Research Article

Cancer Epidemiology, Biomarkers & Prevention

Anal Cancer Incidence in the United States, 1977–2011: Distinct Patterns by Histology and Behavior

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Abstract

Background: Although anal squamous cell carcinoma (SCC) and adenocarcinoma (ADC) are generally combined in cancer surveillance, their etiologies likely differ. Here, we describe demographic characteristics and trends in incidence rates (IR) of anal cancer by histology (SCC, ADC) and behavior (invasive, *in situ*) in the United States.

Methods: With data from the Surveillance, Epidemiology, and End Results (SEER) Program, we estimated age-adjusted anal cancer IRs across behavior/histology by demographic and tumor characteristics for 2000–2011. Trends in IRs and annual percent changes during 1977–2011 were also estimated and compared with rectal cancer.

Results: Women had higher rates of SCC [rate ratio (RR), 1.45; 95% confidence interval (CI), 1.40–1.50] and lower rates of ADC (RR, 0.68; 95% CI, 0.62–0.74) and squamous carcinoma *in situ* (CIS; RR, 0.36; 95% CI, 0.34–0.38) than men. Blacks had lower rates of SCC (RR, 0.82; 95% CI, 0.77–0.87) and CIS (RR, 0.90; 95% CI, 0.83–0.98) than non-Hispanic whites, but higher rates of ADC (RR, 1.48; 95% CI, 1.29–1.70). Anal cancer IRs were higher in men and blacks aged <40 years. During 1992–2011, SCC IRs increased 2.9%/year, ADC IRs declined nonsignificantly, and CIS IRs increased 14.2%/year. SCC and ADC IR patterns and trends were similar across anal and rectal cancers.

Conclusions: Rates of anal SCC and CIS have increased strongly over time, in contrast to rates of anal ADC, similar to trends observed for rectal SCC and ADC.

Impact: Anal SCC and ADC likely have different etiologies, but may have similar etiologies to rectal SCC and ADC, respectively. Strong increases in CIS IRs over time may reflect anal cancer screening patterns. *Cancer Epidemiol Biomarkers Prev; 24(10); 1548–56. ©2015 AACR.*

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Introduction

With only 7,270 cases estimated to occur in the United States during 2015, anal cancer is a relatively rare malignancy (1). However, anal cancer rates have increased steadily for decades in the United States and internationally (2–5). Although the cause of these rising rates is unclear, it has been hypothesized that changing sexual practices, leading to increased prevalence of anal infection with carcinogenic human papillomavirus (HPV), and an increasing number of individuals living with HIV, a group known to have elevated anal cancer risk, have contributed to this increase (6).

The majority of anal cancers are squamous cell carcinomas (SCC), but adenocarcinomas (ADC) make up 9% to 14% of diagnosed cases in the United States, although these proportions may vary considerably internationally (6–9). Although SCC and ADC are usually combined in cancer surveillance, their etiologies may differ. Ninety percent of anal SCCs are caused by infection with oncogenic types of HPV, primarily HPV-16, whereas HPV has been detected in a smaller fraction of ADCs (8, 10, 11). Because of the rarity of anal ADC, little is known about its etiology. Furthermore, it may be difficult to determine whether the primary site of some tumors is the lower rectum or anus; SCCs and ADCs arising across these two sites may have shared etiologies and be prone to misclassification of their primary location.

In the current analysis, we used data from the National Cancer Institute's (NCI) Surveillance, Epidemiology and End Results (SEER) Program to provide a detailed description of the demographic characteristics and temporal trends in incidence rates (IR) of anal cancer by histology (i.e., SCC and ADC) and behavior (i.e., invasive vs. *in situ*) in the United States. We also compare patterns to rectal cancer to assess similarities across these two sites according to histology.

Materials and Methods

We used data from SEER to assess recent IRs in the 18 registries with data for cases diagnosed during 2000–2011 (i.e., SEER 18, including approximately 28% of the U.S. population; ref. 12), and to assess temporal trends in the registries that participated in SEER 9 (1977–2011) and SEER 13 (1992–2011; refs. 13, 14).

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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Microscopically confirmed anal cancers were ascertained using SEER site recode, based on the *International Classification of Diseases for Oncology*, 3rd edn. (ICD-O-3; site code: C21.0–C21.2, C21.8, excluding histology codes 9050–9055, 9140, 9590–9992; ref. 15). Anal cancers were classified by site (anal, not otherwise specified [NOS; C21.0]; anal canal [C21.1], cloacogenic zone [C21.2], and overlapping lesion of rectum, anus, and anal canal [C21.8]). Invasive cases (i.e., behavior = 3) were further classified by histology (SCC: 8050–8076, 8083–8084, 8123–8124; ADC: 8140–8145, 8190–8231, 8260–8263, 8310, 8401, 8480–8490, 8570–8574; melanoma: 8720–8727, 8730–8743, 8745–8790; and other types; based on a modified version of ref. 16). *In situ* cases (i.e., behavior = 2) were restricted to SCCs (8050–8077, 8081, 8083–8084, 8123–8124) or carcinoma *in situ* (CIS), NOS (8010), as these were likely SCCs. For comparison, rates for invasive SCC and ADCs of the rectum (site code: C20.9) were also calculated to assess similarities across sites.

Statistical analysis

Using data from SEER 18, we estimated anal cancer IRs per 1,000,000 person-years, age-adjusted to the 2000 U.S. population across behavior/histology by age group (<30, 30–49, 50–59, 60–69, 70+ years), race/ethnicity (non-Hispanic white, black, Hispanic white, Asian/Pacific Islander, American Indian/Alaskan Native, and other/unknown), cancer registry, and anatomic subsite. IRs for American Indian/Alaskan Natives were restricted to Contract Health Service Delivery Areas (CHSDA). Rate ratios (RR) and 95% confidence intervals (CI) were estimated by sex (women vs. men) and race/ethnicity (blacks and Hispanic whites vs. non-Hispanic whites). Data from SEER 18 were also used to assess patterns across age groups by sex, race/ethnicity, and histology/behavior.

Information on Hispanic ethnicity is not available in SEER <1992. Therefore, trends in age-standardized IRs of anal cancer over calendar time (presented in 5-year calendar periods) were estimated using SEER 9 for whites and blacks (1977–1991) and SEER 13 for non-Hispanic whites, blacks, and Hispanic whites (1992–2011), stratified by sex, race/ethnicity, and histology/behavior. Trends for Asian/Pacific Islanders and American Indians/Alaska Natives were not shown due to scarcity of the data. For comparison, calendar trends (1977–2011) were also assessed for rectal cancers, restricted to whites/non-Hispanic whites, as the data in other racial/ethnic groups were too sparse for analysis. Annual percent changes (APC) in IRs during 1992–2011 were assessed with least squares regression of the natural logarithm of the rate (17). IRs were suppressed if based on <16 cases. All analyses were carried out with SEER*Stat 8.1.5 (18).

Results

During 2000–2011 in the 18 SEER registries, a total of 16,141 cases of invasive anal cancer were diagnosed during 993,234,972 person-years of follow-up (IR = 16.3/1,000,000; Table 1). Cases were primarily SCC (n = 13,274, 82.2%), followed by ADC (n = 1,992; 12.3%), and melanoma (n = 254; 1.6%). There were 621 invasive anal cancers with other/poorly specified histologies (3.8%). An additional 6,686 cases of anal squamous CIS were diagnosed during the same time period. We excluded from analysis the 131 invasive anal cancers that were not microscopically confirmed and the 131 anal CIS with non-SCC or CIS, NOS histologies.

Table 1 presents IRs by behavior/histology across categories of age, sex, race/ethnicity, registry, and anal site. IRs increased across age groups for all invasive cancers. For squamous CIS, the highest IR occurred among 40 to 49 year-olds. The IR for anal SCC was greater among women than among men. In contrast, rates of both anal ADC and squamous CIS were greater in men than in women. The SCC IR was highest among non-Hispanic whites, while the ADC IR was highest among blacks. The IRs varied notably across registries. The total invasive anal cancer rate was highest among Alaska Natives, but the small number of cases precluded estimation of the type-specific rates. The SCC IRs exceeded 15/million in Atlanta, San Francisco-Oakland, Kentucky, and Seattle and were <10/million in Utah and Hawaii. Rates of anal CIS were dramatically higher in San Francisco-Oakland (35.2/million), about three times the next highest rate of 11.9 in Seattle. Eighty-three percent of SCC developed in the anal canal or anus, NOS. In contrast, nearly half of the ADCs had the primary site designated as overlapping lesion of the rectum, anus, and anal canal.

The different age-specific incidence patterns for SCC, ADC, and anal CIS are shown in Fig. 1. Across race/ethnicities, SCC IRs generally increased steeply until ages 50 or 60 years, and then increased more gradually at older ages, except among black males. Among non-Hispanic whites and blacks, anal ADC IRs increased steadily with advancing age, while rates among Hispanic whites were too sparse to evaluate. In contrast, squamous CIS IRs were highest among 40- to 49-year-old men and 50- to 59-year-old women who were non-Hispanic white or black. Among Hispanic whites, CIS rates decreased with age among men and increased among women.

The IR for invasive anal cancer was higher among women compared with men (overall RR, 1.29; 95% CI, 1.25–1.33) with the excess particularly notable among those of ages ≥50 years (RR, 1.32–1.53) and among cases arising in the cloacogenic zone (RR, 2.29; 95% CI, 1.91–2.76; Table 2). There were a few notable exceptions, however, where anal cancer IRs were higher among men; including <40 year-olds (RR, 0.41 and 0.62) and blacks (RR, 0.84; 95% CI, 0.76–0.93). Consistent with data presented in Table 1, IRs of ADC (RR, 0.68; 95% CI, 0.62–0.74) and squamous CIS (RR, 0.36; 95% CI, 0.34–0.38) were also higher in men.

Compared with non-Hispanic whites, Hispanic whites (overall RR, 0.64; 95% CI, 0.60–0.68) and Asian/Pacific Islanders (overall RR, 0.27; 95% CI, 0.25–0.30) had lower rates of invasive anal cancer across sexes, age groups, primary sites, and histology, with the exception of melanoma (Table 3). Compared with non-Hispanic whites, blacks also had somewhat lower rates of invasive anal cancer overall (RR, 0.91; 95% CI, 0.86–0.95), and lower rates among women (RR, 0.72; 95% CI, 0.67–0.77) and 60+ year-olds (RR, 0.72 and 0.80). Rates of anal cancer occurring in the anal canal (RR, 0.81; 95% CI, 0.74–0.88) or cloacogenic zone (RR, 0.62; 95% CI, 0.44–0.85), and SCC (RR, 0.82; 95% CI, 0.77–0.87) were also lower among blacks. In contrast, consistent with Table 2, invasive anal cancer rates were higher among black men overall (RR, 1.19; 95% CI, 1.10–1.28), and particularly among men of ages <40 (RR, 4.56 and1.73), and for ADCs (RR, 1.48; 95% CI, 1.29–1.70).

During 1992–2011 in the 13 SEER registries, invasive anal cancer IRs increased 2.2%/year overall (95% CI, 1.8–2.6) and among men (95% CI, 1.6–2.8), and 2.3%/year (95% CI, 1.9–2.8) among women (Supplementary Table S1 and Fig. 2). The increases were limited to SCC (overall APC, 2.9%; 95% CI,

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Table 1. Anal cancer IRs per 1,000,000 by tumor and case characteristics, SEER 18, 2000–2011[a]

	Invasive anal cancers											
	All		SCC		ADC		Melanoma		Other[b]		*In situ*	
	N	IR	*N*	IR	*N*	IR	*N*	IR	*N*	IR	*N*	IR
Total	16,141	16.3	13,274	13.3	1,992	2.1	254	0.3	621	0.6	6,686	6.7
Age, y												
<30	53	0.1	33	0.1	11	[e]	[e]	[e]	7	[e]	351	0.8
30–39	599	4.3	516	3.7	49	0.3	9	[e]	25	0.2	1,202	8.6
40–49	2,779	18.5	2,490	16.6	177	1.2	19	0.1	93	0.6	2,318	15.6
50–59	4,355	35.4	3,863	31.4	315	2.5	47	0.4	130	1.1	1,673	13.7
60–69	3,483	45.5	2,902	37.9	413	5.4	47	0.6	121	1.6	715	9.2
70+	4,872	59.3	3,470	42.4	1,027	12.4	130	1.6	245	3.0	427	5.3
Sex												
Female	9,730	18.1	8,305	15.5	927	1.7	155	0.3	343	0.6	1,832	3.5
Male	6,411	14.1	4,969	10.7	1,065	2.5	99	0.2	278	0.6	4,854	9.9
Race/ethnicity[c]												
Non-Hispanic white	12,584	18.4	10,552	15.4	1,406	2.0	170	0.2	456	0.7	4,535	7.3
Black	1,689	16.6	1,330	12.6	266	3.0	13	[e]	80	0.8	760	6.6
Hispanic white	1,255	11.8	1,006	9.3	164	1.7	38	0.4	47	0.4	668	4.4
Asian/Pacific Islander	414	5.0	232	2.7	124	1.6	31	0.4	27	0.3	145	1.5
American Indian/Alaskan native[d]	64	11.2	41	6.8	15	[e]	[e]	[e]	6	[e]	22	3.5
Registry												
Alaska Natives	24	25.0	13	[e]	8	[e]	[e]	[e]	[e]	[e]	[e]	[e]
Atlanta	634	19.1	560	16.6	54	1.9	[e]	[e]	15	[e]	268	6.9
San Francisco-Oakland	1,015	18.8	874	16.1	95	1.8	16	0.3	30	0.6	1,917	35.2
Kentucky	1,004	18.6	820	15.2	131	2.4	16	0.3	37	0.7	272	5.2
Seattle (Puget Sound)	1,000	18.5	842	15.5	103	2.0	11	0.2	44	0.8	646	11.9
California excluding SF/SJM/LA	3,920	17.5	3,210	14.2	495	2.3	59	0.3	156	0.7	1,271	5.6
Los Angeles	1,767	16.7	1,397	13.1	259	2.5	52	0.5	59	0.6	1,080	9.5
Louisiana	817	15.7	689	13.2	89	1.8	7	[e]	32	0.6	117	2.3
Greater Georgia	1,073	15.7	895	13.0	112	1.7	15	0.2	51	0.8	145	2.1
Detroit (Metropolitan)	787	15.6	597	11.9	143	2.8	12	0.2	35	0.7	173	3.5
New Jersey	1,710	15.1	1,406	12.4	212	1.9	22	0.2	70	0.6	275	2.5
Iowa	588	14.6	484	12.2	71	1.6	8	[e]	25	0.7	75	2.0
Rural Georgia	23	14.1	20	12.4	[e]	[e]	0	[e]	[e]	[e]	[e]	[e]
Connecticut	664	14.0	557	11.8	85	1.8	[e]	[e]	17	0.4	153	3.4
San Jose-Monterey	365	13.2	299	10.7	48	1.9	8	[e]	10	[e]	137	4.8
New Mexico	325	13.2	279	11.3	31	1.2	6	[e]	9	[e]	46	1.9
Utah	263	11.3	210	9.0	29	1.3	9	[e]	15	[e]	55	2.2
Hawaii	162	9.3	122	7.1	25	1.4	[e]	[e]	13	[e]	52	3.2
Anal site												
C21.0-Anus, NOS	6,114	6.2	5,326	5.3	469	0.5	77	0.1	242	0.3	2,859	2.9
C21.1-Anal canal	6,594	6.6	5,730	5.7	572	0.6	78	0.1	214	0.2	3,501	3.5
C21.2-Cloacogenic zone	620	0.6	600	0.6	9	[e]	[e]	[e]	10	[e]	9	[e]
C21.8-Overlapping lesion of rectum, anus, and anal canal	2,813	2.9	1,618	1.6	942	1.0	98	0.1	155	0.2	317	0.3

[a]IR per 1,000,000, age-adjusted to the 2000 U.S. population standard, restricted to microscopically confirmed cases.
[b]333 of other invasive anal cancers had other specified histologic types and 288 of other invasive anal cancers had poorly/unspecified histologic types.
[c]Excludes 135 cases with other or unknown race.
[d]Restricted to CHSDA.
[e]IRs suppressed because of case counts <16, case counts suppressed when ≤5.

2.5–3.3), with significant increases among non-Hispanic white and black men and women, and nonsignificant increases among Hispanic whites. Among non-Hispanic whites, APCs for SCC increased for both men and women across age groups with the exception of 0 to 39 year-olds (Supplementary Fig. S1). Of note, SCC IRs have been consistently higher among women compared with men over time among non-Hispanic and Hispanic whites; however, rates have been higher among black men compared with black women since 1992–1996. Since 1992, ADC IRs have been stable among men (APC, −0.6; 95% CI, −1.9–0.8) and declined among women (APC, −1.8; 95% CI, −3.5–0.0). Squamous CIS IRs increased 14.2%/year overall (95% CI, 12.6–15.9), with more rapid increases among men (APC, 15.5%; 95% CI, 13.5–17.6) than women (APC, 10.1%; 95% CI, 8.7–11.6); these patterns are apparent in each racial/ethnic group. When the San Francisco-Oakland registry was excluded (i.e., the registry with the highest rates of squamous CIS), a steep incline in rates remained (APCs: overall, 13.4%; 95% CI, 12.0–14.8%; men: 15.2%, 95% CI, 13.4–17.1%; women: 9.3%, 95% CI, 7.7–11.0%).

Because of the juxtaposition of the anus and rectum and the potential for misclassification of site of origin, we additionally examined trends in rectal cancer IRs by histology among whites/non-Hispanic whites during 1977–2011 (Fig. 3). The trends over time were quite similar for rectal and anal SCCs and, to a lesser extent, for rectal and anal ADCs. Like anal cancer, rectal SCC IRs have been consistently higher among women, and rectal ADC IRs have been consistently higher among men. During 1992–2011, similar to the anal cancer APCs, among women, rectal SCC IRs increased 3.9%/year (95% CI, 2.6–5.3) and ADC IRs declined 1.3%/year (95% CI, −1.8, −0.9). In contrast to the significant increase in anal SCC IRs and stable anal ADC IRs among men, rectal SCC IRs have been relatively stable since 1992 (APC, 0.3;

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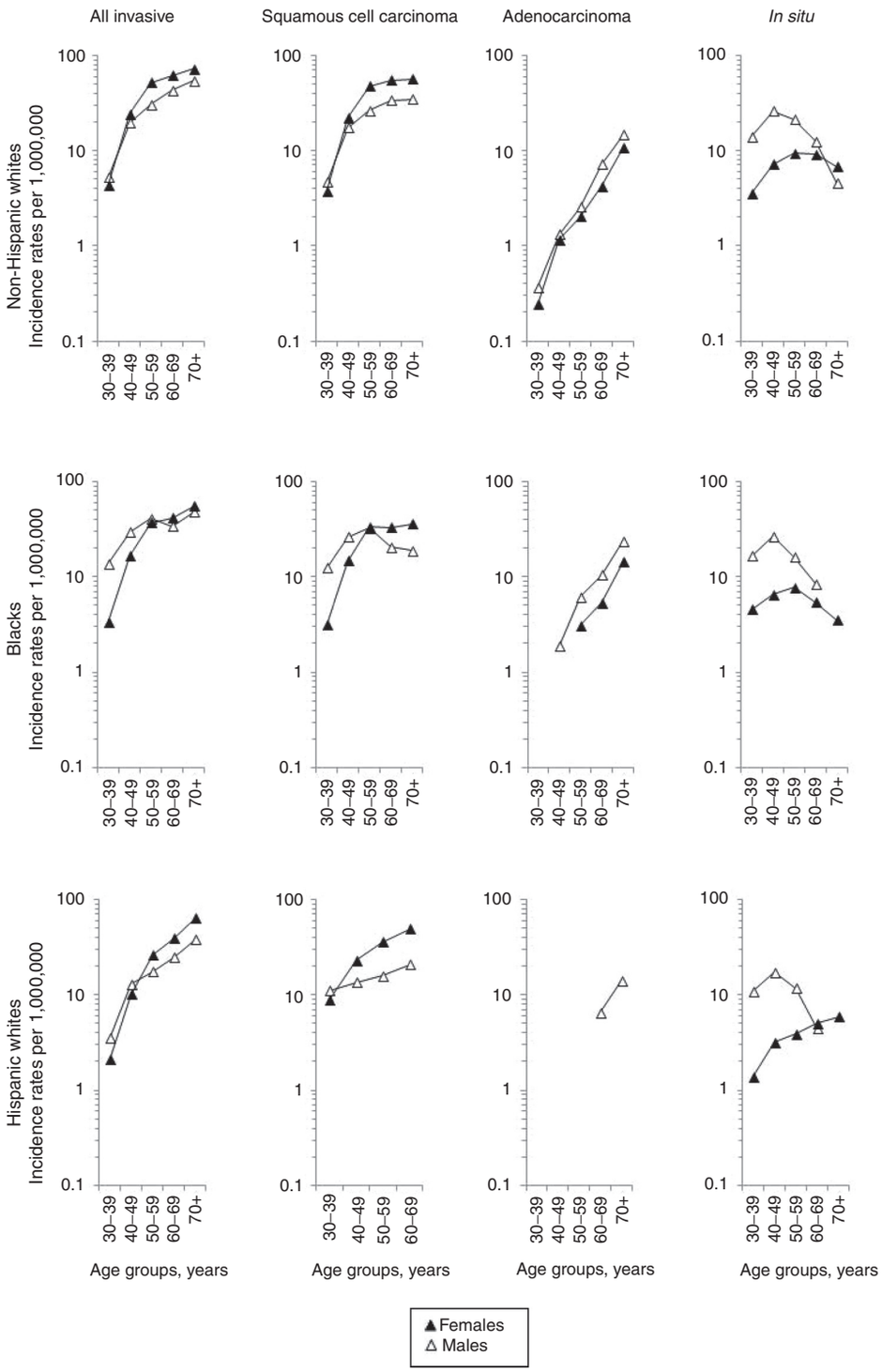

Figure 1.
Anal cancer IRs across age groups by sex, race, histology, and behavior using data from SEER 18, 2000–2011. All rates were age-standardized within age groups to the 2000 U.S. population and restricted to microscopically confirmed cases. Solid triangles indicate rates among women and open triangles indicate rates among men. All points with <16 cases are excluded.

95% CI, −1.7–2.4), and ADC IRs significantly declined (APC, −1.4; 95% CI, −1.9 to −0.8). When rectal and anal cancers were combined, during 2007–2011, ADC rates were 98.3/1,000,000 among men and 56.7/1,000,000 among women, while SCC rates were 13.6/1,000,000 among men and 21.3/1,000,000 among women.

Discussion

Using population-based data from the SEER program, we have shown that the demographic characteristics and temporal trends in anal cancer IRs differ dramatically by histologic type. SCCs are more common among women and occur at younger ages than ADCs.

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Table 2. RRs for anal cancer, comparing females with males, SEER 18 2000–2011

	Female		Male		
	N	**IR**	***N***	**IR**	**RR (95% CI)**
All invasive	9,730	18.1	6,411	14.1	1.29 (1.25–1.33)
Age, y					
<30	15	[a]	38	0.2	**0.41 (0.21–0.77)**
30–39	228	3.3	371	5.3	**0.62 (0.52–0.73)**
40–49	1,436	18.9	1,343	18.1	1.04 (0.97–1.12)
50–59	2,683	42.5	1,672	27.9	**1.53 (1.44–1.62)**
60–69	2,137	52.9	1,346	37.4	**1.42 (1.32–1.52)**
70+	3,231	65.9	1.641	49.8	**1.32 (1.25–1.41)**
Race/ethnicity					
Non-Hispanic white	7,794	21.1	4,790	15.2	**1.39 (1.34–1.44)**
Black	844	15.2	845	18.1	**0.84 (0.76–0.93)**
Hispanic white	737	13.3	518	9.6	**1.38 (1.22–1.57)**
Asian/Pacific Islander	247	5.4	167	4.5	1.19 (0.97–1.46)
American Indian/Alaskan Native	38	12.7	26	9.4	1.35 (0.77–2.44)
Anal site					
C21.0-Anus, NOS	3,501	6.5	2,613	5.7	**1.15 (1.09–1.21)**
C21.1-Anal canal	4,068	7.6	2,526	5.5	**1.38 (1.31–1.45)**
C21.2-Cloacogenic zone	456	0.8	164	0.4	**2.29 (1.91–2.76)**
C21.8-Overlapping lesion of rectum, anus, and anal canal	1,705	3.2	1,108	2.6	**1.23 (1.14–1.33)**
Histology					
SCC	8,305	15.5	4,969	10.7	**1.45 (1.40–1.50)**
ADC	927	1.7	1,065	2.5	**0.68 (0.62–0.74)**
Melanoma	155	0.3	99	0.2	1.24 (0.96–1.62)
Other	343	0.6	278	0.6	1.00 (0.85–1.17)
All *in situ*	1,832	3.5	4,854	9.9	**0.36 (0.34–0.38)**

NOTE: IR per 1,000,000, age-adjusted to the 2000 U.S. population standard.
Statistically significant associations are presented in bold.
RRs compare female with male rates. Restricted to microscopically confirmed cases.
[a]IRs suppressed because of case counts <16.

Furthermore, during 1992–2011, anal SCC IRs increased significantly, whereas ADC IRs declined, at least among women. In addition, anal squamous CIS IRs increased steeply over time, with rates highest among men and in the San Francisco-Oakland registry.

Eighty-two percent of all anal cancers in the United States are SCCs, though ADCs may comprise a larger fraction of cases in some countries (9). Anal SCCs are largely caused by infection with oncogenic HPV, primarily HPV-16 (10, 11, 19). In

Table 3. RRs for anal cancer by race/ethnicity, compared with non-Hispanic whites, SEER 18 2000–2011

	NHW		Black			Hispanic white			Asian/Pacific Islander		
	N	**IR**	***N***	**IR**	**RR (95%CI)**	***N***	**IR**	**RR (95%CI)**	***N***	**IR**	**RR (95%CI)**
All invasive	12,584	18.4	1,689	16.6	**0.91 (0.86–0.95)**	1,255	11.8	**0.64 (0.60–0.68)**	414	**5.0**	**0.27 (0.25–0.30)**
Sex											
Female	7,794	21.1	844	15.2	**0.72 (0.67–0.77)**	737	13.3	**0.63 (0.58–0.68)**	167	**5.4**	**0.26 (0.22–0.29)**
Male	4,790	15.2	845	18.1	**1.19 (1.10–1.28)**	518	9.6	**0.63 (0.57–0.70)**	247	**4.5**	**0.30 (0.25–0.35)**
Age, y											
<30	20	0.1	24	0.4	**4.56 (2.40–8.68)**	7	[a]	[a]	[a]	[a]	[a]
30–39	355	4.7	143	8.2	**1.73 (1.41–2.10)**	84	2.8	**0.60 (0.47–0.76)**	9	[a]	[a]
40–49	2,000	21.8	405	22.6	1.04 (0.93–1.15)	271	11.5	**0.53 (0.46–0.60)**	53	**3.7**	**0.17 (0.13–0.22)**
50–59	3,381	40.9	510	38.3	0.93 (0.85–1.03)	318	21.9	**0.53 (0.47–0.60)**	104	**9.3**	**0.23 (0.19–0.28)**
60–69	2,817	52.1	277	37.7	**0.72 (0.64–0.82)**	246	32.2	**0.62 (0.54–0.70)**	91	**13.7**	**0.26 (0.21–0.32)**
70+	4,011	64.0	330	51.5	**0.80 (0.72–0.90)**	329	51.9	**0.81 (0.72–0.91)**	155	**25.3**	**0.39 (0.33–0.46)**
Anal site											
C21.0-Anus, NOS	4,740	7.0	707	6.8	0.98 (0.91–1.07)	469	4.2	**0.61 (0.55–0.67)**	106	**1.3**	**0.19 (0.15–0.23)**
C21.1-Anal canal	5,230	7.6	640	6.2	**0.81 (0.74–0.88)**	473	4.4	**0.58 (0.52–0.64)**	183	**2.2**	**0.29 (0.24–0.33)**
C21.2-Cloacogenic zone	495	0.7	43	0.4	**0.62 (0.44–0.85)**	61	0.6	0.84 (0.63–1.11)	16	**0.2**	**0.25 (0.14–0.42)**
C21.8-Overlapping lesion of rectum, anus, and anal canal	2,119	3.1	299	3.2	1.04 (0.92–1.18)	252	2.5	**0.83 (0.72–0.95)**	109	**1.4**	**0.45 (0.37–0.55)**
Histology											
SCC	10,552	15.4	1,330	12.6	**0.82 (0.77–0.87)**	1,006	9.3	**0.60 (0.56–0.64)**	232	2.7	**0.18 (0.16–0.20)**
ADC	1,406	2.0	266	3.0	**1.48 (1.29–1.70)**	164	1.7	**0.82 (0.68–0.97)**	124	1.6	**0.78 (0.64–0.94)**
Melanoma	170	0.2	13	[a]	[a]	38	0.4	**1.74 (1.16–2.51)**	31	0.4	**1.58 (1.03–2.33)**
Other	456	0.7	80	0.8	1.26 (0.97–1.61)	47	0.4	**0.65 (0.46–0.89)**	27	0.3	**0.49 (0.32–0.73)**
All *in situ*	4,535	7.3	760	6.6	**0.90 (0.83–0.98)**	668	4.4	**0.61 (0.55–0.66)**	145	1.5	**0.21 (0.18–0.25)**

NOTE: IR per 1,000,000, age-adjusted to the 2000 US population standard; RR compared with NHW; statistically significant associations are presented in bold.
Abbreviation: NHW, non-Hispanic whites.
[a]IRs and RRs suppressed because of case counts <16, case counts suppressed when ≤5. Restricted to microscopically confirmed cases.

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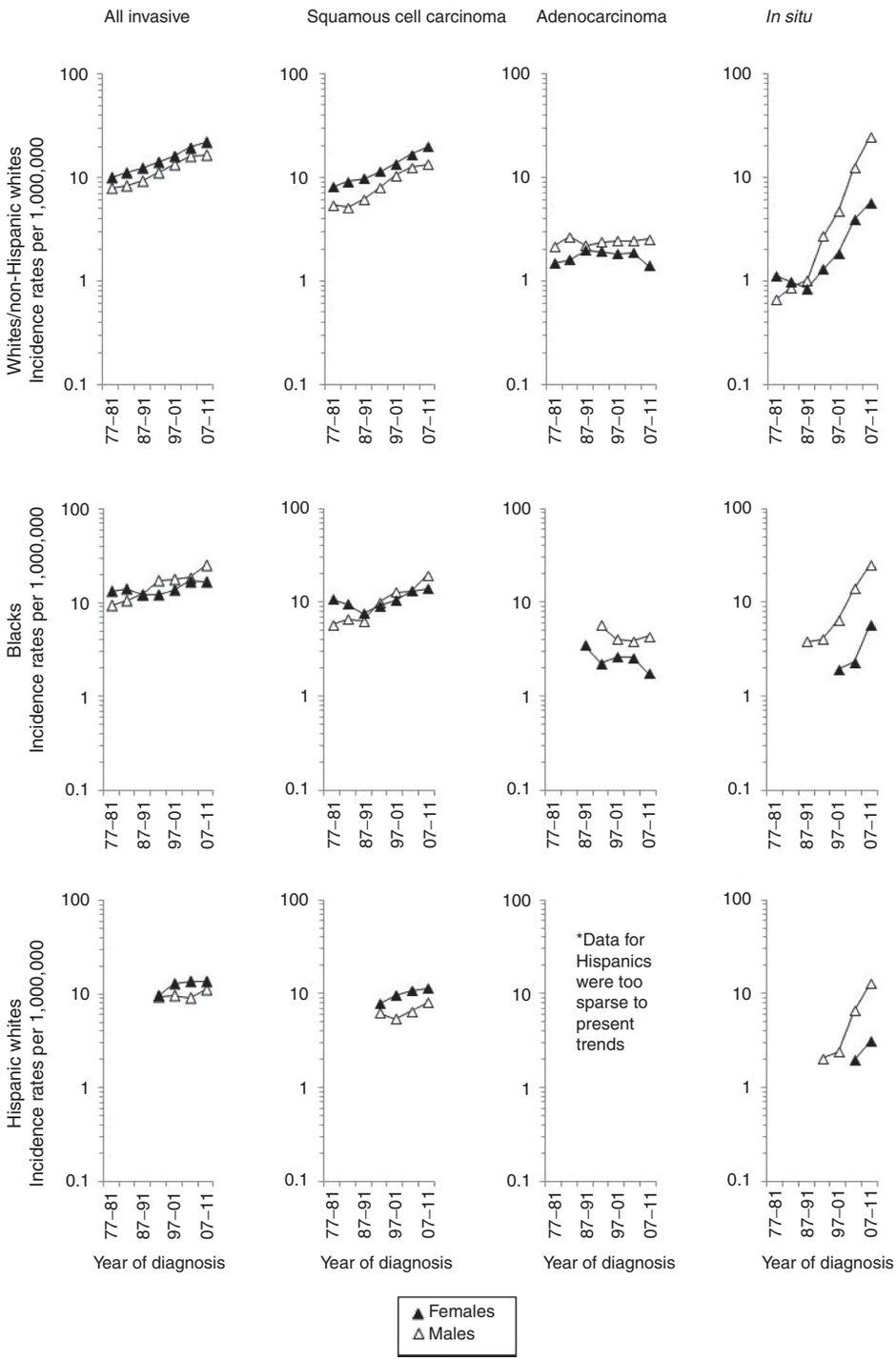

Figure 2.
Age-adjusted anal cancer IRs across calendar years by sex, race, histology, and behavior using data from SEER 13, 1992–2011 and SEER 9, 1977–1991. All rates were age-standardized to the 2000 U.S. population and restricted to microscopically confirmed cases. Rates for whites and blacks are presented using data from SEER 9 during 1977–1991, and rates for non-Hispanic whites, blacks, and Hispanic whites are presented using data from SEER 13, 1992–2011. Solid triangles indicate rates among women and open triangles indicate rates among men. Rates based on <16 cases are excluded.

contrast, there are very limited data on the cause of anal ADC. In a meta-analysis, based on only seven anal ADCs, three were positive for HPV infection (10). Many of the risk factors that have been described for anal cancer reflect infection with or persistence of anal HPV infection, including lifetime number of sexual partners, receptive anal intercourse, and HIV infection (8, 20). Given the predominance of SCCs among anal cancers, these risk factors likely reflect the causal association between HPV infection and anal SCC. In contrast to SCC, little is known about risk factors for anal ADC. Descriptively, anal ADC differs from SCC in case demographics and temporal trends, with higher rates among males, steep increases in rates with age and stable or declining rates over time, providing evidence that ADC is etiologically distinct from SCC.

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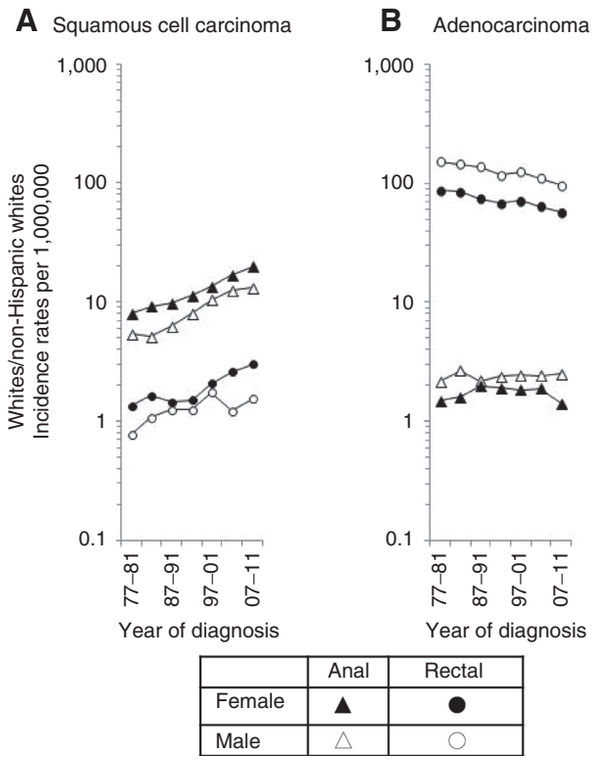

Figure 3.
Age-adjusted invasive IRs among whites/non-Hispanic whites by sex for anal and rectal SCC (A) and anal and rectal ADC (B). Primary sites were defined by *International Classification of Diseases for Oncology*, 3rd edn. (ICD-O-3; anal cancer: C21.0–C21.2, C21.8 and rectal cancer: C20.9). All rates were age-standardized to the 2000 U.S. population and restricted to microscopically confirmed cases. Rates are presented using data for whites from SEER 9 during 1977–1991 and for non-Hispanic whites from SEER 13 during 1992–2011. Triangles (solid for women, open for men) indicate rates of anal cancer and circles (solid for women, open for men) indicate rates of rectal cancer.

Anal SCC IRs are higher among women than men, and consistently lower among Hispanic whites and Asian/Pacific Islanders than among non-Hispanic whites. These differences are likely driven by a higher prevalence of anal infection with carcinogenic HPV among women and non-Hispanic whites. Compared with men, women are more likely to engage in anal receptive intercourse, which is known to be associated with anal HPV infection (21). In addition, transmission of cervical HPV infection to the anus may occur independent of anal intercourse, as those with cervical HPV infection have three times the risk of anal HPV infection (22). Although not established in the literature, it is possible that Hispanics and Asian/Pacific Islanders may also have a lower rate of anal HPV infection than non-Hispanic whites. In the Hawaii Multiethnic Cohort Study, anal and cervical HPV infections (either detected singularly or with infection at both anatomic sites) tended to be more common among Caucasian women compared with women who were Japanese, Hawaiian, or Filipino (22). Increasing rates over time across sexes and race/ethnicities are likely driven by changes in sexual behavior and are consistent with the rise of other HPV-associated cancers (23).

Unlike non-Hispanic whites, anal SCC IRs have been higher in black men than black women in recent years. In addition, among those <40 years old, IRs are higher in men than women, particularly among young, black men. These patterns are consistent with the impact of HIV on anal cancer rates. HIV-infected individuals have a 30-fold increased risk of anal cancer compared with the general population, due to an elevated prevalence of anal intercourse among men who have sex with men and other sexual behaviors leading to increased HPV acquisition and a role of immunosuppression (24, 25). Approximately 28% of male and 1% of female anal cancers in the United States occur among people with HIV (6). The HIV prevalence is particularly high (84%) among anal cancer cases occurring in young, black men (6). In addition, HIV-infected anal cancer cases have contributed strongly to the rising anal cancer rates in men but not women (6). The HIV status of anal cancer cases is not collected by SEER; thus, we could not address HIV directly in the current analysis.

Although anal SCC and ADC differ from each other, they resemble rectal SCC and ADC, respectively, particularly among women. For example, both rectal and anal SCCs are more common among women, and the rates among women have increased for both sites over time. Similarly, both rectal and anal ADCs are more common in men, and rates for both malignancies have declined significantly over time among women. These similarities within histologic types could have multiple explanations, including distinct malignancies arising in the anus and the rectum with similar etiologies and difficulties determining the primary site.

Although rare, rectal SCC and anal ADC may be distinct cancers that share etiologic risk factors with anal SCC and rectal ADC, respectively. There have been case reports of HPV detected in rectal SCC tumors (26, 27), and one small study found 77% of rectal SCCs to be HPV positive (8). Another study showed an increased risk of rectal SCC in HIV-infected individuals, similar to what is observed for anal SCC (28), implicating a potential role of HPV in the development of rectal SCC. In addition, there is limited evidence that Crohn's disease and chronic inflammation may be associated with anal ADC risk, similar to colorectal cancer (29).

Given the juxtapostion of the anus and the rectum, it is also likely that some tumors arising in the anus or the lower part of the rectum would overlap these two anatomic sites. Therefore, anal SCCs may be misclassified as rectal SCCs and the rarer primary anal ADCs may be misclassified rectal ADCs. For example, as nearly half of the ADCs had the primary site designated as overlapping lesion of the rectum, anus, and anal canal, it is possible that many anal ADCs actually arose in the rectum. The anal canal is slightly shorter in women than men, perhaps leading to a greater degree of misclassification consistent with the data in this study (30).

The anal squamous CIS IRs increased dramatically during 1992–2011 across sexes and racial groups and were highest in middle age, likely reflecting the uptake of anal cancer screening in certain geographic areas. The consistency across racial/ethnic groups suggests a lack of racial/ethnic disparities in anal cancer screening, and the higher rates among men than women likely reflect increased anal cancer screening, particularly among men who have sex with men. Several organizations now recommend anal cancer screening for HIV-infected individuals (31). Notably, the anal squamous CIS IR in San Francisco is three to 17 times higher than other registry areas, likely due to the establishment of

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an anal neoplasia clinic at the University of California San Francisco in 1990 (32). It is unclear whether anal cancer screening and subsequent treatment prevents the development of anal cancer; however, the Anal Cancer/HSIL Outcomes Research (ANCHOR) Study (NIH clinical trials identification number: NCT02135419), has been undertaken to directly assess the benefits of treating precancerous anal lesions. Given the rapid increase in anal SCC rates over time, there is an urgent need for prevention and early detection strategies, particularly in high-risk populations. Although HPV vaccination has been shown to protect against anal HPV infection (33, 34), uptake remains suboptimal among adolescents, with only 57% of females and 35% of males receiving at least one dose in 2013 (35). Furthermore, the reduction of anal cancer due to vaccination will not be seen for decades.

The use of high-quality, population-based SEER cancer registry data is the main strength of this analysis. We provide a detailed analysis of rates and trends by primary site, histology and behavior, and, for the first time, provide comparisons between anal and rectal cancer rates by histology. We separate Hispanic whites from non-Hispanic whites during 1992–2011, which is important as the fraction of whites who were of Hispanic ethnicity in SEER 13 increased from 21% in 1992–96 to 28% in 2007–11. In addition, due to the expansion of the SEER Program over time, we used data from both SEER 9 and 13 to assess temporal trends. Although rates were similar in SEER 9 and 13 (Supplementary Fig. S2), changes in IRs between 1977–1991 and 1992–2011 reflect small changes attributable to the inclusions of additional registries with somewhat different population compositions, in addition to changes due to the separation of Hispanic whites and non-Hispanic whites. During 1992–1996, total invasive anal cancer rates among whites were 11.8/million in SEER 9 and 12.3/million in SEER 13, where rates were higher among non-Hispanic whites (12.7/million) compared with Hispanic whites (9.4/million). Rates among blacks were also similar in SEER 9 (14.2/million) and SEER 13 (14.5/million). The main limitation of this analysis is the lack of direct information on HPV or HIV infection and anal cancer screening, important factors that have likely influenced temporal trends. Furthermore, although anal squamous CIS is reportable to SEER registries, because it is primarily detected via screening, it is possible that it is not completely ascertained. Thus, rates of CIS may be underestimated and should be interpreted with caution. Only in San Francisco was the CIS rate higher than the invasive SCC rate, reflecting active screening programs in San Francisco, which are not as prominent in other registry areas.

In an analysis of several decades of U.S. data on anal cancer, we have shown that anal SCC rates have increased rapidly over time. Importantly, we have highlighted the differences in anal SCC and ADC, which likely have different etiologies, and reveal the importance of analyzing these histologic types separately. Furthermore, we have shown the similarity of rectal SCC to anal SCC, which may call for the reclassification of anal and rectal cancer tumors based on their histologies. Finally, we have shown dramatic increases in the detection of anal squamous CIS, presumably reflecting anal cancer screening in certain geographic locations in the United States.

Disclosure of Potential Conflicts of Interest

T.M. Darragh has received speakers bureau honoraria from Roche and Ventana Roche, is a consultant/advisory board member for TheVax, and has provided expert testimony for Hologic. No potential conflicts of interest were disclosed by the other authors.

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Writing, review, and/or revision of the manuscript: M.S. Shiels, A.R. Kreimer, A.E. Coghill, T.M. Darragh, S.S. Devesa
Study supervision: S.S. Devesa

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