HHS Public Access

Author manuscript

J Low Genit Tract Dis. Author manuscript; available in PMC 2014 October 01.

Published in final edited form as:

J Low Genit Tract Dis. 2013 October ; 17(4): 397–403. doi:10.1097/LGT.0b013e31827ed372.

Human Papillomavirus Prevalence in Invasive Anal Cancers in the United States prior to Vaccine Introduction

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Abstract

Objective—Conduct a representative survey of Human papillomavirus (HPV) prevalence and its genotype distribution in invasive anal cancer specimens in the U.S.

Methods—Population-based archival anal cancer specimens were identified from Florida, Kentucky, Louisiana and Michigan cancer registries and SEER tissue repositories in Hawaii, Iowa and Los Angeles. Sections from one representative block per case were used for DNA extraction.

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There are no financial disclosures from any of the authors.

All extracts were assayed first by Linear Array and re-tested with INNO-LiPA if inadequate or HPV negative.

Results—Among 146 unique invasive anal cancer cases, 93 (63.7%) were from women and 53 (36.3%) from men. HPV (any type) was detected in 133 (91.1%) cases and 129 (88.4%) contained at least one high risk type, most (80.1%) as a single genotype. HPV16 had the highest prevalence (113 cases, 77.4%); HPV6, 11, 18 and 33 were also found multiple times. Among HPV16 positive cases, 37% were identified as prototype variant Ep and 63% were non-prototypes: 33% Em, 12% E-G131G, 5% Af1, 4% AA/NA-1, 3% E-C109G, 3% E-G131T, 2% As and 1% Af2. No significant differences in the distributions of HPV (any), high-risk types, or HPV16/18 were seen between gender, race or age group.

Conclusions—The establishment of pre-vaccine HPV prevalence in the U.S. is critical to the surveillance of vaccine efficacy. Almost 80% of anal cancers were positive for the vaccine types HPV16 or HPV18 and in 70% these were the only types detected suggesting that a high proportion might be preventable by current vaccines.

Keywords

anal cancer; HPV typing; Human papillomavirus; archived tissue; cancer registry

Introduction

Anal cancers are relatively rare malignancies, most of which occur as squamous cell carcinomas (SCC) of the anal tract. According to 2009 NPCR/SEER combined data, the incident rate for invasive anal cancer in the U.S. was 1.8 per 100,000, totaling 2236 cases in males (rate 1.5) and 3692 among females (rate 2.1) annually (1). While incidence is relatively low, the number of anal malignancies has steadily increased over the past three decades (2). Many of the recognized risk factors for anal cancer, such as number of sexual partners and anal receptive intercourse, are associated with persistent human papillomavirus (HPV) infection of the anal canal (3;4). Anal histology shares common anatomic characteristics with the cervix, including a transformation zone where most HPV-associated neoplastic transformation occurs. It is therefore anticipated that available HPV vaccines will provide protection against anal cancer too and clinical trials of the quadrivalent Gardasil (Merck & Co, Inc., Whitehouse Station, NJ) showed good efficacy against anal intraepithelial neoplasia (5;6).

The proportion of anal carcinomas attributable to HPV has been estimated to be about 90% (7–9) attributing the majority to HPV16 and HPV18. However, no population-based data are available for the United States regarding the type-specific HPV prevalence in anal cancers preceding vaccine implementation. Such information will provide a baseline to monitor vaccine effectiveness against this malignancy. To meet this surveillance objective, population-based sampling of anal cancer tissue from US central state registries was conducted to determine the type-specific HPV prevalence in these cases.

HPV 16 cases were further evaluated to determine HPV16 genotype variants since some reports had indicated that certain non-prototype sequences have a disproportionally high representation in anal diseases (10;11).

Materials and Methods

Selection of anal cancer tissues

Representative tissue specimens were obtained as part of the Centers for Disease Control Central Cancer Registries (CDC CCR) study to provide a baseline prevalence of HPV types in HPV-associated cancers from a representative sample of the US population. A systematic full case selection of anatomic regions coded as anal canal was pursued depending on specimen availability. Cases were recruited from seven participating registries, including four central cancer registries (CCRs) in Florida, Kentucky, Louisiana and Michigan as well as three SEER cancer registry-based residual tissue repositories (RTRs) in Los Angeles County, Hawaii and Iowa. CCR associated pathology laboratories and RTRs were asked to select one representative archived, formalin-fixed paraffin-embedded (FFPE) tissue block from each anal cancer case that was diagnosed between 1995 and 2005. CDC and each participating state received approval from the Institutional Review Board (IRB) for the study.

Specimen preparation and DNA extraction

Six microtome sections were prepared from each block using a fresh disposable blade and applicator for each case. The first and last sections were stained with Hematoxylin and Eosin (H&E) and intervening sections - two 5-μm sections per sample - were transferred into 2 ml conical screw cap tubes with tether cap (Simport, Beloeil, Canada). H&E sections were reviewed by a study pathologist (ERU) to confirm that the sections included viable tumor. Cases that did not have representative material were excluded; otherwise samples were processed as previously described using high temperature-assisted tissue lysis (12) and automated DNA purification with a Chemagic MSM1 (PerkinElmer, Waltham, MA, USA). The resulting 100 μL DNA eluate was tested immediately or stored at −20°C. A blank sample without tissue was included in every extraction batch to monitor potential cross contamination.

HPV Genotyping

All extracts were tested with the Linear Array HPV Genotyping Test (LA, Roche Diagnostics, Indianapolis, IN), which distinguishes 37 different HPV genotypes (6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51, 52(XR), 53, 54, 55, 56, 58, 59, 61, 62, 64, 66, 67, 68, 69, 70, 71, 72, 73, 81, 82, 83, 84, 89, IS39). Templates for the PCR reaction were prepared with 10 μl DNA and 40 μl H_2O, otherwise following the manufacturer's protocol. The reverse line blot hybridization was performed with an automated platform (Beeblot instruments (Bee Robotics, Caernarfon, UK)). Samples with negative or inadequate (negative for HPV and cellular β-Globin control) LA results were re-tested with the INNO-LiPA HPV Genotyping Assay (LiPA, Innogenetics, Gent, Belgium) which detects 29 HPV types (6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 43, 44, 45, 51, 52, 53, 54, 56, 58, 59, 66, 68, 69, 70, 71, 73, 74, 81, 82). The assay was performed according to the manufacturers

specifications using an Autoblot 3000 (MedTec, Buffalo Grove, IL) for the line-blot procedure.

HPV16 variant determination

All samples positive for HPV16 by either LA or LiPA genotyping assays were subjected to variant analysis with a pyrosequencing assay (13). Briefly, 10 μl of the extracted DNA was used as a template to amplify a 314 bp fragment of the E6 region. If no amplicon was visible by gel electrophoresis, the procedure was repeated with an enriched template that was first amplified by whole genome amplification with the GenomePlex WGA2 kit (Sigma-Aldrich, St Louis, MO, USA) in accordance with the manufacturer's recommendations. Subsequently, nucleotide identities at position 109, 131, 132, 143, 145, 178, 350 were determined with a Pyromark Q96 MD (Qiagen, Valencia, CA, USA) to identify the variants AA/NA-1, Af1, Af2, As, E-C109G, E-G131G, E-G350, Em, Ep. In cases, where the pyro signals were ambiguous, the E6 amplicon was also sequenced by the traditional Sanger method as described previously (14).

Analysis

Prevalence was consistently calculated as percentage of positives from the total number of cases tested. HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 were considered high-risk (hr) with regards to oncogenic potential (15) and all other types as low-risk. Differences in prevalence for any HPV type, hr HPV positive or HPV16 and 18 positive by gender, race, age, and disease stage were evaluated using Fisher's Exact Test. Age was grouped into 10-year intervals. Cancer stage was crudely classified as local, regional, distant, or unknown, and termed SEER stage.

Hierarchical categories for HPV status were assigned as follows: (1) HPV16 – includes all cases positive for this type regardless of other results, (2) HPV18 - adds all case positive for HPV18, but not for HPV16, (3) other hr HPV – adds cases positive for any high risk type as listed above, but not HPV16 or 18, (4) any HPV – adds all cases positive for any HPV type not included in the previous groups.

Results

Within the time period between 1995 and 2005, a total of 401 eligible anal cancer cases were identified from the records of the seven registries and RTRs. Due to lack of availability or participation tissues were not received from 222 cases. An additional 32 cases were excluded for insufficient malignant representation and one sample was inadequate in HPV testing. Despite this reduction, the admitted tissue samples appeared to be representative of cancers diagnosed in participating registries, based on demographic variables such as age, race, and sex (data not shown).

Specimens from the remaining 146 anal cancer cases were successfully tested. The patient's gender, race and age were distributed as shown in Table 1. HPV genotyping results were obtained by LA from 127 cases and by LiPA for the remaining 19. Any HPV was detected in 133 (91.1%) cases. A high risk-type was found in 129 cases (88.4%) and four (2.7%) contained only low risk HPV (two each with HPV6 and HPV26). In 117 (80.1%) cases a

single HPV infection was detected. Multiple types (2 – 6) were observed in 16 (11%) cases averaging 1.17 types per positive sample. HPV16 was present in 113 (77.4%) cases, HPV18 in 5 (3.4%) and two of them (1.4%) had both of these types. Other frequently identified types included HPV33 (9 cases, 6.2%), as well as HPV6 (6 cases, 4.1%) and 11 (5 cases, 3.4%) (see Table 2 for further details).

By histological type, hr HPV types were found in 126 of 133 (94.7%) squamous cell carcinomas (SCC), in 2 of 11 (18.2%) adenocarcinomas (both HPV16) and in one of the tumors with “other” histology (HPV31). Applying hierarchical assignment, 113 anal cancers (77.4%) were attributable to HPV16, an additional 3 (2.1%) to HPV18, a further 13 (8.9%) to all other high risk types, and 4 (2.7%) to all remaining HPV types (Fig. 1). Proportions of cases positive for HPV (any type tested), hr HPV or HPV16/18 were not statistically different by sex, race, age group, or SEER stage (Table 1).

Pyrosequencing allowed determination of HPV 16 variant lineage in 98 HPV16 positive cases. An additional 2 were clarified by Sanger sequencing. For the remaining 13, PCR amplification or sequencing could not be achieved at a quality necessary for unambiguous variant typing. As detailed in Table 3, the majority of HPV16 variants were European (88%) followed by African and Asian variants (6% each).

Discussion

The tissues obtained for this study were requested from seven state cancer registries and provide the first U.S. population-based assessment of HPV prevalence and type distribution in anal cancers. As expected, HPV prevalence was high and at least one hr type was found in almost 90% of the anal cancer cases. Internationally, findings have varied substantially, likely a result of small sample sizes, as well as disparate HPV detection methodologies and sensitivity. Nonetheless, most studies based on consensus primer PCR systems also have reported HPV prevalence in anal cancer tissue of 80% or greater (3;16;17). While the combined use of the LA and LiPA HPV genotyping tests has potentially increased overall detection sensitivity in our study, the type-specific prevalence was similar to that reported in a meta-analysis including North American studies mainly among MSM (3), where over 70% were HPV16-positive and prevalence of HPV6, 18 and 33 were observed at 5 and 10% each. It is unclear if the remaining small proportion of anal cancer specimens are HPV negative as a result of sampling artifact, deficiencies in the HPV detection methodology, or if these cases were truly triggered by alternative carcinogenic agents. By histological examination, only 4 of the 13 HPV negative tumors were squamous carcinomas. The rest were adenocarcinomas that could be of colorectal origin (7), Paget’s disease (1) or undifferentiated (1).

No evidence was found for differences in HPV prevalence between any of the demographic subgroups or cancer stage included in the analysis. This was not surprising considering the high HPV prevalence, especially for HPV16, and the modest size of the study population.

Distribution of HVP16 variants was dominated by European lineages and was very similar to results found in cervical cytology samples in the United States (18). The frequency of the

HPV16 G131 variants in our invasive anal tumors was 2.5-fold greater than that reported by Da Costa et al. (10) in anal neoplasia tissue from a mostly HIV positive population, which may support their hypothesis that infection with the E-G131G or E-G131T genotypes pose elevated risk for malignant progression. It is not known if HIV infection plays any role in this regard and information on HIV status was not collected in our study.

This study represents the first assessment of HPV type distribution in anal cancers derived from a random sample of population based U.S. cancer registries representing different geographical regions. HPV16 and HPV18 DNA were found in almost 80% of the anal cancers in this study, and 103 anal cancers (70%) were exclusively positive for these two types. These results will assist in the establishment of a baseline for etiologic fractions of anal cancer attributable to specific HPV genotypes. The data will be integral to the surveillance and evaluation of prophylactic HPV vaccine efficacy for anal cancer in the United States.

Acknowledgment

We thank all members of HPV typing of Cancers Workgroup for contributions made toward this study:

- CDC:
  - Mona Saraiya, MD, MPH, CDC, Division of Cancer Prevention and Control
  - Elizabeth R Unger, MD, PhD, CDC, CCID/NCEZID/DHCPP/CVDB
  - Martin Steinau, PhD, CDC, CCID/NCEZID/DHCPP/CVDB
  - Mariela Z Scarbrough, BS, CCID/NCEZID/DHCPP/CVDB
  - Meg Watson, MPH, Division of Cancer Prevention and Control
  - Mangalathu Rajeevan, PhD, CDC, CCID/NCEZID/DHCPP/CVDB
  - Daisy Lee, MS, CDC, CCID/NCZVED, HPV Lab
  - Maung Maung Khin, MS, CCID/NCEZID/DHCPP/CVDB
  - Juanita Onyekwuluje, MS, CDC, CCID/NCEZID/DHCPP/CVDB
  - Deblina Datta, MD, Division of STD Prevention
  - Susan Hariri, PhD, Division of STD Prevention
- Florida:
  - Jill MacKinnon, PhD, University of Miami, Florida Cancer Data System
  - Youjie Huang, MD, DrPH, MPH, Florida State Department of Health
  - Carlos Alvarez, BBA, University of Miami, Florida Cancer Data System
  - Edward Wilkinson, MD, University of Florida
  - Martha Campbell-Thompson, DVM, PhD, University of Florida
  - Amy Wright, MS, University of Florida
  - Kelley Durden, HT (ASCP), University of Florida
- Hawaii:
  - Brenda Hernandez, PhD, University of Hawaii, Cancer Research Center of Hawaii
  - Marc Goodman, PhD, University of Hawaii, Cancer Research Center of Hawaii
  - Hugh Luk, BS, HTL, University of Hawaii, Cancer Research Center of Hawaii
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- Shoji Ikeda, BA, University of Hawaii, Cancer Research Center of Hawaii
- Michael Green, CTR, University of Hawaii, Cancer Research Center of Hawaii
- Catherine Grafel-Anderson, BS, University of Hawaii, Cancer Research Center of Hawaii
- Rayna Weise, MPH, University of Hawaii, Cancer Research Center of Hawaii

- Iowa:
  - Freda Selk, AAS, University of Iowa
  - Dan Olson, MS, University of Iowa
- Kentucky:
  - Thomas Tucker, PhD, MPH, University of Kentucky
  - Claudia Hopenhayn, PhD, MPH, University of Kentucky
  - Amy Christian, MSPH, University of Kentucky
- Los Angeles County, California:
  - Joe House, University of Southern California
  - Myles G. Cockburn, PhD, University of Southern California
  - Andre Kim, MPH, University of Southern California
- Louisiana:
  - Edward Peters, DMD, SM, ScD, Louisiana State University
  - Lauren Cole, PhD, MPH Candidate, Louisiana State University
  - Tara Ruhlen, MPH, Carolinas Rehabilitation, Charlotte, NC
- Michigan:
  - Glenn Copeland, MS, Michigan Department of Community Health
  - Lana Ashley, Michigan Department of Community Health
  - Jetty Alverson, Michigan Department of Community Health
  - Michelle Hulbert, Michigan Department of Community Health
  - Won Silva, MA, Michigan Department of Community Health
  - Samuel Hirsch, MD, St Joseph Mercy Hospital, Ann Arbor, Michigan
- Battelle:
  - Christopher Lyu, MPA, Battelle, Durham, NC
  - Bruce Ellis, MS, Battelle, Arlington, VA
  - Natalie Madero, BS, Battelle, Baltimore, MD
  - Emily Reid, BA, Battelle, Durham, NC
  - Donna Little, BS, Battelle, Baltimore, MD
  - April Greek, PhD, Battelle, Seattle, WA
  - Dale Rhoda, PhD, Battelle, Columbus, OH
  - Susan Brossoie, CTR/RHIT, UNC Hospitals Cancer Registry, Chapel Hill, NC
  - Katherine Gideon, Battelle, Toxicology Northwest, Richland, WA
  - Linda Delma Gieseke, Battelle, Columbus, OH
  - Stephanie Ashcraft, Battelle, Columbus, OH

Financial Disclosures: The support for collection of original specimens from non-repositories (Kentucky, Florida, Michigan, Louisiana), coordination of genotyping data from both SEER and NPCR registries, and genotyping was largely supported by CDC intramural funds and Vaccine For Children Funds. This project has been supported in part with Federal funds by the Centers for Disease Control and Prevention (CDC) under grant number NO.

5U58DP000810-5 (Kentucky), 5U58DP000844-5 (Florida), 5U58DP000812-5 (Michigan), and 5U58DP000769-5 (Louisiana) and with Federal funds for Residual Tissue Repositories from the National Cancer Institute SEER Population-based Registry Program, National Institutes of Health, Department of Health and Human Services, under Contract No. N01-PC-35139 (Los Angeles), N01-PC-35143 (Iowa) and N01-PC-35137 (Hawaii).

The collection of data from California used in this publication was largely supported by the California Department of Health Services as part of the statewide cancer reporting program mandated by California Health and Safety Code Section 103885; by the National Cancer Institute, National Institutes of Health, Department of Health and Human Services under Contract No. N01-PC-2010-00035; and grant number 1U58DP000807-3 from the Centers for Disease Control and Prevention.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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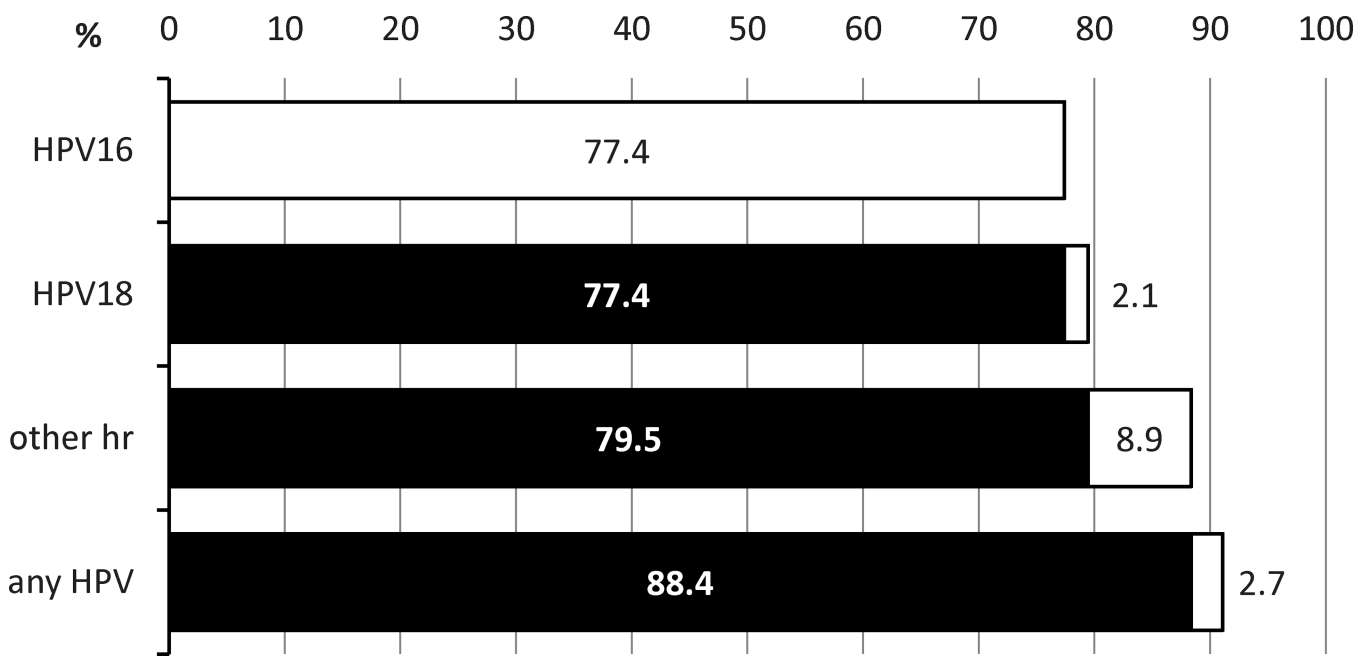

Figure 1.
Hierarchical attribution of HPV types to anal cancers. White fields indicating attribution of the specific type or group and black the cumulative prevalence of types with higher hierarchy.

Table 1

HPV prevalence in anal cancers by gender, race, age and SEER stage

	n	HPV[2] (%)		hr HPV (%)		HPV16/18 (%)	
Gender							
Female	93	86	(92.5)	84	(90.3)	74	(79.6)
Male	53	47	(88.7)	45	(84.9)	42	(79.2)
		P = 0.548		P ≥ 0.422		P = 1.000	
Race							
Asian Pac. Islands	5	5	(100)	5	(100)	3	(60.0)
Black	15	14	(93.3)	13	(86.7)	12	(80.0)
Hispanic	21	20	(95.2)	19	(90.5)	17	(81.0)
White	105	94	(89.5)	92	(87.6)	84	(80.0)
		P ≥ 0.928		P = 1.000		P ≥ 0.684	
Age Groups							
≤ 39	10	10	(100)	10	(100)	8	(80.0)
40 – 49	23	21	(91.3)	21	(91.3)	19	(82.6)
50 – 59	40	37	(92.5)	35	(87.5)	30	(75.0)
60 – 69	28	26	(92.9)	25	(89.3)	22	(78.6)
70 – 79	30	28	(93.3)	27	(90.0)	26	(86.7)
≥ 80	15	11	(73.3)	11	(73.3)	11	(73.3)
		P ≥ 0.337		P ≥ 0.541		P ≥ 0.846	
SEER stage							
Local	83	75	(90.4)	73	(88.0)	67	(80.7)
Regional	30	27	(90.0)	26	(86.7)	23	(76.7)
Distant	9	9	(100)	9	(100)	8	(88.9)
Unknown	24	22	(91.7)	21	(87.5)	18	(75.0)
		P = 1.000		P ≥ 0.899		P ≥ 0.824	

HPV = positive for any of the types tested
hr HPV = positive for one of the high risk types HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68
HPV16/18 = positive for HPV16 or HPV18
P-values for differences between categories were calculated by Fisher's Exact Test. Percentage from each category's total (in n column) are stated in brackets

Table 2

Summary of HPV detection in anal cancers

Adequate, eligible samples	**146**	
HPV positive (any type)	**133**	**91.1%**
High Risk[a] only	116	79.5%
Low Risk[b] only	4	2.7%
High and low risk	13	8.9%
Single type	117	80.1%
Multiple types (2 – 6)	16	11.0%
HPV16	**113**	**77.4%**
HPV33	9	6.2%
HPV6	6	4.1%
HPV11	5	3.4%
HPV18	5	3.4%
HPV26	2	1.4%
HPV31	2	1.4%
HPV51	2	1.4%
HPV58	2	1.4%
HPV62	2	1.4%
HPV66	2	1.4%
Other types (one case each)	8	5.5%

[a] HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68

[b] any HPV not included in the high risk HPV types

Table 3

Variants determined in 100 HPV16 positive anal cancers

	Variant	Found in Anal Cancers (= %)
African	Af1	5
	Af2	1
Asian American or North American	AA/NA-1	4
Asian	As	2
European	Ep	37
	Em	33
	E-C109G	3
	E-G131G	12
	E-G131T	3

100 of 113 HPV16 positive anal cancer specimens were successfully sequenced, the remaining 13 did not yield data at sufficient quality.