1). Similar results were observed when the sexual risk behavior analyzed was number of unprotected receptive anal sex partners reported during the initial three study visits (p-trend=0.03) or lifetime number of sexual partners reported at baseline (p-trend=0.07). In analysis limited to confirmed ASCC, history of more than 100 lifetime sexual partners was similarly associated with increased cancer risk (HR=5.5, 95%CI=0.67–44) but did not reach statistical significance due to the smaller number of cases.

HIV-positive men had a significantly higher risk of anal cancer (RH=5.1, 95%CI=2.1–12.6) or confirmed ASCC (RH=10.4, 95%CI= 2.1–50) than HIV-negative men. Among HIV-positive men, anal cancer risk was significantly elevated in men with nadir CD4 cell count <200 cells/μL (RH=3.3, 95%CI=1.4–7.9) but was not associated with HIV viral load (Table 2). Risk of anal cancer was also significantly higher in ever-smokers than never-smokers (RH=3.9, 95%CI=1.2–12.8) but there was no evidence of increasing risk with current dose of tobacco used (Table 2).

To evaluate whether HAART therapy had an effect on anal cancer risk we considered both ever and current HAART use. In analysis restricted to data during the HAART era, risk of anal cancer was elevated but was not significantly different in HIV-positive current HAART users and non-users (RH=1.8, 95%CI=0.5–6.4) or HIV-positive ever and never HAART

users (RH=1.7, 95%CI=0.23–13). In contrast, risk of rectal adenocarcinomas was more than 4-fold lower among ever than never HAART users (RH=0.22, 95%CI=0.02–3.13), suggesting a possible decrease in risk of these cancers with HAART use.

As age is an important risk factor for anal cancer, we further evaluated the difference in anal cancer risk in the HAART and pre-HAART eras using a Kaplan-Meier curve to examine risk in each era by participants' age (Figure 2). These data suggest greater cancer risk (i.e. shorter time to anal cancer) among HIV-positive than HIV-negative men ($p<0.001$). These differences were more pronounced in the HAART than the pre-HAART era. Among HIV-positive men, anal cancer risk for younger men (< 50 years of age) was similar in the HAART and pre-HAART eras. However, as age increased above 50 years of age, HIV-positive men in the HAART era appear to have more risk of anal cancer than HIV-positive men in the pre-HAART era ($p=0.16$, Figure 2). Evaluation of the difference in cancer risk among HIV-positive men at older ages is limited by the smaller number of men available for analysis in the older age categories. Considerably fewer HIV-positive men from the pre-HAART enrollment lived to contribute data at ages above 60 (n=36 men) compared to men alive in the HAART era (n=115 men).

Due to the high mortality in the pre-HAART era and the difference in anal cancer risk in the HAART and pre-HAART eras, and to better evaluate anal cancer risk factors we restricted multivariable analysis to time and events contributed by participants in the HAART era (1996 onwards). In the *multivariate* analyses of all men in the HAART era, risk of anal cancer was elevated in participants with HIV infection (RH=4.7, 95%CI=1.3–17), and men with more unprotected anal receptive sex partners at the first three study visits (p-trend=0.03). As HIV infection was an important risk factor, the effect of other risk factors was then evaluated in analysis limited to HIV-positive participants. Number of unprotected anal receptive sexual partners at the initial three study visits (p-trend=0.014; Table 3) remained strongly associated with increased anal cancer risk in this analysis. Nadir CD4 cell count and ever tobacco use were associated with elevated but not statistically significant increased cancer risk (Table 3). As only one HAART-era anal cancer case was HAART-naïve at time of anal cancer diagnosis, the effect of *ever* HAART use could not be evaluated in this model. Current HAART use, race and age were not associated with increased cancer risk. Results were similar when restricted to ASCC (data not shown).

Case-control analysis

Risk factors identified in univariate case-control analysis were consistent with those observed in longitudinal analysis (Table 2). The effect of HIV, HAART, and age could not be evaluated because these factors were used for matching cases and controls. However, after controlling for these factors through matching, number of unprotected anal receptive sex partners at the first three study visits (p-trend=0.027) was associated with significantly increased odds of anal cancer. Nadir CD4 <200 cells/μL (OR=1.6, 95%CI=0.54–4.5) and ever tobacco use (OR=3.6, 95%CI=0.78–16.9) were associated with elevated but not statistically significant increased odds of anal cancer.

In multivariate analyses of all subjects the odds of anal cancer were elevated in those with seven or more anal receptive sex partners reported at the first three study visits (p-

trend=0.05), ever smokers (OR=4.5, 95%CI=0.89–23), and HIV-positive men with nadir CD4 <200 cells/μL (OR=2.1, 95%CI=0.65–6.6). Results were similar when restricted to HIV-positive men (Table 3) or to ASCC (data not shown).

DISCUSSION

Registry data suggests higher anal cancer incidence among HIV-positive than HIV-negative individuals (RR=10–352) [18, 30–36] and increasing anal cancer rates in the past few decades [1, 18, 37], however few longitudinal studies have evaluated anal cancer incidence.[38, 39] The cohort study presented here utilized 22 years of longitudinal data from a well characterized multicenter cohort study population with high participant retention. MACS data have an additional strength, compared to registry data, in that the exposure information analyzed was collected before cancer diagnosis. This study demonstrates significantly higher incidence of anal cancer in HIV-positive MSM than in HIV-negative MSM. Consistent with the temporal trend of increasing anal cancer incidence suggested in several studies,[1, 37, 40–43] this study found significantly higher anal cancer incidence in the HAART era (1996–2006) than the pre-HAART era (1984–1995) era. This trend is likely related to premature mortality witnessed in the pre-HAART period among HIV-positive men. In the MACS, the median age for diagnosis of AIDS before 1995 was 39 years [44], while the median age for anal cancer is above 50 years. [45] Other explanations for the increase in anal cancer incidence could include a direct toxic effect of HAART or incomplete adjustment for the aging of the study cohort. Improved diagnosis or reporting of these cancers is less likely but can not be excluded. Thus, anal cancer incidence may continue to increase in this population as HAART improves survival, thus allowing HIV-positive MSM to survive long enough to develop anal cancer.

Observed incidence rates among HIV-positive men in this study were comparable to those reported in other studies of HIV-positive persons in the HAART era (92–144 per 100,000 person-years) and pre-HAART era (12–69 per 100,000 person-years).[18, 37, 38] Discrepancies between estimates may be partially explained by heterogeneity in definitions of which cancer sub-sites and morphologies are included as anal cancers as well as inclusion or exclusion of in-situ cancers. Incidence of anal cancer among the high-risk HIV-negative men in this study was higher than incidence rates reported in some population-based samples during the same time period (0.4–0.8 and 1.0 per 100,000 person-years in pre-HAART and HAART eras respectively [37, 40, 43]) but similar to estimates in two other studies during a similar time-period.[37, 42]

Sexual risk behaviors at study entry were strongly associated with risk of subsequently developing anal cancer in this study, supporting an HPV etiology to these cancers. This is consistent with the results of anal cancer case-control studies which have shown increased odds of anal cancer in those with higher number of sexual partners[5, 10, 16], ever receptive anal sex[5, 14, 16], and number of receptive anal sex partners.[17] Associations with sexual risk are likely attenuated in this study as most MACS participants were over 30 years of age at study entry and it is highly likely that many of the men were exposed to HPV before study entry. It takes many years from HPV infection to development of cancer and as some of the anal cancer cases in this study occurred only a few years after study entry the baseline

sexual behaviors in these men may not be representative of their sexual risk when initially infected with HPV. Sexual risk behavior was similarly associated with anal cancer risk when rectal cases were included and when limited to only ASCC, suggesting some rectal cancers may have an HPV-associated etiology.

As suggested in this study, tobacco use has been associated with increased odds of anal cancer (OR=1.9–7.7) in most case-control studies of anal cancer.[16, 17, 46, 47] This study may have been underpowered to detect the effect of tobacco and did not have a measure of lifetime tobacco use. Sexual behavior is strongly associated with tobacco use[48, 49], so residual confounding by sexual behavior could explain the observed moderate associations between tobacco and anal cancer risk. However, increased risk of other HPV-associated malignancies has also been observed in tobacco users[46, 50, 51], suggesting a possible effect of tobacco on HPV persistence or progression of HPV-associated dysplasias to cancer. The effect of tobacco may be small in relation to the effect of HIV and may therefore be harder to observe in a population of HIV-positive individuals.

While cervical cancer is considered an AIDS defining illness, anal cancer currently is not. However studies suggest that individuals with HIV infection are at increased risk of anal high-grade squamous intraepithelial lesions (HSIL) [8, 52, 53] and, as shown in this and other studies, at increased risk of anal cancer.[2, 30, 36] While HAART has reduced the risk of many HIV-associated morbidities[54], initial studies suggest HAART does not decrease risk of HPV-associated anal, genital and oropharyngeal cancers. [2, 22, 54, 55] Longitudinal analysis of the effect of HAART on anal HPV progression is limited but shows no apparent effect of HAART on anal HPV natural history [23, 56] and cross-sectional analysis demonstrates a high prevalence of anal HPV infection in HIV-positive men despite HAART related immune restoration.[23, 57] In this study, anal cancer cases that occurred during the HAART era were primarily in men currently on HAART. Many of these men had low HIV viral load and CD4 cell counts above 200 cells/μL, suggesting HAART related immune restoration may not be effective (or may have a modest effect) against progression of anal HPV-associated cellular abnormality. As HAART leads to improved survival for HIV-positive individuals it may thus allow sufficient time for development of invasive anal disease. Anal cancer incidence in individuals on HAART may therefore continue to rise.

This study was limited by the lack of tumor tissue for HPV DNA testing. Central pathology review of all cancers was also not possible although detailed review of existing pathology reports was performed to reduce misclassification. Longitudinal data was included from men enrolled into the MACS cohort in three different waves with variable characteristics and follow-up time. Additionally, baseline measures of sexual risk behaviors were used in this study and as these may be after the peak time of sexual risk taking in some men these measures may not accurately represent the behaviors when the men were most as risk at HPV infection.

Anal cancer incidence has increased significantly in the past ten years and is currently estimated to be ~1.5 per 100,000 in the general U.S. population[58]. MSM and HIV-positive individuals have substantially higher rates of anal cancer[59]. Anal cancer may be preventable but the benefits of screening for and treating anal cancers have not yet been well evaluated.

Further research is needed to determine the benefits and costs of risk reduction interventions, screening and treating anal cancer precursors in high-risk populations such as HIV-positive individuals.

Acknowledgments

The Multicenter AIDS Cohort Study (MACS) includes the following: Baltimore: The Johns Hopkins University Bloomberg School of Public Health: Joseph B. Margolick (Principal Investigator), Haroutune Armenian, Barbara Crain, Adrian Dobs, Homayoon Farzadegan, Joel Gallant, John Hylton, Lisette Johnson, Shenghan Lai, Ned Sacktor, Ola Selnes, James Shepard, Chloe Thio. Chicago: Howard Brown Health Center, Feinberg School of Medicine, Northwestern University, and Cook County Bureau of Health Services: John P. Phair (Principal Investigator), Joan S. Chmiel (Co-Principal Investigator), Sheila Badri, Bruce Cohen, Craig Conover, Maurice O'Gorman, David Ostrow, Frank Palella, Daina Variakojis, Steven M. Wolinsky. Los Angeles: University of California, UCLA Schools of Public Health and Medicine: Roger Detels (Principal Investigator), Barbara R. Visscher (Co-Principal Investigator), Aaron Aronow, Robert Bolan, Elizabeth Breen, Anthony Butch, Thomas Coates, Rita Effros, John Fahey, Beth Jamieson, Otoniel Martínez-Maza, Eric N. Miller, John Oishi, Paul Satz, Harry Vinters, Dorothy Wiley, Mallory Witt, Otto Yang, Stephen Young, Zuo Feng Zhang. Pittsburgh: University of Pittsburgh, Graduate School of Public Health: Charles R. Rinaldo (Principal Investigator), Lawrence Kingsley (Co-Principal Investigator), James T. Becker, Robert L. Cook, Robert W. Evans, John Mellors, Sharon Riddler, Anthony Silvestre. Data Coordinating Center: The Johns Hopkins University Bloomberg School of Public Health: Lisa P. Jacobson (Principal Investigator), Alvaro Muñoz (Co-Principal Investigator), Stephen R. Cole, Christopher Cox, Gypsyamber D'Souza, Stephen J. Gange, Janet Schollenberger, Eric C. Seaberg, Sol Su. NIH: National Institute of Allergy and Infectious Diseases: Robin E. Huebner; National Cancer Institute: Geraldina Dominguez; National Heart, Lung and Blood Institute: Cheryl McDonald. UO1-AI-35042, 5-MO1-RR-00722 (GCRC), UO1-AI-35043, UO1-AI-37984, UO1-AI-35039, UO1-AI-35040, UO1-AI-37613, UO1-AI-35041. Website located at http://www.statepi.jhsph.edu/macs/macs.html.

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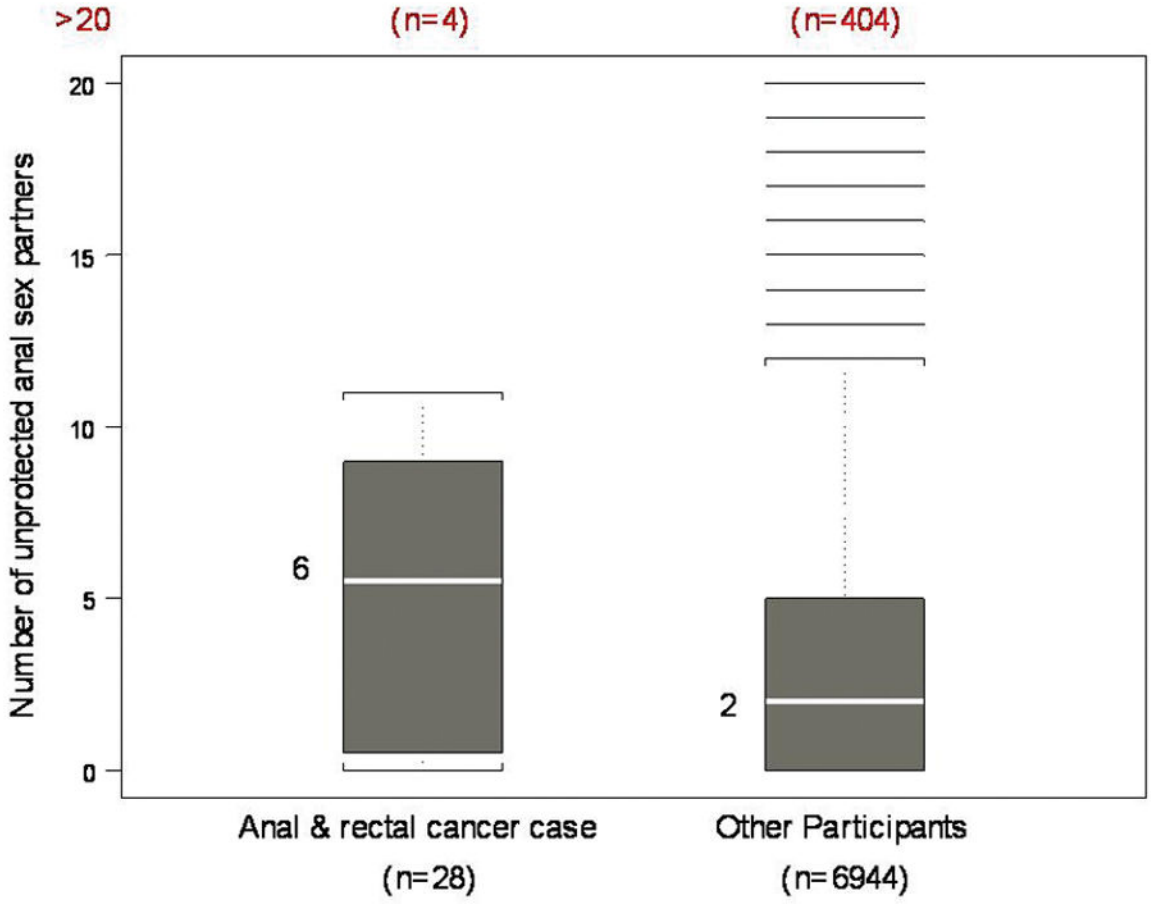

Figure 1.

Comparison of the number of unprotected receptive anal sexual partners reported at the first three semi-annual study visits in those men in the study who later developed anal cancer compared to all other study participants. Median (white line), 25% and 75% (upper and lower bounds of box), 95% confidence limits (bracketed lines), and outliers are displayed above.

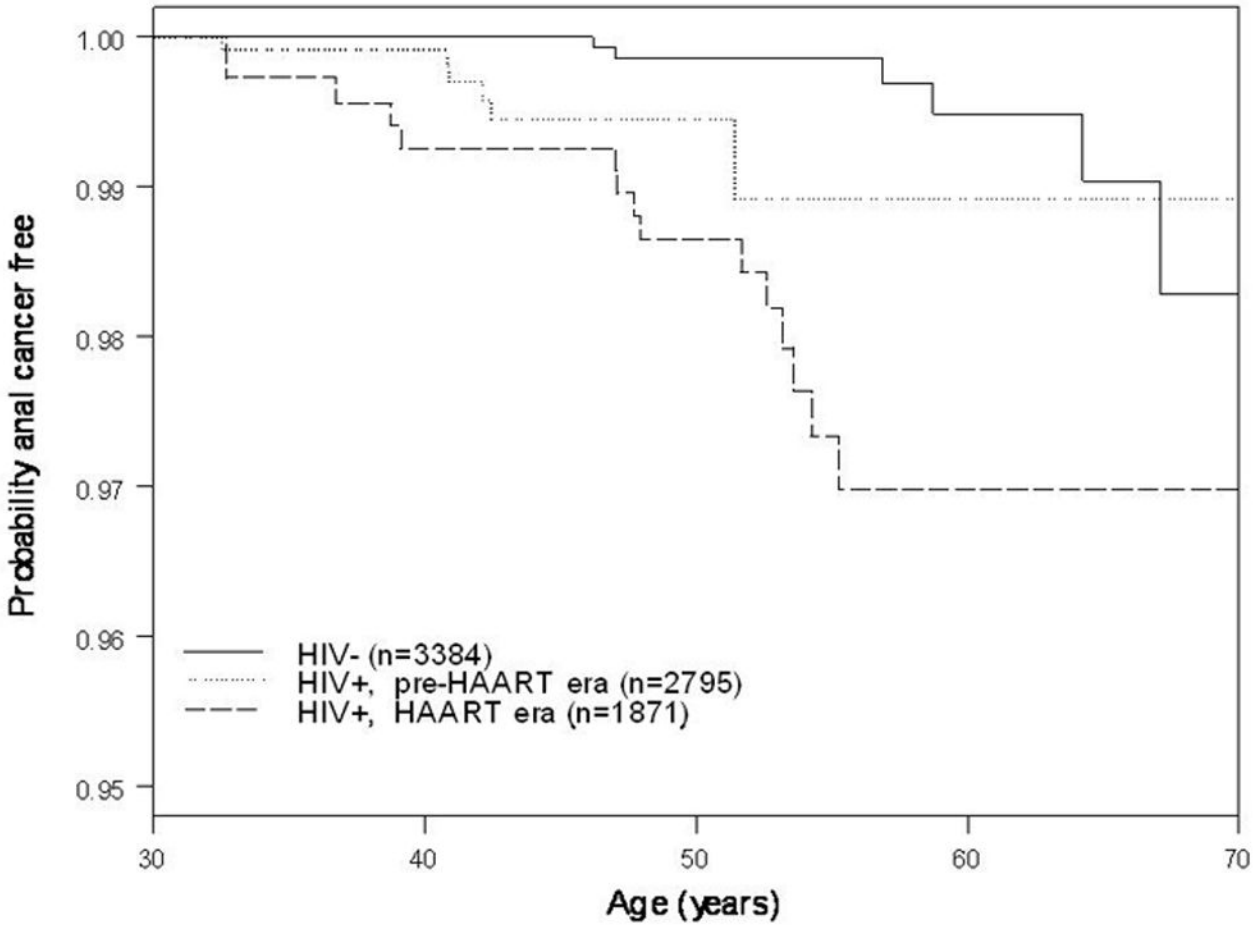

Figure 2.

Kaplan-Meier probability curve of time free of anal cancer in HIV-positive (HIV+) men in the pre-HAART(1984–1995) and HAART (1996–2006) eras compared to HIV-negative (HIV-) men. Age is used as the time axis. Staggered entry is used to assume time of origin back to age 30 for all participants. This includes men enrolled in each of the three study enrollment calendar periods (1984–85, 1987–91, and 2001–03).

Table 1

Description and incidence of anal cancers detected in the MACS 1984–2006 and the subset of anal squamous cell carcinomas.

	All anal & rectal cancers		Confirmed anal squamous cell cancers only	
	Incidence (95%CI)			
Incidence per 100,000 person-years				
HIV-negative	14 (6 – 30)		5 (1 – 18)	
HIV-positive	69 (46 – 105)		47 (28 – 78)	
pre-HAART era (<1996)	30 (13 – 66)		15 (5–46)	
HAART era (≥1996)	137 (84–224)		103 (58 – 181)	
	N=28		N=17	
	N	%	N	%
HIV Status				
Negative	6	21%	2	12%
Seroprevalent at entry	21	75%	14	82%
Seroincident	1	4%	1	6%
MACS enrollment wave				
Enrolled 1984–85 or 87–91	24	86%	13	76%
Enrolled 2001–2003	4	14%	4	24%
Year anal cancer diagnosed				
1984 – 1990	3	11%	1	6%
1991–1995	6	21%	3	18%
1996 – 2000	4	14%	2	12%
2001 – 2006	15	54%	11	65%
Cancer morphology				
Squamous cell	19	68%	17	100%
Adenocarcinoma	5	18%	NA	
Small cell neroenedocrine carcinoma	1	4%	NA	
Unknown	3	11%	NA	
Age at anal cancer diagnosis				
30 – 39	5	18%	5	29%
40 – 49	10	36%	5	29%
50 – 59	9	32%	5	29%
≥ 60	4	14%	2	12%
HIV-INFECTED CASES ONLY	N=22		N=15	
AIDS before anal cancer diagnosis				
No	11	50%	8	53%
Yes	11	50%	7	47%
HAART before anal cancer diagnosis				

	All anal & rectal cancers		Confirmed anal squamous cell cancers only	
No	1	5%	1	7%
Yes	15	68%	11	73%
Anal cancer before 1996	6	27%	3	20%
Year first started HAART				
Never HAART	6	27%	3	20%
After anal cancer diagnosis	1	5%	1	7%
Before anal cancer diagnosis				
1996	6	27%	4	27%
1997–1998	4	18%	2	13%
2001	2	9%	2	13%
2003	2	9%	2	13%
2005	1	5%	1	7%
CD4 cell count at diagnosis (cells/μL)				
Unknown	6	27%	3	20%
≤ 200	5	23%	5	33%
201 – 400	5	23%	2	13%
401 – 600	5	23%	4	27%
> 600	1	5%	1	7%
HIV viral load at diagnosis (RNA copies/mL)				
Unknown	8	36%	3	20%
Undetectable	5	23%	5	33%
50 – 10,000	4	18%	2	13%
10,001 – 100,000	3	14%	3	20%
> 100,000	2	9%	2	13%

* CD4 cell count and HIV viral load measures up to one year before cancer diagnosis (using the available measure closest to diagnosis) were included in these measures.

Table 2

Univariate relative hazard (RH) and odds ratios (OR) for anal cancer by select risk factors.

	Time-to-event analysis	Case-control analysis
	RH (95%CI)	**OR (95%CI)**
DEMOGRAPHICS		
Age at baseline (in years)		
< 30	1.0	NA *
30 – 39	2.1 (0.76 – 5.7)	NA
40 – 49	2.6 (0.82 – 8.2)	NA
≥ 50	1.8 (0.21–15.3)	NA
p-trend	*p=0.15*	
SEXUAL RISK		
Cumulative number of unprotected anal receptive sexual partners at first 3 visits (summed)		
0–1	1.0	1.0
2–6	0.96 (0.36–2.6)	1.47 (0.46–4.7)
≥ 7	2.66 (1.08–6.5)	4.04 (1.12–14.6)
p-trend	*0.033*	*0.027*
Number of unprotected anal receptive sex partners in 6 months before baseline		
0	1.0	1.0
1–3	0.51 (0.18–1.5)	0.52 (0.15–1.2)
≥ 4	2.32 (0.95–5.7)	2.24 (0.71–7.1)
p-trend	*0.061*	*0.12*
Number of lifetime sex partners reported at baseline		
<50 ∞	1.0	1.0
50–99	1.69 (0.34–8.4)	0.99 (0.14–6.8)
100–249	2.8 (0.71–10.7)	2.6 (0.50–13.9)
≥ 250	2.9 (0.83–10.3)	1.26 (0.27–5.9)
p-trend	*0.072*	*0.83*
TOBACCO USE		
Tobacco Use		
Never smoker	1.0	1.0
Former smoker	3.5 (1.0–12.2)	4.3 (0.85–22.0)
Current smoker	4.4 (1.2–15.8)	3.1 (0.62–15.8)
p-trend	*p=0.021*	*p=0.31*
Current tobacco dose ^		
None	1.0	1.0
<1 pack/day	2.5 (0.99–6.4)	1.0 (0.34–3.2)
≥1 pack/day	1.3 (0.43–3.9)	0.91 (0.25–3.3)

	Time-to-event analysis	Case-control analysis
	RH (95%CI)	**OR (95%CI)**
p-trend	*p=0.23*	*p=0.96*
HIV STATUS		
HIV-uninfected	1.0	NA
HIV-infected - HAART naïve	5.3 (1.7 – 17)	NA
HIV-infected - HAART ever	5.1 (2.0 – 13)	NA
HAART AND IMMUNOSUPRESSION (AMONG HIV-INFECTED MEN ONLY) ^		
Current HAART use		
No	1.0	NA
Yes	2.3 (0.8–6.7)	NA
Current HAART use (≥1996 only)		
No	1.0	NA
Yes	1.8 (0.5–6.4)	NA
Ever HAART use (≥1996 only)		
Never	1.0	NA
Ever	1.7 (0.23–13.3)	NA
Nadir CD4 cell count (cells/μL)		
>200	1.0	1.0
≤ 200	3.3 (1.4–7.9)	1.6 (0.54–4.5)
HIV viral load (RNA copies/mL)		
Per log increase	1.0 (0.75 – 1.6)	1.4 (0.87–2.3)

* Risk factors that were used for matching cases and controls are indicated by "NA" (not applicable).

^ For time-to-event analysis, covariates measuring current use and immunologic measures were considered in a time-updated manner. For case-control analysis, current tobacco use and HIV viral load at diagnosis were used.

∞ There were no ASCC cases with < 40 lifetime sexual partners at baseline so comparisons to lower reference categories could not be performed.

Table 3

Multivariate relative hazard (RH) and odds ratios (OR) for anal cancer by selected risk factors in HIV-positive subjects.

	Limited to HIV-positive subjects	
	Time to event analysis limited to ≥1996	Case control analysis
	RH (95%CI)	OR (95%CI)
Cumulative number of unprotected anal receptive partners reported first 3 visits		
0–1	1.0	1.0
2–6	1.3 (0.23–7.6)	1.6 (0.27–10.0)
≥7	5.2 (1.12–25)	15.4 (1.6–146)
p-trend	*0.014*	*0.008*
Tobacco Use		
Never	1.0	1.0
Ever	2.2 (0.50–9.9)	6.4 (0.70–59)
Nadir CD4 cell count among HIV+		
>200	1.0	1.0
≤ 200	2.3 (0.80–6.7)	3.5 (0.80–15.5)
Current HAART use among HIV+		
No	1.0	NA
Yes	1.3(0.37–4.9)	NA

* Cases and controls were matched by HAART use. Therefore current HAART use could not be evaluated in this analysis and is indicated by "NA" (not applicable).