Changing Patterns of Anal Canal Carcinoma in the United States

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ABSTRACT

Purpose

Persistent human papillomavirus infection is associated with squamous cell carcinoma of the anal canal (SCCA). With changing sexual behaviors, SCCA incidence and patient demographics may also have changed in recent years.

Methods

The Surveillance, Epidemiology, and End Results public-use data set from 1973 to 2009 was analyzed to determine incidence trends for and demographic factors characterizing SCCA. Joinpoint analyses identified time points when incidence rates changed. For comparison, similar analyses were conducted for anal adenocarcinoma.

Results

Joinpoint analyses identified 1997 as the single inflection point among 11,231 patients with SCCA, at which the slope of incidence rates statistically increased (1997 to 2009 v 1973 to 1996: risk ratio [RR], 2.2; 95% CI, 2.1 to 2.3). Annual percent change (APC) increased for all SCCA stages and was the greatest for anal carcinoma in situ (CIS; APC, 14.2; 95% CI, 10.2 to 18.4). Demographic changes characterizing later versus earlier time period included younger age at diagnosis and rising incidence rates in all stage, sex, and racial groups. During 1997 to 2009, women were less likely to present with CIS (RR, 0.3; 95% CI, 0.3 to 0.3) but more likely to present with localized (RR, 1.2; 95% CI, 1.1 to 1.3) and regional SCCA (RR, 1.5; 95% CI, 1.4 to 1.7). In contrast, adenocarcinoma APCs among 1,791 patients remained stable during this time period.

Conclusion

CIS and SCCA incidence increased dramatically after 1997 for men and women, although men were more likely to be diagnosed with CIS. These changes likely resulted from available screening in men and argue for efforts to identify high-risk individuals who may benefit from screening.

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INTRODUCTION

The US National Cancer Institute estimates that there will be 6,239 new cases and 780 deaths attributable to anal cancer in 2012.¹ Although anal cancer represents approximately 1% of all GI cancers,² evidence from the United States,³ Denmark,⁴ and Australia⁵ suggests that the overall age-adjusted incidence rates of this cancer have been increasing over the past 30 years.

The most common pathologic type of cancer arising from the anal canal is squamous cell carcinoma (SCCA), which accounts for approximately 85% of all cases.^{3,6} The remaining cases comprise anal adenocarcinoma (AAC; 10%) and other types (5%). Over the last decade, evidence has accumulated indicating that oncogenic types of human papillomavirus (HPV), notably subtypes 16 and 18, are etiologically linked to SCCA.^{7,8}

The identification of HPV as a major contributing factor to the development of SCCA suggests that incidence patterns as well as demographic characteristics of the disease may have changed over time. To better delineate these changes, we examined data from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) cancer registries for 1973 to 2009 to identify specific trends in incidence of SCCA, focusing on demographic factors such as age, sex, and race/ethnicity.

METHODS

SEER registry data were analyzed to assess trends in anal cancer incidence rates over time. Included in our analyses were patients with anal cancer age $\geq$ 20 years diagnosed with SCCA or AAC. We compared the overall incidence rates and annual percent changes (APCs) of SCCA with those of AAC. We also performed further

Table 1. Combined Demographics, Incidence Rates, APCs, and Rate Ratios by Sex for Patients With CIS and SCCA, 1997 to 2009

Characteristic	Men					Women					Risk Ratio*	95% CI†
	No. of Patients	Incidence Rate*	95% CI†	APC	95% CI†	No. of Patients	Incidence Rate*	95% CI†	APC	95% CI†		
All patients	5,248	3.0	2.9 to 3.1	9.5	8.1 to 10.9	4,473	2.3	2.3 to 2.4	4.5	3.5 to 5.4	0.8	0.7 to 0.8
CIS	2,723	1.5	1.4 to 1.6	16.7	12.9 to 20.6	772	0.4	0.4 to 0.4	10.1	7.1 to 13.1	0.3	0.3 to 0.3
SCCA stage‡												
Local	1,354	0.8	0.8 to 0.9	3.2	2.2 to 4.3	1,841	1.0	0.9 to 1.0	3.1	1.8 to 4.4	1.2	1.1 to 1.3
Regional	672	0.4	0.4 to 0.4	1.6	−0.8 to 4.2	1,177	0.6	0.6 to 0.7	3.4	1.1 to 5.8	1.5	1.4 to 1.7
Distant	297	0.2	0.2 to 0.2	7.6	4.3 to 11.0	361	0.2	0.2 to 0.2	9.1	6.5 to 11.8	1.1	0.9 to 1.2
Age group, years												
20 to 34	449	0.8	0.7 to 0.8	10.7	7.2 to 14.4	89	0.2	0.1 to 0.2	4.0	−2.4 to 10.9	0.2	0.2 to 0.3
35 to 49	2,332	3.9	3.8 to 4.1	10.9	8.0 to 13.9	949	1.6	1.5 to 1.7	3.6	1.6 to 5.6	0.4	0.4 to 0.4
50 to 64	1,607	4.1	3.9 to 4.3	11.2	9.3 to 13.0	1,703	4.1	3.9 to 4.3	6.9	5.3 to 8.4	1.0	0.9 to 1.1
≥ 65	860	3.6	3.3 to 3.8	3.9	2.0 to 5.9	1,732	5.1	4.9 to 5.4	2.8	1.7 to 4.0	1.4	1.3 to 1.6
Race/ethnicity§												
Non-Hispanic white	3,657	3.3	3.2 to 3.4	9.4	7.8 to 11.0	3,475	2.8	2.7 to 2.9	5.2	4.2 to 6.1	0.8	0.8 to 0.9
Black	705	4.1	3.8 to 4.4	9.3	6.3 to 12.3	411	2.2	2.0 to 2.5	4.9	2.4 to 7.4	0.5	0.5 to 0.6
Hispanic white	476	1.8	1.6 to 2.0	10.3	6.9 to 13.8	384	1.8	1.6 to 2.0	0.8	−2.5 to 4.3	1.0	0.9 to 1.2
API	105	0.6	0.5 to 0.7	10.7	3.0 to 18.9	126	0.6	0.5 to 0.7	3.5	−2.6 to 10.0	1.0	0.8 to 1.3
AI/AN	25	1.4	0.9 to 2.2	−2.2	−12.0 to 8.6	27	1.6	1.0 to 2.3	−2.7	−8.7 to 3.8	1.1	0.6 to 1.9

Abbreviations: AI/AN, American Indian/Alaska Native; APC, annual percent change; API, Asian/Pacific Islander; CIS, anal carcinoma in situ; SCCA, squamous cell carcinoma of the anal canal.

*Rates are per 100,000 and age adjusted to the 2000 US standard population (19 age groups; census P25-1130).

†CIs (Tiwari modification) are 95% for rates, APCs, and rate ratios.

‡Stage was missing for 202 men and 322 women; these patients were excluded from stage analyses.

§Race/ethnicity was classified as other, unknown, or nonwhite Hispanic for 247 men and 40 women; these patients were excluded from race/ethnicity analyses.

analysis of the incidence rates and APCs by stage, age at diagnosis, sex, and race/ethnicity.

The SEER registry program currently collects data on cancer incidence and survival for approximately 28% of the US population.^{9,10} The various SEER registry regions have joined SEER at different times since 1973. To better understand the longitudinal changes in incidence over time, the older SEER9 data set was used. The SEER13 data set was used to better examine demographic changes after 1996 because of the larger catchment area and more granular race/ethnicity coding. We confirmed that there was no significant difference between the SEER9 and SEER13 data sets with respect to overall incidence rates, APCs and results on joinpoint analyses (Table 1; Appendix Table A1, online only).

From 1973 to 2009, 13,022 patients were diagnosed with SCCA or AAC within the SEER9 regions. Anal cancers were identified using the International Classification of Diseases for Oncology version 3 (ICD-O-3) site codes: C21.0 (anus, not otherwise specified), C21.1 (anal canal), C21.2 (cloacogenic zone), and C21.8 (overlapping lesion of rectum, anus, and anal canal). Anal cancer histologies were divided into three categories: squamous cell carcinoma (n = 11,231; ICD-O-3 codes: 8000 to 8131, 8980 to 8981), adenocarcinoma (n = 1,791; ICD-O-3 codes: 8140 to 8151, 8154 to 8231, 8243 to 8245, 8250 to 8576), and other (composed mostly of melanomas, sarcomas, and carcinoid and neuroendocrine tumors). Patients with other histologies were excluded from all analyses.

Stage was classified using the SEER historical stage category (in situ, localized, regional, or distant). In addition, we analyzed carcinoma in situ (CIS) and invasive disease (SCCA) separately. For SEER9 data, race was classified as white, black, or other. For SEER13 data, race/ethnicity was classified as non-Hispanic white, black, Hispanic white, Asian/Pacific Islander, or American Indian/Alaska Native. Because of low case numbers, nonwhite Hispanics in SEER13 were excluded from race/ethnicity-specific analyses. Patients with unknown disease stage, unknown race, and unknown or other race/ethnicity classifications were excluded from stage-, race-, and race/ethnicity-related analyses, respectively. Analyses were conducted using patients with AAC as a comparison.

Statistical Analysis

To determine the time point at which the histology-specific incidence trends changed, joinpoint regression models were used.¹¹ Data were modeled using an algorithm to select the optimal number of inflection points at which incidence rates changed in direction or magnitude, limiting the maximum number of joinpoints to five. The simplest model was chosen based on significance tests using a Monte Carlo permutation method.¹²

The age-specific incidence rate was calculated as the number of incident cases over the number of individuals at risk in each of 19 age groups within the relevant SEER catchment area during a particular year. These rates were age adjusted using the 2000 US standard population (19 age groups; census P25-1130)¹³ and are expressed as per 100,000 individuals at risk. Incidence rate changes over time are expressed as APCs, which represent the log-transformed slopes across time. To compare rates between groups, rate ratios (RRs) were computed. Using Tiwari-modified gamma (rates) and F interval (RRs) methods,¹⁴ 95% CIs were estimated.

All analyses except joinpoint regression were performed using SAS software (SAS Institute, Cary, NC) and SEER Stat software (version 7.0.9; <http://seer.cancer.gov/seerstat/>). Joinpoint regression was performed using the Joinpoint regression software program (version 3.5.2; <http://surveillance.cancer.gov/joinpoint>). SEER public-use research data from 1973 to 2009 were obtained from the SEER Web site (April 2012 release) and were based on the November 2011 submission.⁹ The US population data were also obtained from SEER (January 2011 release).¹⁵

RESULTS

A single joinpoint occurring in 1997 (95% CI, 1994 to 2000; Fig 1A) provided the optimal fit to the data, reflecting the year at which combined CIS and SCCA average annual incidence rates shifted most markedly during the four decades studied (1997 to 2009 v 1973 to 1996: RR, 2.2; 95% CI, 2.1 to 2.3; Table 2). Separate joinpoint analyses

Fig 1. (A) Jointpoint analysis of squamous cell carcinoma of the anal canal (SCCA) and anal adenocarcinoma (AAC) from 1973 to 2009. Blue line with open squares represents the combined anal carcinoma in situ (CIS) and SCCA trend over time; gold line with open circles represents combined adenocarcinoma in situ (AIS) and AAC trend over time. One jointpoint identified for SCCA at 1997 (95% CI, 1994 to 2000); one for AAC at 1998 (95% CI, 1982 to 1993). (B) Jointpoint analysis of SCCA from 1973 to 2009. Blue line with open squares represents SCCA trend over time; gold line with open circles represents AAC trend over time. One jointpoint identified for SCCA at 1991 (95% CI, 1988 to 1995); one for AAC at 1991 (95% CI, 1979 to 1996). (C) Jointpoint analysis of CIS trend from 1973 to 2009. Blue line with open squares represents CIS trend over time; gold line with open circles represents AIS trend over time. Three jointpoints identified for SCCA at 1999 (95% CI, 1982 to 2000), 2002 (95% CI, 1997 to 2003), and 2005 (95% CI, 2003 to 2007); zero for AAC. The jointpoint model assesses the best fit of the data and allows up to five jointpoint segments.

were conducted for invasive cancer (SCCA) and noninvasive disease (CIS), with an earlier jointpoint identified for SCCA (1991; 95% CI, 1988 to 1995) compared with CIS (1999; 95% CI, 1982 to 2000; Figs 1B and 1C). When combined CIS- and SCCA-specific jointpoint models were examined across sex and race, the subgroup analyses yielded results similar to those of the combined group, with all jointpoint 95% CIs containing 1997 (Data Supplement). On the other hand, jointpoint regression applied to combined adenocarcinoma in situ (AIS) and AAC incidence rates revealed a single jointpoint occurring in 1989, after which rates began declining (Fig 1).

CIS- and stage-specific increases in SCCA incidence rates across time periods 1997 to 2009 versus 1973 to 1996 were higher for CIS (RR, 6.3; 95% CI, 5.7 to 6.9) and localized SCCA (RR, 2.0; 95% CI, 1.9 to 2.2) than for regional (RR, 1.4; 95% CI, 1.3 to 1.5) and distant-stage cancers (RR, 1.8; 95% CI, 1.6 to 2.1). APCs were also highest for CIS (APC, 14.2%; 95% CI, 10.2% to 18.4%); however, all stages demonstrated significantly rising APCs (Table 2; Data Supplement). In comparison, APC changes across the same time periods were statistically stable for AIS and for all stages of AAC (Data Supplement).

As shown in Table 2 and in the Data Supplement, when demographic factors were compared across time periods, all incidence rates for age, sex, and race groups were significantly higher during the time period after 1997. RRs were highest in the age group of 35 to 49 years (RR, 3.8; 95% CI, 3.5 to 4.1; Data Supplement), higher among men (RR, 3.0; 95% CI, 2.8 to 3.2) than women (RR, 1.7; 95% CI, 1.6 to 1.8; Data Supplement), and higher among whites (RR, 2.2; 95% CI, 2.1 to 2.3) and blacks (RR, 2.2; 95% CI, 2.0 to 2.5) than the race group categorized as other (RR, 1.5; 95% CI, 1.2 to 1.9; Data Supplement). To determine if the demographic differences were relevant for SCCA alone, all analyses were repeated with the CIS patient cases excluded. Although the RRs remained statistically significant across time periods, the magnitude of the differences was diminished (Data Supplement). Analyses of patients with AIS and AAC did not yield similar results (Data Supplement).

To better understand the demographic changes after 1997, we examined differences by sex during the time period of 1997 to 2009 using SEER13 data (Table 1; Data Supplement). We found RRs were significantly higher in women than in men for localized (RR, 1.2; 95% CI, 1.1 to 1.3) and regional stages of SCCA (RR, 1.5; 95% CI, 1.4 to 1.7) but significantly lower for CIS (RR, 0.3; 95% CI, 0.3 to 0.3). RRs for women were also significantly lower in the younger age groups (age 20 to 34 years: RR, 0.2; 95% CI, 0.2 to 0.3; age 35 to 49 years: RR, 0.4; 95% CI, 0.4 to 0.4) and among non-Hispanic whites (RR, 0.8; 95% CI, 0.8 to 0.9) and blacks (RR, 0.5; 95% CI, 0.5 to 0.6); these lower RRs were not seen among Hispanic whites, Asians/Pacific Islanders or American Indians/Alaska Natives. Similar analyses were conducted for AAC (Data Supplement).

We further analyzed incidence rates, APCs, and incidence RRs between non-Hispanic whites and blacks to determine whether sex-specific differences accounted for the decreased RRs in women compared with men in these race groups. As shown in Table 3 (and graphed in Data Supplement), the RRs were higher in black men than non-Hispanic white men for CIS and all SCCA stages except regional (CIS: RR, 1.2; 95% CI, 1.1 to 1.4; localized: RR, 1.2; 95% CI, 1.0 to 1.5; distant: RR, 1.4; 95% CI, 1.0 to 2.1). In addition, the RRs were higher in the younger age groups in black men compared with white men (age 20 to 34 years: RR, 2.2; 95% CI, 1.6 to 2.9; age 35 to 49 years: RR,

Table 2. Combined Demographics, Incidence Rates, APCs, and Rate Ratios for Patients With CIS and SCCA by Time Period (1973 to 1996 v 1997 to 2009)

Characteristic	1973 to 1996					1997 to 2009					Risk Ratio*	95% CI†
	No. of Patients	Incidence Rate*	95% CI†	APC	95% CI†	No. of Patients	Incidence Rate*	95% CI†	APC	95% CI†		
All	4,224	1.2	1.2 to 1.3	2.4	1.8 to 2.9	7,007	2.8	2.7 to 2.8	7.2	6.0 to 8.4	2.2	2.1 to 2.3
CIS	545	0.2	0.1 to 0.2	5.1	3.5 to 6.6	2,508	1.0	0.9 to 1.0	14.2	10.2 to 18.4	6.3	5.7 to 6.9
SCCA stage‡												
Local	1,569	0.5	0.4 to 0.5	3.2	2.3 to 4.1	2,408	1.0	0.9 to 1.0	3.4	2.5 to 4.2	2.0	1.9 to 2.2
Regional	1,253	0.4	0.4 to 0.4	0.3	−0.7 to 1.2	1,342	0.5	0.5 to 0.6	3.6	1.6 to 5.5	1.4	1.3 to 1.5
Distant	342	0.1	0.1 to 0.1	−1.4	−3.0 to 0.1	466	0.2	0.2 to 0.2	9.1	6.6 to 11.5	1.8	1.6 to 2.1
Sex												
Men	1,594	1.0	1.0 to 1.1	3.7	2.8 to 4.5	3,731	3.0	2.9 to 3.1	9.3	7.5 to 11.2	3.0	2.8 to 3.2
Women	2,630	1.4	1.4 to 1.5	1.5	0.8 to 2.3	3,276	2.4	2.3 to 2.5	4.8	3.9 to 5.7	1.7	1.6 to 1.8
Age group, years												
20 to 34	214	0.2	0.1 to 0.2	8.3	6.0 to 10.7	385	0.5	0.5 to 0.6	9.6	4.7 to 14.7	3.2	2.6 to 3.8
35 to 49	767	0.8	0.7 to 0.8	4.1	2.8 to 5.5	2,388	2.9	2.8 to 3.0	8.4	5.7 to 11.1	3.8	3.5 to 4.1
50 to 64	1,373	1.8	1.7 to 1.9	1.5	0.7 to 2.2	2,397	4.2	4.0 to 4.3	8.7	7.2 to 10.2	2.3	2.1 to 2.4
≥ 65	1,870	3.2	3.1 to 3.4	1.8	1.0 to 2.5	1,837	4.4	4.2 to 4.6	3.6	2.4 to 4.8	1.4	1.3 to 1.5
Race§												
White	3,701	1.3	1.2 to 1.3	2.5	1.9 to 3.0	5,776	2.9	2.8 to 2.9	7.0	5.8 to 8.2	2.2	2.1 to 2.3
Black	400	1.4	1.3 to 1.6	2.3	0.4 to 4.1	866	3.2	3.0 to 3.4	7.4	5.2 to 9.6	2.2	2.0 to 2.5
Other	111	0.5	0.4 to 0.6	1.3	−1.7 to 4.5	206	0.8	0.7 to 0.9	8.1	3.4 to 13.0	1.5	1.2 to 1.9

Abbreviations: APC, annual percent change; CIS, anal carcinoma in situ; SCCA, squamous cell carcinoma of the anal canal.

*Rates are per 100,000 and age adjusted to the 2000 US standard population (19 age groups; census P25-1130).

†CIs (Tiwari modification) are 95% for rates, APCs, and rate ratios.

‡Stage was missing for 515 patients from 1973 to 1996 and 283 patients from 1997 to 2009; these patients were excluded from stage analyses.

§Race was classified as other or unknown for 12 patients from 1973 to 1996 and 159 patients from 1997 to 2009; these patients were excluded from race analyses.

||Other consists of Asian, Pacific Islander, American Indian, and Alaska Native.

1.6; 95% CI, 1.4 to 1.8; Table 3). In women, the RRs were lower in black women than non-Hispanic white women for localized and regional SCCAs (local: RR, 0.7; 95% CI, 0.6 to 0.8; regional: RR, 0.8; 95% CI, 0.7 to 1.0). In addition, the RR was lower in all age groups in black women except for those age 20 to 34 years (age 35 to 49 years: RR, 0.8; 95% CI, 0.6 to 0.9; age 50 to 65 years: RR, 0.8; 95% CI, 0.7 to 0.9; age ≥ 65 years: RR, 0.8; 95% CI, 0.6 to 0.9). Interestingly, APCs did not differ between the two races in either men or women. Similar analyses were conducted for AIS and AAC (Data Supplement).

DISCUSSION

Anal canal cancer arises anatomically from 1 to 2 cm proximal to the dentate line to the intersphincteric groove separating the anal margin from the anal canal¹⁶ and pathologically from the glandular, transitional, and/or squamous mucosa.¹⁷ SCCA is the dominant histologic type of anal canal cancer.⁶ Advancing knowledge of the biology of SCCA as well as multimodality therapy employing combination chemotherapy and radiation have improved outcome for these patients over the last three decades.³ However, the continuing increase in number of cases in the United States and worldwide portends an escalating public health problem.

HPV is associated with 65% to 89% of all SCCAs^{18,19} and is implicated as a cause of the disease. Much of the current understanding of the mechanisms of oncogenesis induced by HPV infection is based on studies of the progression of cervical squamous intraepithelial neoplasia to invasive cervical cancer in HPV-infected women.^{7,20-22} The overall prevalence of HPV infection in the United

States varies depending on the population under study but ranges between 10% and 55%.^{23,24} In particular, the prevalence of anal HPV infection approaches 90% in HIV-infected individuals.^{25,26} Risk factors associated with HPV infection have been well described and include number of lifetime sex partners, sexual practices, race, age, homosexual contact, and underlying HIV infection.^{22,23} Although HPV infection is common among young adults, most individuals subsequently test negative for HPV. Whether negative HPV tests represent viral clearance or viral latency remains controversial.^{27,28} Persistent infection, however, does occur, especially in conjunction with HIV infection, and has been associated with increased risk of epithelial changes progressing to cancer.²⁹⁻³² The high prevalence rate of HPV and recognition of its oncogenic potential⁸ have been paralleled clinically by the emerging epidemic of SCCA.^{3,4,33}

The association of HPV infection with CIS and SCCA^{8,20} suggests that a rise in the behavioral and lifestyle factors identified with HPV infection may lead to increases in CIS and SCCA. Our analyses highlight the increasing incidence of combined CIS and SCCA and the associated patient characteristics. Applying joint-point regression analyses to SEER data from 1973 to 2009, we found that 1997 optimally represented the time point when the combined CIS and SCCA trajectory changed most dramatically, with APCs of 2.4% before 1997 and of 7.2% after 1997, a 2.2-fold change (Fig 1). To ensure that the increase was specific to HPV-related SCCA, we performed similar analyses for combined AIS and AAC, a pathologic type not known to be associated with HPV. Interestingly, the APC for combined AIS and AAC has been decreasing over time since 1989 (Fig 1).

Table 3. Combined Demographics, Incidence Rates, APCs, and Rate Ratios by Sex and Race/Ethnicity for Patients With CIS and SCCA (1997 to 2009)

Characteristic	Non-Hispanic Whites					Blacks					Risk Ratio*	95% CI†
	No. of Patients	Incidence Rate*	95% CI†	APC	95% CI†	No. of Patients	Incidence Rate*	95% CI†	APC	95% CI†		
Men												
CIS	1,774	1.6	1.5 to 1.7	16.6	12.5 to 21.0	356	2.0	1.8 to 2.2	14.2	10.0 to 18.5	1.2	1.1 to 1.4
SCCA stage‡												
Local	1,020	0.9	0.9 to 1.0	3.4	1.8 to 5.0	187	1.2	1.0 to 1.3	2.8	−1.6 to 7.3	1.2	1.0 to 1.5
Regional	509	0.5	0.4 to 0.5	2.4	−1.0 to 5.9	87	0.5	0.4 to 0.6	1.6	−4.8 to 8.4	1.1	0.9 to 1.4
Distant	217	0.2	0.2 to 0.2	6.0	0.7 to 11.7	47	0.3	0.2 to 0.4	19.9	10.0 to 30.6	1.4	1.0 to 2.1
Age group, years												
20 to 34	225	0.8	0.7 to 0.9	10.4	4.8 to 16.3	103	1.7	1.4 to 2.1	9.5	4.8 to 14.4	2.2	1.6 to 2.9
35 to 49	1,458	4.1	3.9 to 4.4	10.9	7.9 to 13.9	385	6.5	5.8 to 7.2	10.0	6.0 to 14.2	1.6	1.4 to 1.8
50 to 64	1,233	4.7	4.4 to 5.0	11.2	9.1 to 13.4	178	5.2	4.4 to 6.0	9.1	4.2 to 14.4	1.1	0.9 to 1.3
≥ 65	741	4.2	3.9 to 4.6	4.1	1.9 to 6.4	39	2.3	1.6 to 3.2	7.4	−3.9 to 20.0	0.5	0.4 to 0.7
Women												
CIS	559	0.5	0.4 to 0.5	9.8	6.0 to 13.7	82	0.4	0.3 to 0.5	8.8	3.4 to 14.4	0.9	0.7 to 1.1
SCCA stage‡												
Local	1,487	1.2	1.1 to 1.2	4.1	2.8 to 5.4	154	0.8	0.7 to 1.0	2.7	−2.0 to 7.6	0.7	0.6 to 0.8
Regional	922	0.7	0.7 to 0.8	3.8	1.3 to 6.3	108	0.6	0.5 to 0.7	6.6	2.2 to 11.2	0.8	0.7 to 1.0
Distant	266	0.2	0.2 to 0.2	9.1	6.5 to 11.8	37	0.2	0.1 to 0.3	8.5	−7.5 to 27.3	1.0	0.7 to 1.4
Age group, years												
20 to 34	48	0.2	0.1 to 0.2	1.9	−5.8 to 10.3	20	0.3	0.2 to 0.5	−3.4	−18.0 to 13.8	1.7	0.9 to 3.2
35 to 49	719	2.0	1.9 to 2.2	4.0	2.2 to 6.0	107	1.6	1.3 to 1.9	3.2	−1.9 to 8.5	0.8	0.6 to 0.9
50 to 64	1,311	4.9	4.6 to 5.2	7.5	5.8 to 9.3	166	4.0	3.4 to 4.7	5.4	1.8 to 9.2	0.8	0.7 to 0.9
≥ 65	1,397	5.8	5.5 to 6.1	3.7	2.6 to 4.7	118	4.4	3.7 to 5.3	5.8	1.7 to 10.1	0.8	0.6 to 0.9

Abbreviations: APC, annual percent change; CIS, anal carcinoma in situ; SCCA, squamous cell carcinoma of the anal canal.

*Rates are per 100,000 and age adjusted to the 2000 US standard population (19 age groups; census P25-1130).

†CIs (Tiwari modification) are 95% for rates, APCs, and rate ratios.

‡Stage was missing for 137 non-Hispanic men, 28 black men, 241 non-Hispanic women, and 30 black women; these patients were excluded from stage analyses.

The identification of 1997 as the time point at which SCCA rates shifted is consistent with the impact HIV has had on the acquisition and persistence of HPV. Although the APC of SCCA has increased among all population and risk groups, previous studies have also shown a temporal relationship between the onset of the HIV epidemic and the increase in SCCA incidence,³⁴ with recent data indicating that the risk of SCCA increases with the duration of HIV infection and progression to AIDS.³⁵ This relationship was further characterized by Crum-Cianflone et al,³⁶ who reported that patients infected with HIV for ≥ 15 years had a 12-fold greater risk of SCCA when compared with patients infected for ≤ 5 years. In addition, the same study determined that risk of SCCA was not reduced with the use of highly active antiretroviral therapy (HAART). Others have shown that the incidence of SCCA continued to increase after the availability of HAART (before 1996),³⁴ further supporting the lack of direct impact of HAART on HPV-related cancers.³⁷ With the HIV epidemic beginning in the early 1980s, the dramatic increase in anal cancer incidence after 1997, as defined by our joinpoint analysis, supports the expected time progression from acquisition of both HIV and HPV infections to HPV-associated epithelial changes to full development of SCCA.

When comparing the patient demographic factors before and after 1997, we identified several distinct trends (Table 2). First, although the incidence rates for CIS and all stages of SCCA increased, CIS had the highest APC and RR. Second, CIS and SCCA were increasing in younger patients, with APCs rising fastest in those who were age

35 to 49 years. Third, although our results confirm prior reports showing higher combined CIS and SCCA incidence rates in women before 2000,^{3,33} our inclusion of data through 2009 demonstrated that the incidence was now higher in men than women. After 1997, the APC for men was almost twice that for women, and much of this difference resulted from the dramatic rise in CIS reported in men. Lastly, the combined CIS and SCCA incidence rates were increasing for all racial groups. There was no parallel change in incidence rates of AAC overall or by demographic characteristics during the same time period (Data Supplement).

Although overall incidence rates were similar between men and women, CIS and stage-specific SCCA rates were not. For men, the incidence was highest, and rising the most rapidly, for CIS, exceeding that of all SCCA stages in both men and women (Table 1; Data Supplement). As Chiao et al³⁴ and others have suggested, early detection in high-risk men (eg, HIV-positive men and men who have sex with men) because of other symptoms related to the anal region, as well as to the availability of anal cancer screening programs, may have contributed to the early detection of CIS and SCCA. In addition, if screening does increase the number of CIS patient cases, the proportion of CIS should increase relative to the stages of SCCA.³⁵ Indeed, CIS increased in proportion from 12% before 1997 to 36% after 1997 among all anal canal cases reported to the SEER registry (Table 2). In men, CIS accounted for 51% of patient cases compared with 17% of cases among women (Table 1).

In women, the incidence rate of SCCA was increasing, exceeding that of men in all SCCA stages. However, CIS incidence was not changing (Table 1; Data Supplement). Although HIV coinfection greatly increases the risk of anal HPV infection and abnormal anal cytology,^{26,38} the incidence of SCCA in women began to rise before the AIDS epidemic.³⁴ Screening of HIV-infected and high-risk HIV-uninfected women documented higher rates of HPV detection in the anal canal than in the cervix regardless of HIV status.²⁶ Importantly, HPV infection in one site (eg, cervix) may be concurrent with infection in another localized site (eg, anus).³⁹ In a study by Crawford et al,⁴⁰ 91% of 100 HIV-uninfected women with HPV-related abnormal cervical cytology were simultaneously infected with anal HPV. In addition, cervical HPV infection markedly increased the relative risk of anal HPV infection, suggesting sequential transmission of HPV from one anogenital region to another.⁴¹

When assessing SCCA trends over time, it is important to consider the impact of better recognition, acceptance, and standardization of pathologic terminology for in situ disease.¹⁷ In the mid 1980s, the classification schema for anal intraepithelial neoplasia (AIN) was first described. AIN III became the equivalent term for high-grade squamous intraepithelial lesion and carcinoma in situ.⁴² A recent consensus panel recommended the use of standardized terminology for all HPV-associated squamous lesions of the lower anogenital tract sites.⁴³ Once accepted and implemented, such standardized language will greatly improve on the ability to discern the incidence of CIS and SCCA and administer treatment according to recurrence risks.

To ensure that our findings were not solely the result of better diagnostic standardization and ascertainment bias, we limited our analyses of CIS to the time period after 1997, more than 10 years after standard definitions for AIN III and in situ disease had been established. We also analyzed the data set with and without CIS and found that the results were similar with respect to increasing incidence rates, the year at which change occurred most dramatically, and the demographic changes across time periods. In addition, many of our analyses

focused on comparisons between groups during the same time period and not across time periods, limiting the potential for misinterpretation secondary to changing definitions.

To our knowledge, this study is the first to demonstrate the dramatic rise in incidence of CIS and SCCA in the context of the stable rates of AIS and AAC. In addition, the increased incidence is disproportionate, favoring CIS and early-stage SCCA. The demographic changes in SCCA identified over the last two decades may result from the increased incidence of SCCA in specific screened populations. We suggest that high-risk men as well as women with high-grade anogenital HPV-related epithelial changes be considered for anal cancer screening. Importantly, the recent availability of several vaccines directed against both oncogenic and nononcogenic subtypes of HPV has resulted in the nearly complete prevention of HPV-related epithelial changes in vaccinated individuals. Thus, there remains a possibility that the sharp rise in incidence in SCCA noted in this study is transient and will be followed by potential eradication of this disease in vaccinated populations. For the present, however, with the long-term outcome from vaccination not yet characterized, specific populations known to be at risk for SCCA may benefit from systematic screening for oncogenic HPV and anal SCCA precursor lesions.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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