

# Human Papillomavirus-Associated Carcinomas in Hawaii and the Mainland U.S.

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**BACKGROUND.** To the authors' knowledge, human papillomavirus (HPV)-associated carcinomas in Hawaii have not been studied in detail.

**METHODS.** Surveillance, Epidemiology, and End Results data (from 1973–1996) were used to study rate of incidence patterns of squamous cell carcinomas (SCCs) of the uterine cervix, vulva/vagina, anus, penis, and palatine tonsils among Asian/Pacific Islanders and whites in Hawaii and among whites in the U.S. in general.

**RESULTS.** With the exception of invasive cervical SCC, male and female Asian/Pacific Islanders in Hawaii had considerably lower incidence rates of HPV-associated SCCs than Hawaii whites and U.S. whites. Among women, Hawaii whites and U.S. whites had rather similar rates of invasive anogenital and tonsillar SCCs, but in situ SCC of the cervix or vulva/vagina was diagnosed less often among Asian/Pacific Islanders and whites in Hawaii than among whites in the general U.S. Among men, Hawaii whites had higher rates than U.S. whites of both anal and tonsillar, but not penile, SCCs. Among Hawaiian men with anal carcinoma, 43% (15 of 35) had remained unmarried versus 3% (2 of 65) of Hawaiian women with anal carcinoma.

**CONCLUSIONS.** Asian/Pacific Islanders in Hawaii generally have lower incidence rates of HPV-associated SCCs than whites. However, low ratios of in situ to invasive cervical SCCs suggest that many Hawaii women, notably Asian/Pacific Islanders, are not diagnosed and treated for cervical neoplasias at a preinvasive stage. The high rate of incidence of anal SCC in male Hawaiian whites and the high proportions of unmarried men among patients with this disease suggest the transmission of HPV through homosexual contact. These men may be targeted in future screening programs for anal carcinoma. *Cancer* 2000;88:1464–9.

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**KEYWORDS:** human papillomaviruses, cervical neoplasms, vulvar/vaginal neoplasms, anal neoplasms, penile neoplasms, tonsillar neoplasms, Hawaii, U.S.

**H**uman papillomaviruses (HPVs) are involved causally in the majority of squamous cell carcinomas (SCCs) of the uterine cervix<sup>1</sup> and anal canal,<sup>2</sup> as well as in a proportion of SCCs of the vulva, vagina, perianal skin, and penis.<sup>3</sup> A percentage of intraoral/mesopharyngeal SCCs also appear to be linked etiologically to HPVs, notably those tumors originating in the palatine tonsils.<sup>4,5</sup> We recently noted that, among whites of both sexes in the U.S., the highest incidence rates for tonsillar SCC were in Hawaii (unpublished data). That observation and the lack of descriptive epidemiologic studies of HPV-associated anogenital SCCs in Hawaii prompted the current investigation. We studied temporal trends in the rate of incidence of HPV-associated anogenital and tonsillar SCCs in Asian/Pacific Islanders and whites in Hawaii and compared these with corresponding trends among U.S. whites in general.

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## MATERIALS AND METHODS

The Surveillance, Epidemiology, and End Results (SEER) Program has collected cancer incidence rate data from designated population-based cancer registries in various areas of the U.S. since 1973. The population covered by SEER was 36 million in 1994, approximately 14% of the U.S. population. SEER cancer data are believed to be representative of the cancer pattern in the entire nation.<sup>6</sup> We studied data for the period 1973 through 1996 from Hawaii (population in 1994: 1.17 million, 69% of whom were Asian/Pacific Islanders, 27% white, 3% Black, and 0.6% American Indian/Aleutian Islander) and from 8 other SEER locations: San Francisco-Oakland, Detroit, Atlanta, Seattle, Connecticut, Iowa, New Mexico, and Utah.

The tumors studied were those with histology codes 8050-8076, 8094, or 8120-8124 (SCC variants); behavior codes 2 (in situ) or 3 (invasive); and topography codes C530-C539 (uterine cervix), C510-C529 (vulva/vagina), C209-C218 (anus), C600-C609 (penis), or C090-C099 (palatine tonsils), according to the International Classification of Diseases for Oncology, Second Edition (ICD-O2).<sup>7</sup> Cancer cases entered into the SEER system under earlier versions of the ICD-O were converted automatically to conform to the ICD-O2 coding system.

For people in Hawaii, we calculated incidence rates separately for whites and for the racial/ethnic category termed "Other" in the SEER system. Data from 1992–1996, for which period a more detailed ethnic categorization is available, show that in Hawaii, people in this "Other" group are comprised of > 99% Asian/Pacific Islanders. Consequently, people in the "Other" group are referred to as Asian/Pacific Islanders in this study. Due to the small numbers of blacks and American Indians/Aleutian Islanders in Hawaii, rate of incidence figures for these groupings are not considered. Age-standardized (U.S. 1970) incidence rates were calculated in 6 4-year calendar intervals for the period 1973–1996. Estimated annual percent change in the incidence rate and tests for linear trend were performed using linear regression by the method of least squares. *P* values < 0.05 (two-sided) were considered statistically significant.

## RESULTS

### Cervical SCC

A total of 857 invasive cervical SCCs and 544 in situ cervical SCCs were diagnosed in Hawaii during the period 1973–1996 (Table 1). Average age-standardized incidence rates of invasive cervical SCC per million person-years were 63.8 in Asian/Pacific Islanders, 68.9 in Hawaii whites, and 62.6 in U.S. whites in general. The rate of incidence of invasive cervical SCCs

dropped by 2.4–2.7% annually in all 3 groups between 1973 and 1996 (all three *P* values for trend < 0.05) (Fig. 1). Incidence rates of in situ cervical SCC were considerably lower in Hawaii, notably among Asian/Pacific Islanders, than among U.S. whites in general (Table 1) (Fig. 1).

Ratios of in situ to invasive cervical SCCs were markedly higher for U.S. whites than for Hawaiian women. This difference was particularly pronounced in age groups that are subject to cervical carcinoma screening. Among U.S. whites ages 20–29 years, nearly 13 cases of in situ cervical SCC were registered for each case of invasive cervical SCC. Corresponding ratios of in situ to invasive cervical SCC in this young age group were only approximately 2:1 among both Hawaii whites and Asian/Pacific Islanders (Table 1). A further breakdown by ethnic group of Asian/Pacific Islanders diagnosed with cervical SCC during 1992–1996 (all age groups combined) showed low in situ to invasive SCCs ratios of 0.4:1 among native Hawaiians (16 in situ cases and 39 invasive cases), 0.1:1 among Filipinos (3 in situ cases and 29 invasive cases), and 0.3:1 among Japanese women (14 in situ cases and 41 invasive cases) compared with 0.9:1 among Hawaii whites (41 in situ cases and 46 invasive cases). Among U.S. whites in general, the corresponding in situ to invasive SCC ratio for this period was 2.0:1 (6209 in situ cases and 3051 invasive cases).

### Vulvar/Vaginal SCC

A total of 106 invasive SCCs of the vulva/vagina and 39 in situ vulvar/vaginal SCC lesions were diagnosed in Hawaii between 1973–1996. Incidence rates of invasive vulvar/vaginal SCC remained relatively stable but were approximately three times higher in both U.S. whites and Hawaii Whites than in Asian/Pacific Islanders (Fig. 2). Incidence rates of vulvar/vaginal SCC in situ increased significantly among U.S. whites during 1973–1996 (*P* value for trend < 0.05) but remained rather constant among women in Hawaii. Among the latter group, the average rate of incidence of vulvar/vaginal SCC in situ was 6 times higher in Hawaii whites (7.9 per million person-years) than in Asian/Pacific Islanders (1.3 per million person-years). Accordingly, the average ratio of in situ to invasive vulvar/vaginal SCC was higher in U.S. whites (0.6:1) than among Hawaii whites (0.5:1) and Asian/Pacific Islanders (0.2:1) (Table 1).

### Anal SCC

Anal SCC was the only HPV-associated invasive carcinoma in U.S. whites whose age-standardized incidence rate increased significantly between 1973–1996 (Fig. 3). Estimated annual increases were 1.5% in women and 2.6% in men (both *P* values for trend < 0.05). Although diagnosed considerably more rarely

**TABLE 1**  
**Numbers and Incidence Rates of SCCs of the Uterine Cervix, Vulva/Vagina, Anus, Penis, and Tonsils in U.S. Whites and Whites and Asian/Pacific Islanders in Hawaii, 1973–1996**

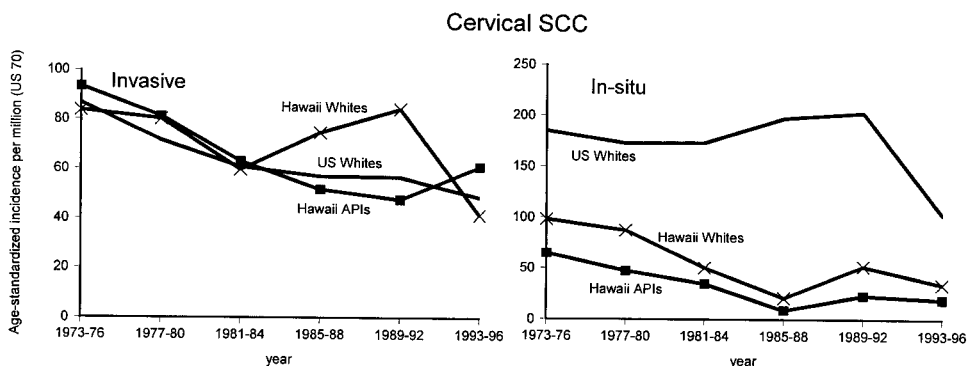
	U.S. whites <sup>a</sup>		Hawaii whites		Hawaii APIs	
	No. of patients	Incidence rate <sup>b</sup>	No. of patients	Incidence rate <sup>b</sup>	No. of patients	Incidence rate <sup>b</sup>
<b>Cervix</b>						
Invasive	16,157	62.6	258	68.9	599	63.8
By age group						
20–29 yrs	1377		35		25	
30–39 yrs	3476		79		128	
40–49 yrs	3064		41		136	
In situ	44,986	170.5	246	54.7	298	30.0
By age group						
20–29 yrs	17,780		69		63	
30–39 yrs	16,230		112		109	
40–49 yrs	5788		36		75	
<b>Vulva/vagina</b>						
Invasive	4792	16.6	56	17.3	50	5.5
In situ	2822	11.1	27	7.9	12	1.3
<b>Anus (invasive)</b>						
Women	2416	9.1	30	10.0	35	3.8
Men	1256	5.8	26	8.3	10	1.2
<b>Penis (invasive)</b>						
	1402	2.9	13	2.2	18	1.0
<b>Tonsil (invasive)</b>						
Women	1487	6.0	36	12.7	16	1.7
Men	3123	14.8	84	27.4	56	6.6

SCC: squamous cell carcinoma; APIs: Asian/Pacific Islanders.

<sup>a</sup> Whites in nine Surveillance, Epidemiology, and End Results registries (San Francisco—Oakland, Detroit, Atlanta, Seattle, Connecticut, Iowa, New Mexico, Utah, and Hawaii).

<sup>b</sup> Average age-standardized (U.S. population 1970) incidence rate per million person-years for the period 1973–1996.

**FIGURE 1.** Incidence rates per million person-years for the period 1973–1996 (standardized to the U.S. population in 1970) for invasive and in situ cervical squamous cell carcinoma (SCC). APIs: Asian/Pacific Islanders.

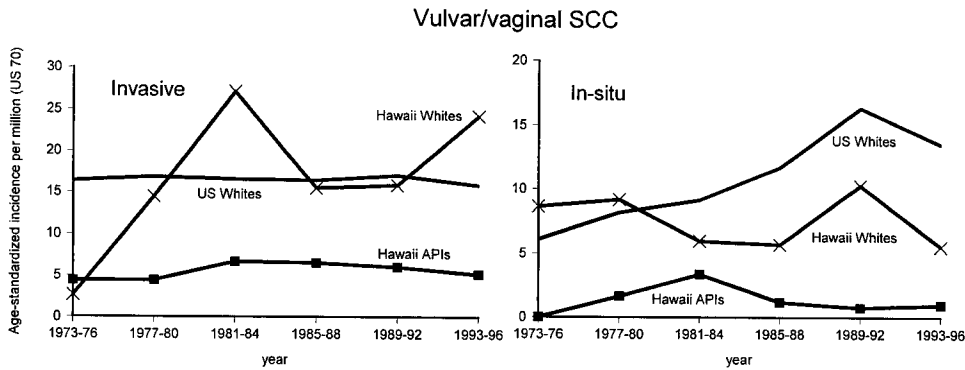


than invasive anal lesions, anal SCC in situ among U.S. whites (161 cases in women and 193 cases in men) exhibited even steeper trends with annual increases in the age-standardized incidence rate of 4.6% in women and 6.6% in men (both *P* values for trend < 0.05).

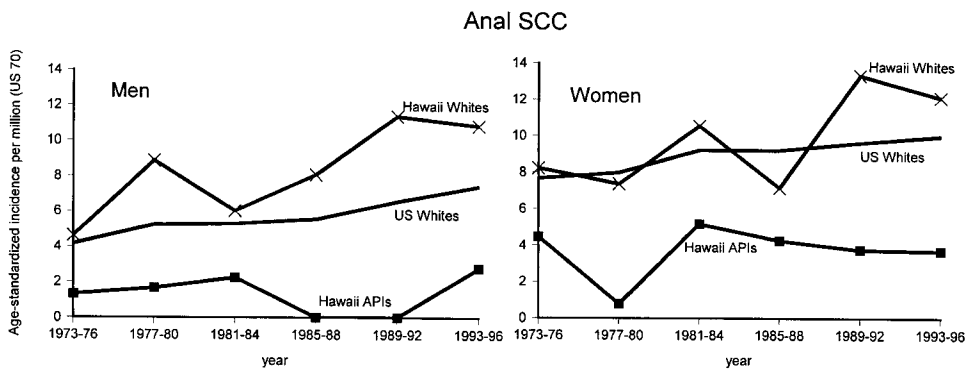
In Hawaii, 101 invasive anal SCCs were diagnosed between 1973–1996 (Table 1). In addition, eight cases of anal SCC in situ (two female Asian/Pacific Islanders and six male whites) were diagnosed. Among men, the age-standardized incidence rates of invasive anal SCC in Hawaii whites was nearly sevenfold higher than in

Asian/Pacific Islanders, and rates among Hawaii whites constantly exceeded those for U.S. whites in general (Fig. 3). Although based on few cases, the average age-standardized incidence rate of anal SCC in situ among men for the period 1973–1996 also was higher among Hawaii whites than among U.S. whites (1.9 vs. 0.8 per million person-years). Among women, Hawaii whites and U.S. whites had consistently higher incidence rates of invasive anal SCC than did Asian/Pacific Islanders in Hawaii (Table 1) (Fig. 3).

Marital status was registered for > 95% of all anal



**FIGURE 2.** Incidence rates per million person-years for the period 1973–1996 (standardized to the U.S. population in 1970) for invasive and in situ vulvar/vaginal squamous cell carcinoma (SCC). APIs: Asian/Pacific Islanders.



**FIGURE 3.** Incidence rates per million person-years for the period 1973–1996 (standardized to the U.S. population in 1970) for invasive anal squamous cell carcinoma (SCC). APIs: Asian/Pacific Islanders.

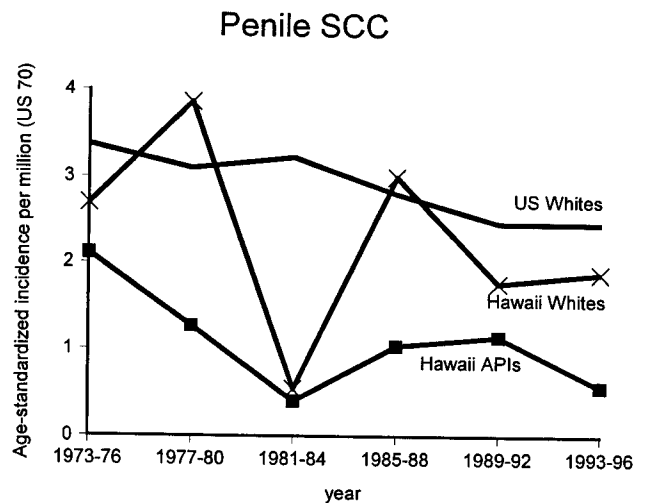
SCC patients in SEER. Among males, high proportions of patients had never been married: 50% (5 of 10) among Asian/Pacific Islanders, 40% (10 of 25) among Hawaii whites, and 35% (430 of 1217) among U.S. whites. In contrast, women with anal carcinoma rarely remained unmarried; 6% (2 of 35) among Asian/Pacific Islanders, 0% among Hawaii whites (0 of 30), and 7% among U.S. whites (152 of 2330).

**Penile SCC**

A total of 31 invasive penile SCCs were diagnosed among Hawaii men between 1973–1996 (Table 1). Similar to the incidence rate of invasive penile SCC in U.S. whites, which dropped significantly over the study period (*P* value for trend < 0.05), there was a tendency toward a decline in this malignancy in Hawaii (Fig. 4), but numbers were unstable. Asian/Pacific Islanders had consistently lower rates than whites.

**Tonsillar SCC**

A total of 192 cases of invasive tonsillar SCC were diagnosed in Hawaii between 1973–1996 (Table 1). Among men, age-standardized incidence rates clearly were higher in Hawaii whites than in Asian/Pacific Islanders, and Hawaii whites experienced higher rates than did U.S. whites. Among women, the age-standardized incidence rate among Hawaii whites

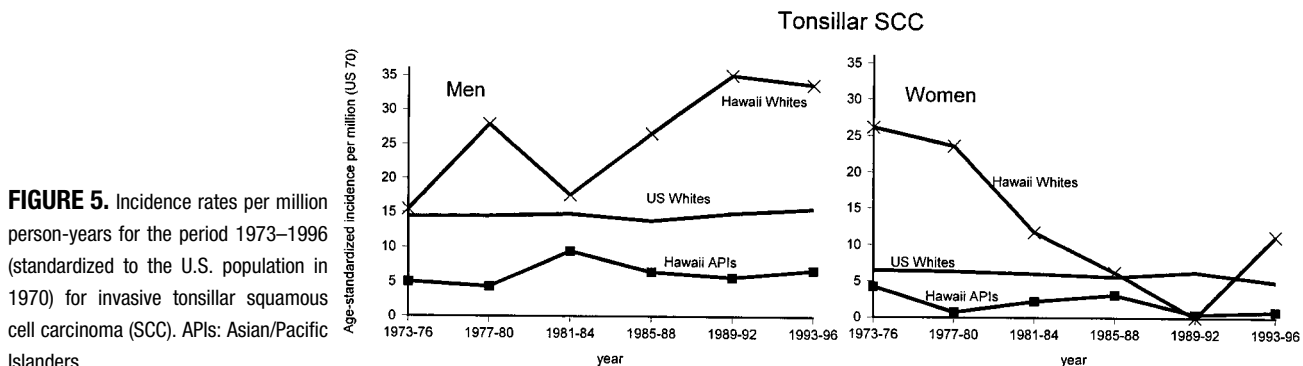


**FIGURE 4.** Incidence rates per million person-years for the period 1973–1996 (standardized to the U.S. population in 1970) for invasive penile squamous cell carcinoma (SCC). APIs: Asian/Pacific Islanders.

dropped from 26.1 to 13.1 per million person-years between 1973–1976 and 1993–1996 (Fig. 5).

**DISCUSSION**

To our knowledge the current study is the first to address temporal rate of incidence patterns for all major HPV-associated cancers. Our data provide a



**FIGURE 5.** Incidence rates per million person-years for the period 1973–1996 (standardized to the U.S. population in 1970) for invasive tonsillar squamous cell carcinoma (SCC). APIs: Asian/Pacific Islanders.

detailed, descriptive epidemiologic scrutiny of SCCs of the anogenital region and palatine tonsils in Hawaii compared with the white population of the U.S. Based on 1287 invasive anogenital and tonsillar SCCs registered over a 24-year period in Hawaii, we found marked differences in HPV-related cancer rates of incidence between Asian/Pacific Islanders and whites in Hawaii and, particularly among men, between Hawaii whites and U.S. whites in general.

Among women, incidence rates of invasive HPV-associated anogenital SCCs in Hawaii whites were rather similar to those for U.S. whites. However, at all sites studied except invasive cervical SCC, Asian/Pacific Islanders in Hawaii had consistently lower incidence rates of both in situ and invasive SCCs. The lower rate of incidence in Asian/Pacific Islanders of carcinomas of the vulva/vagina, anus, penis, and tonsils, for which the influence of screening is not an issue, suggests that the relevant HPVs may be less prevalent in this group than in whites. Behavioral differences are likely, at least in part, to explain the ethnic differences in rates. Asian/Pacific Islanders start sexual activity later and have lower incidence rates of the acquired immunodeficiency syndrome than other ethnic/racial groups in the U.S.<sup>8–10</sup> Because cancer-associated HPVs are transmitted predominantly through sexual contact, such behavioral differences may well have contributed to the lower risk of HPV-associated cancers among Asian/Pacific Islanders. The lower prevalence among Asian/Pacific Islanders of women who smoke and of women who drink two or more alcoholic drinks per day<sup>11,12</sup> also may have contributed. Smoking is believed to be involved etiologically in several of the anogenital carcinomas studied,<sup>13–15</sup> and both tobacco and alcohol presumably are involved in tonsillar carcinogenesis.<sup>16</sup>

Alternatively, the low rate of incidence of HPV-associated, noncervical SCCs in Asian/Pacific Islanders could be due to genetic differences that render this group less susceptible to tumor development after exposure to HPVs. Ethnic differences in lung carcinoma risk appear to be determined, in part, by poly-

morphisms in the CYP1A1 gene.<sup>17</sup> To the extent tobacco smoking also is involved in HPV-associated cancers, polymorphisms in this gene might have contributed to the observed ethnic differences in the rate of incidence of these tumors (unpublished data). Regardless of ethnic differences in the rate of incidence rate of noncervical SCCs in Hawaii are explained by behavioral or genetic differences or a combination of the two, it is interesting to note that invasive cervical SCCs occurred equally frequently in all three groups studied. This, combined with lower ratios of in situ to invasive cervical and vulvar/vaginal SCCs in Hawaii, suggests that Hawaiian women, notably Asian/Pacific Islanders, may be considerably underdiagnosed and undertreated for cervical neoplasia at preinvasive stages. The observation that whites have higher rates of Papanicolaou (Pap) smear screening than other ethnic groups in Hawaii supports this suspicion (unpublished data). Moreover, in the U.S. as a whole, Asian/Pacific Islanders constitute the ethnic group with the highest proportion of women age  $\geq 18$  years who fail to attend regular Pap smear screening programs.<sup>12</sup>

Among men, a relatively large proportion of Hawaii whites appear to have life-styles associated with high risks of both anal and tonsillar SCCs. Anal SCC is known to occur in excess among homosexual men.<sup>18</sup> The high rate of incidence of invasive anal SCC therefore may reflect the existence of an active community of homosexual white men in Hawaii. Except for the San Francisco-Oakland area, which is known to have a large homosexual population,<sup>19</sup> Hawaii had a higher rate of incidence of anal SCC among white men than any other area studied (data not shown). High proportions of these men, but not women with anal SCC, had remained unmarried. Further characterization of this group of white men is warranted if anal carcinoma screening programs in high risk homosexual/bisexual men are to be implemented.<sup>20</sup>

Similar to anal carcinoma, tonsillar SCC occurred in excess among Hawaii whites. Although risk factor studies of oral and pharyngeal carcinomas have not provided causal clues specifically for tonsillar SCCs,<sup>21</sup>

it is likely that the major risk factors acting at other oral and pharyngeal sites, notably tobacco and alcohol,<sup>16</sup> also are involved in a considerable proportion of tonsillar SCCs. Lower consumption of tobacco and alcohol in Asian/Pacific Islanders<sup>11,12</sup> thus may partly explain the lower risk of tonsillar SCC in this group. Recently, tonsillar SCC has been linked etiologically to the types of HPV that cause carcinoma in the anogenital region.<sup>4,5,22,23</sup> However, at present it is not known whether the high and increasing rate of incidence observed among white men in Hawaii is due to increasing proportions of HPV-associated tonsillar SCCs.

In contrast to anal and tonsillar SCCs, Hawaii whites did not experience any unusual rate of incidence of penile SCC compared with U.S. whites but, again, Asian/Pacific Islanders were at lower risk. This lack of an excess in Hawaii whites is not in opposition to our other findings in men. Penile SCC is the anogenital carcinoma studied with the weakest association to HPVs,<sup>3</sup> and unlike anal carcinoma, penile SCC is not strongly linked to male homosexuality.

Patterns of HPV-associated anogenital and tonsillar SCCs differ considerably between Asian/Pacific Islanders and whites in Hawaii. Generally, Asian/Pacific Islanders are at lower risk of HPV-associated carcinomas than whites, suggesting major differences in behavior or/and genetic susceptibility between these populations. Compared with U.S. whites in general, low ratios of in situ to invasive cervical SCC in Asian/Pacific Islanders and, to a lesser extent, Hawaii whites, deserve further scrutiny because this may reflect considerable underdiagnosis of preinvasive cervical neoplasia in Hawaii. Among Hawaii whites, the high rate of incidence of anal SCC in men most likely reflects the existence of an active homosexual community that might be targeted in future screening programs for anal carcinoma.

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