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Comparing Human Papillomavirus Prevalence in Rectal and Anal Cancer Using US Cancer Registries, 2014–2015

Jacqueline Mix, PhD, MPH[a,b], **Mona Saraiya, MD, MPH**[a], **Charles F. Lynch, MD, PhD**[c], **Trevor D. Thompson, BS**[a], **April Greek, PhD**[d], **Thomas C. Tucker, PhD**[e], **Edward S. Peters, ScD, DMD**[f], **Troy D. Querec, PhD**[a], **Elizabeth R. Unger, MD, PhD**[a]

[a]Centers for Disease Control and Prevention, Atlanta, Georgia

[b]Oak Ridge Institute for Science and Education, Oak Ridge, Tennessee

[c]University of Iowa, Iowa City, Iowa

[d]Battelle, Seattle, Washington

[e]University of Kentucky College of Public Health, Lexington, Kentucky

[f]Louisiana State University, Health Science Center School of Public Health, New Orleans, Louisiana

Abstract

Background and Aims: Rectal squamous cell carcinoma (SCC) is a rare malignancy, and the causal role of human papillomavirus (HPV) in these cancers is thought to be similar to anal cancer. We compared type-specific prevalence of HPV in rectal SCC to anal cancer. In rectal SCC, we evaluated the agreement between HPV prevalence and positivity for p16, a marker of oncogenic activity.

Methods: A stratified random sample of rectal SCCs and anal cancers diagnosed between 2014 and 2015 were identified from 3 statewide cancer registries in Iowa, Kentucky, and Louisiana. HPV testing was performed at the HPV laboratory at the Centers for Disease Control and Prevention. HPV types were described using hierarchical attribution to HPV16 and other oncogenic types, weighted for sampling design. In rectal SCC, we computed concordance and Cohen's kappa coefficient (κ) between HPV status and p16 positivity.

Results: A total of 39 rectal and 72 anal cancers were analyzed. HPV16 was the most common type in both rectal and anal cancer and did not differ significantly between sites (71.4% vs 82.1%; $P = .32$). Concordance between the presence of any HPV type and p16 positivity in rectal SCC was 92% with $\kappa = 0.77$.

Conclusions: Rectal SCC and anal cancer have similar type-specific HPV prevalence, with HPV16 found most frequently. Substantial agreement between p16 and HPV status in rectal SCC lends additional support for the etiologic role of HPV in both anal and rectal cancer. Larger studies could be conducted to replicate these findings.

Address correspondence to Mona Saraiya, MD, MPH. yzs2@cdc.gov. Telephone: (770) 488-4293.

Keywords

anal; cancer; HPV; human papillomavirus; rectal; squamous cell carcinoma

Introduction

Rectal squamous cell carcinoma (SCC) is a rare malignancy (comprising 1%–2% of rectal tumors) and has an incidence rate per year of 1.54 per million persons among males and 3.0 per million persons among females.[1] Both rectal SCC and anal cancer develop near the anal transition zone where rectal and anal epithelium converge, an area particularly vulnerable to human papillomavirus (HPV) infection. Whereas 90% of anal cancers are caused by HPV,[2] studies on HPV prevalence in rectal SCC are limited, although the association is likely to be similar.[3] The close anatomic proximity of rectal and anal cancer makes precise distinction between rectal and anal origin difficult and misclassification of the anatomic site may occur. However, evidence suggests that rectal SCC may arise as a primary tumor.[4] The aim of the current study was to utilize cancer tissues derived from US state cancer registries to describe the distribution of HPV types detected in rectal SCC and compare type prevalence to anal cancer. In addition, we evaluated the concordance between HPV status and overexpression of p16, a marker of HPV oncogenic activity, in rectal SCC to provide additional evidence of the role of HPV in its etiology.

Methods

Study Population and Design

Routine population-based tracking of HPV types in HPV-associated cancers is not currently conducted in the United States, but the Centers for Disease Control and Prevention (CDC) has supported 2 special HPV typing studies using statewide cancer registries.[2] In the first study, the CDC Cancer Registry Sentinel Surveillance System (CRSSS) was developed in partnership with 7 cancer registries and provided the first population-based HPV typing prevalence data in the United States from 1993–2005. In a second study, the CDC partnered with 3 cancer registries in Iowa, Kentucky, and Louisiana to collect HPV typing information from select cancer sites in 2014–2015. We analyzed invasive, microscopically confirmed rectal and anal cancers from the second study, which were identified by the cancer registries using the *International Classification of Diseases for Oncology*, 3rd Edition (ICD-O-3) site codes: C20.9 (rectal) and C21.0–C21.8 (anal). Rectal cancers were limited to ICD-O-3 morphology codes 8050–8084 and 8120–8131. All anal ICD-O-3 morphology codes were included except for melanomas (8720–8790), sarcomas (8800–8991), mesotheliomas (9050–9055), Kaposi sarcomas (9140), and leukemias/lymphomas (9590–9992).[2] Anal cancer cases were sampled by the cancer registries using a stratified random sampling design based on age (<50 years, ≥50 years) and race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, non-Hispanic other). Due to their rarity, all rectal cancer cases were sampled, regardless of age or race/ethnicity. All protocols were reviewed and approved by the institutional review boards of all participating organizations and the CDC.

Tissue Processing Histology Review and Laboratory Methods

Tissue processing, histology review, and laboratory methods have been described previously.[2,5] Briefly, central pathology laboratories associated with the cancer registries were asked to select 1 representative archived, formalin-fixed paraffin-embedded (FFPE) tissue block from each rectal and anal case. Tissue sections were prepared by taking six 5-μm sections (8 for rectal cancers) from each block and performing hematoxylin and eosin (H&E) staining on the first and last sections. All tissue blocks were processed with a standardized protocol to prevent contamination of samples.

A study pathologist reviewed submitted H&E sections to provide confirmation that intervening sections had tumor. Samples passing histologic review were extracted for DNA as previously described.[5] All samples were tested with the Linear Array HPV Genotyping assay (LA; Roche Diagnostics) that detects 37 HPV types (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). Samples that were inadequate or HPV-negative were retested with the RHA kit HPV SPF-10-LiPA25, version 1 (Labo Biomedical Products B.V.) that detects 25 types (HPV 6, 11, 16, 18, 31, 33, 34, 35, 39, 40, 42, 43, 44, 45, 51, 52, 53, 54, 56, 58, 59, 66, 68, 70, 74). P16 immunohistochemistry (IHC) was performed using Ventana BenchMark XT automated system with monoclonal anti-p16INK4a (clone E6H4 in CINtec p16 assay, Ventana Roche) and ultraView Universal DAB Detection kit (Ventana Roche). A positive tissue control (FFPE cell pellet of HPV-positive cancer cell line) was included with each assay. Interpretation of p16 results (p16 positive, p16 negative, or inadequate) was performed by a pathologist using light microscopic examination of slides processed with and without primary antibody using criteria established by Cooperative Group Trials for Oropharyngeal Cancer.[6] All HPV typing and p16 IHC was conducted at the CDC HPV laboratory using standardized procedures. Cancer registries provided demographic and clinical data about each case including sex, race, age at diagnosis, and SEER Summary tumor stage at diagnosis.

Statistical Analysis

Sampling weights were calculated based on the probability of selection within each registry to weight analyses to the age and race/ethnicity distributions in the underlying registry populations. Demographic characteristics were summarized using sampling weights. Age was grouped into 10-year intervals. Tumor stage at diagnosis was categorized into local, regional, distant, or unstaged using the SEER Summary Stage guidelines.[7]

HPV type prevalence was summarized by anatomic site. HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 were considered oncogenic.[8,9] HPV types were classified using a hierarchical attribution into 3 mutually exclusive categories: (1) *HPV16:* positive for HPV16 regardless of single or multiple infection; (2) *all other oncogenic HPV types:* all cases positive for other oncogenic types except for HPV16; (3) *nononcogenic or HPV negative:* any other nononcogenic type that is not positive for any other oncogenic HPV type, or cases that are HPV negative. Hierarchical classification is based on a ranking of HPV types and attributes cancers to a single type group, even if multiple HPV types are detected. For this reason, we additionally examined the prevalence of single and multiple

HPV infections. Ninety-five percent Wilson confidence limits around the HPV prevalence estimates were calculated. Statistical testing was performed using first order Rao-Scott χ^2 tests using PROC SURVEYFREQ. Statistical analysis was performed using SAS version 9.4, taking into account the stratified sampling design and allowing for weighted estimates.

We used positive p16 IHC results as supporting HPV oncogenic activity and a surrogate for HPV detection. Agreement between the detection of any HPV and p16 positivity was evaluated using concordance and Cohen's kappa coefficient. Substantial agreement has been defined as a kappa coefficient from 0.61 to 0.80.[10]

Results

Rectal and anal cancer cases included in the study population are shown in Figure 1. During 2014–2015, a total of 66 rectal and 552 anal cancer cases were identified as eligible samples by the cancer registries. According to the proposed sample size for anal cancer, a total of 80 cases were randomly selected within age and race strata for retrieval by the cancer registries and submitted to the CDC HPV laboratory. A total of 44 rectal cancer cases were obtainable and sent to the CDC HPV laboratory. Of these, 1 rectal and 6 anal cancer cases were excluded because of ineligible histology or nonrepresentative tissue. A total of 43 rectal and 74 anal cancer cases underwent HPV testing. Typed cases were further excluded if typing was insufficient (1 rectal and 1 anal cancer case), ineligible because of an out-of-state residence (2 rectal cancer cases), or both (1 rectal cancer case). A total of 39 rectal and 73 anal cancer cases had eligible and adequate samples. For final analyses we further excluded 1 anal cancer case in order to limit the sample to white or black race/ethnicity.

Study characteristics evaluated did not differ significantly by sex, race, age, or tumor stage (Table 1). The type-specific HPV prevalence for rectal and anal cancer cases is summarized in Table 2. Any HPV type was detected in 82.4% of rectal and 90.6% of anal cancers (P = .43). Oncogenic HPV types were found in 82.4% of rectal and 88.7% of anal cancers. Nononcogenic HPV types were found in 7.3% of rectal cases and 12.5% of anal cancer cases. In 69.6% of rectal and 77.5% of anal cancer cases, a single HPV type was detected. Multiple types were detected in 12.9% in rectal and 13.2% of anal cancers. Most cases were attributed to HPV16, 71.4% and 82.1% in rectal and anal cancer, respectively. There were no statistically significant differences between rectal and anal cancer cases in any HPV type grouping examined. The overall prevalence of single HPV types detected were similar and are reported in Table 3. Concordance between detection of any HPV and p16 positivity in rectal SCC was 92%, $\kappa = 0.77$, indicating substantial agreement (data not shown).

Discussion

In this study, we found HPV prevalence was high and similar for rectal (82.4%) and anal cancer (90.6%), with predominance of HPV16 (71.4% rectal, 82.1% anal). In addition, we were able to demonstrate that substantial agreement exists between presence of HPV DNA and p16 overexpression in rectal cancer, which lends support to the etiologic role of HPV in rectal SCC.

HPV has been proposed as a risk factor for rectal SCC, given its close proximity to the anal transition zone, and the known association between HPV and anal cancer. In a study of anal cancers diagnosed during 1986 to 1998 in Washington State, 13 rectal SCC were tested for HPV and 77% were found to be HPV16 positive.[11] Another study, performing genotyping on 24 rectal SCC samples from the Hawaii and Iowa cancer registries, found that 63% tested positive for HPV16 DNA.[4] Several small studies have also indicated the presence of HPV16[12–15]; however, other case studies and small studies did not detect any HPV.[16–18] The lack of large genotyping studies investigating rectal SCC could be due to the low incidence of this cancer.

Both anal and rectal cancer have shown a similar trend of increased incidence over time, particularly in women, which suggests a shared etiology.[19] Furthermore, excess risk for rectal SCC occurs in HIV-positive and transplant patients compared to the general population[19], which is also observed in anal cancer. Since anal and rectal cancers share similar epidemiologic patterns and anatomic origin can be ambiguous, it has been suggested that rectal SCC could be misclassified as anal SCC.[1] However, there is some evidence to suggest that rectal SCC can arise as a primary tumor. One study, using CAM5.2 cytokeratin as a marker for rectal epithelium, found similar prevalence of HPV16 in anal and rectal SCC, but CAM5.2 was restricted to rectal SCC. [1,4] For simplicity, rectal SCC are often combined with anal cancer and are reported in national statistics of HPV-associated anal cancers.[2,20] From a cancer surveillance perspective, this is done because of the overall low burden of disease and similar HPV type distribution profile, as demonstrated in this analysis.

Our findings can be interpreted in the context of the study's limitations and strengths. We utilized a population-based strategy to obtain rectal and anal cancer cases from cancer registries in 3 US states. Despite the population-based efforts, the number of cases we were able to obtain was still relatively small, which limits the conclusions we are able to draw regarding the association between HPV and rectal SCC. Nonetheless, the high concordance and agreement between HPV status and p16 overexpression may lend support to the association.

Conclusion

CDC has traditionally combined rectal SCC with anal cancers for its count of HPV-associated cancers. This study confirms that for surveillance purposes it is justified to combine these 2 when describing HPV-associated cancers. The agreement between p16 and HPV status in both rectal and anal cancers lends additional support for the role of HPV in the etiology of these cancer types. Larger studies could be conducted to replicate these findings.

Acknowledgments

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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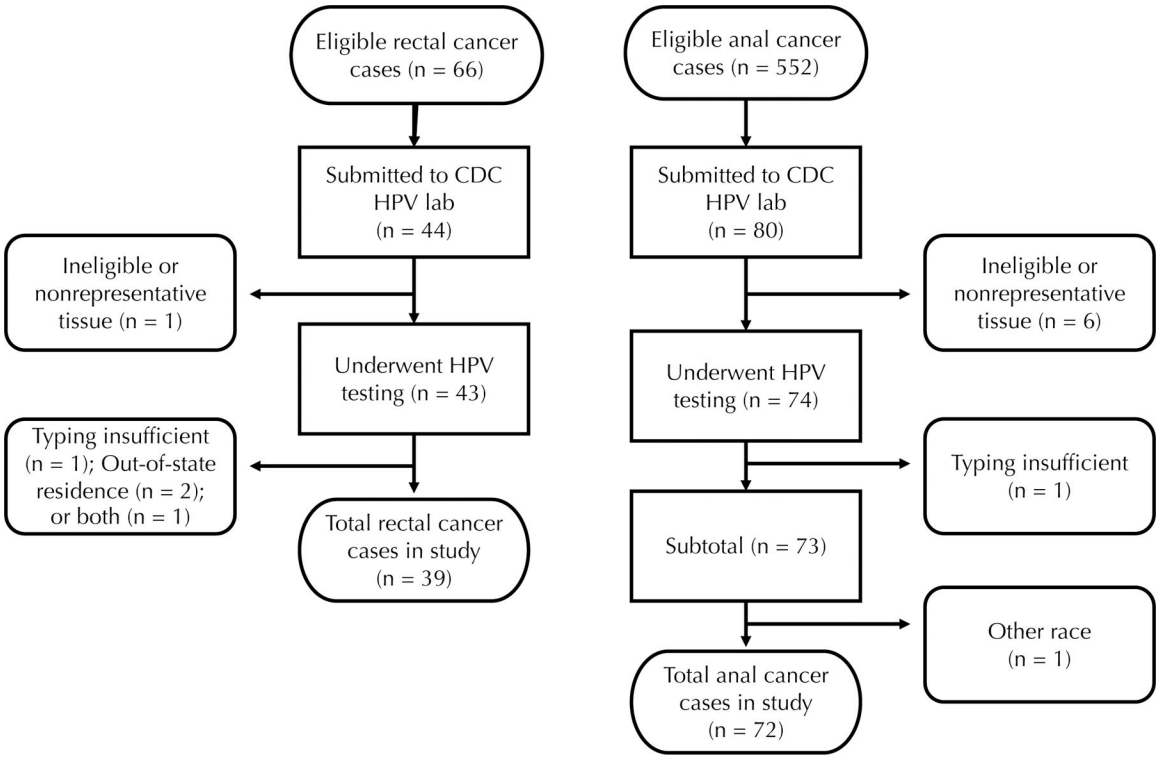

Figure 1.
Study Population, CDC CRSSS, 2014–2015

Table 1.

Study Characteristics of Rectal and Anal Cancer by Sex, Race, Age and Tumor Stage, CDC CRSSS, 2014–2015

	Rectal[a] (n = 39)		Anal[b] (n = 72)		
Characteristics	**n**	**%[c]**	**n**	**%[c]**	***P* Value[d]**
Sex					.08
Male	20	50.8	29	29.9	
Female	19	49.2	43	70.1	
Race					.53
White	34	88.3	57	91.2	
Black	5	11.7	15	8.8	
Age (y)					.34
30–39	3	7.3	9	3.4	
40–49	7	17.6	28	13.7	
50–59	5	11.7	14	25.4	
≥60	24	63.5	21	57.5	
Stage[e]					.25
Early	14	37	36	45.7	
Late	21	52.9	33	51.5	
Unknown	4	10.1	3	2.7	

CDC, Centers for Disease Control and Prevention; CRSSS, Cancer Registry Sentinel Surveillance System; HPV, human papillomavirus.

[a] Rectal cancer includes ICD-O-3 site code C20.9 and morphology codes 8050–8084 and 8120–8131.

[b] Anal cancer includes ICD-O-3 site codes C21.0–C21.8; morphology codes 8720–8790 (melanoma), 8800–8991 (sarcoma), 9050–9055 (mesothelioma), 9140 (Kaposi sarcoma), and 9590–9992 (leukemias/lymphomas) were excluded.

[c] Weighted percentages take into account sampling frame for age and race/ethnicity.

[d] Statistical testing performed with first order Rao-Scott χ^2 statistics with $\alpha = .05$.

[e] Surveillance, Epidemiology, and End Results (SEER) summary stage, early stage includes localized cancers, late stage includes regional and distant cancers.

Table 2.

HPV Type Prevalence in Rectal and Anal Cancer, CDC CRSSS, 2014–2015

	Rectal[a] (n = 39)			Anal[b] (n = 72)			
HPV Types	**n**	**%[c]**	**(95% CI)**	**n**	**%[c]**	**(95% CI)**	***P* Value[d]**
Any type[e]	32	82.4	(67.5–91.4)	68	90.6	(69.7–97.6)	.43
Oncogenic[f]	32	82.4	(67.5–91.4)	65	88.7	(69.2–96.5)	.53
Nononcogenic[g]	3	7.3	(2.4–19.8)	12	12.5	(5.8–24.9)	.44
Single type	27	69.6	(53.7–81.8)	56	77.5	(59.3–89.0)	.48
Multiple types[h]	5	12.9	(5.6–26.8)	12	13.2	(6.1–26.0)	.97
Hierarchical HPV groups[i]							.58
HPV16	28	71.4	(55.5–83.4)	53	82.1	(64.8–92.0)	
Other oncogenic	4	11.0	(4.4–25.2)	12	6.7	(2.8–14.9)	
Negative/nononcogenic[j]	7	17.6	(8.6–32.5)	7	11.2	(3.5–30.8)	

CDC, Centers for Disease Control and Prevention; CRSSS, Cancer Registry Sentinel Surveillance System; HPV, human papillomavirus.

[a]Rectal cancer includes ICD-O-3 site code C20.9 and morphology codes 8050–8084 and 8120–8131.

[b]Anal cancer includes ICD-O-3 site codes C21.0–C21.8; morphology codes 8720–8790 (melanoma), 8800–8991 (sarcoma), 9050–9055 (mesothelioma), 9140 (Kaposi sarcoma), and 9590–9992 (leukemias/lymphomas) were excluded.

[c]Weighted percentages take into account sampling frame for age and race/ethnicity.

[d]Statistical testing performed with first order Rao-Scott χ^2 statistics with $\alpha = .05$.

[e]Positive for any HPV type tested for.

[f]Positive for HPV types 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, or 68.

[g]Positive for HPV types 6, 11, 26, 34, 40, 42, 43, 44, 53, 54, 55, 61, 62, 64, 67, 69, 70, 71, 72, 73, 74, 81, 82, 83, 84, 89, or HPVIS39.

[h]Range of multiple types was 2–7.

[i]See methods section for further explanation of HPV type hierarchical classification.

[j]A total of 7 rectal and 4 anal cancer cases were HPV negative; 3 anal cancer cases were attributed to HPV6.

Table 3.

Distribution of Single HPV Types in Rectal and Anal Cancer, CDC CRSSS, 2014–2015

	Rectal[a] (n = 39)		Anal[b] (n = 72)	
HPV Type[c]	**n**	**%[d]**	**n**	**%[d]**
HPV16	28	71.4	53	82.1
HPV33	2	4.9	6	3.1
HPV6	1	1.6	7	4.3
HPV18	1	2.8	4	3.0
HPV31	1	6.1	2	0.7
HPV11	1	2.8	1	1.8
HPV45	1	2.8	0	0.0
HPV52	1	2.8	0	0.0
HPV58	1	2.8	0	0.0
HPV73	1	2.8	0	0.0
HPV55	1	1.6	0	0.0
HPV67	1	1.6	0	0.0
HPV42	0	0.0	2	1.6
HPV59	0	0.0	2	0.6
HPV61	0	0.0	2	5.4
HPV66	0	0.0	2	1.6
HPV51	0	0.0	1	0.4
HPV53	0	0.0	1	0.2
HPV68	0	0.0	1	1.8
HPV70	0	0.0	1	0.9
HPV82	0	0.0	1	0.9
HPV89	0	0.0	1	0.9

CDC, Centers for Disease Control and Prevention; CRSSS, Cancer Registry Sentinel Surveillance System; HPV, human papillomavirus.

[a] Rectal cancer includes ICD-O-3 site code C20.9 and morphology codes 8050–8084 and 8120–8131.

[b] Anal cancer includes ICD-O-3 site codes C21.0–C21.8; morphology codes 8720–8790 (melanoma), 8800–8991 (sarcoma), 9050–9055 (mesothelioma), 9140 (Kaposi sarcoma), and 9590–9992 (leukemias/lymphomas) were excluded.

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