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Incidence of potentially HPV-related neoplasms in the United States, 1978–2007

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Abstract

Background—Population-based studies comprehensively describing incidence patterns of human papillomavirus (HPV)-related preinvasive and invasive neoplasms prior to widespread HPV vaccination are sparse.

Methods—We calculated age-adjusted incidence rates (IRs), IR ratios (IRRs), and annual percent changes (APC) in IRs for potentially HPV-related tumors diagnosed in the Surveillance, Epidemiology and End Results Program during 1978–2007.

Results—Overall IRs for preinvasive tumors were significantly higher than for invasive squamous cell tumors of cervix (IRR=3.42), vulva (IRR=1.87), and vagina (IRR=1.19) and significantly lower for adenomatous cervical tumors (IRR=0.43), and squamous cell tumors of penis (IRR=0.64), anus (males, IRR=0.53; females, IRR=0.14), and head and neck (H&N) (males, IRR=0.01; females, IRR=0.02). Incidence of preinvasive squamous tumors of cervix, vagina, and penis rose rapidly over time and decreased for invasive neoplasms. The most rapid increases occurred for preinvasive (males, APC=16.0; females, APC=7.3) and invasive anal tumors (males, APC=3.6; females, APC=2.3). IR patterns were generally similar among evaluable racial/ethnic groups, with the exception of H&N invasive tumor IRs which increased exclusively among white males.

Conclusion—Contrary to the opposing trends of preinvasive and invasive squamous tumors of cervix, vagina, and penis, preinvasive and invasive anal tumor IRs increased significantly over time by gender, age, and racial/ethnic groups. Successful HPV vaccination programs are needed to measurably reduce incidence of HPV-related neoplasms in the future, particularly for cancer sites with rising incidence rates for which effective screening modalities are limited.

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Keywords

HPV-associated neoplasms; preinvasive tumors; cancer incidence; epidemiology; squamous cell neoplasms

In 2006, the U.S. Food and Drug Administration approved the human papillomavirus (HPV) vaccine for females 9–26 years to protect against cervical, vulvar, and vaginal cancers caused by HPV types 16 and 18 and genital warts caused by HPV types 6 and 11.¹ This was followed by the approval of the vaccine in 2009 for males 9–26 years for the prevention of genital warts due to HPV types 6 and 11. Population-wide interventions can have notable and immediate impacts on disease incidence rates (IRs). One recent study suggested that a decrease in the incidence of high-grade cervical abnormalities observed in Australia was linked to implementation of a population-wide HPV vaccination program.²

Considerable efforts have been made to estimate the burden of HPV-related cancers so that the impact of vaccination can be assessed.³ Based upon review of the world literature, the estimated proportion of cancers of the cervix, anus, vagina, oropharynx, vulva, and penis in the U.S. attributable to HPV are 96%, 93%, 64%, 63%, 51%, and 36%, respectively.³ Despite the importance of detection and treatment of preinvasive disease burden and its potential impact on subsequent invasive carcinoma, few studies have assessed preinvasive and invasive disease IRs simultaneously.^{4–7}

We comprehensively assessed incidence of potentially HPV-related tumors prior to widespread HPV vaccination and describe disease patterns, identify high-risk groups, and evaluate baseline trends prior to this public health intervention. As exemplified by the recently proposed lower anogenital squamous standardization (LAST) terminology,⁸ histopathologic nomenclature is dynamic and undergoes refinement to allow standardized, reproducible, and biologically and clinically relevant diagnoses. We acknowledge the limitation of changing terminology over time, particularly for preinvasive or premalignant disease that includes carcinoma in situ (CIS), intraepithelial neoplasia (CIN), and intraepithelial lesions, and therefore include these entities within an all-encompassing category of “preinvasive” disease. We include data through 2007 because recommendations for HPV vaccination in the U.S. were published in that year.⁹

Methods

Utilizing data from the National Cancer Institute’s Surveillance, Epidemiology and End Results (SEER) Program, we describe incidence of squamous cell tumors of the cervix (cervix-squamous), vagina, vulva, penis, anus, potentially HPV-related head and neck (H&N) sites,¹⁰ and adenomatous tumors of the cervix (cervix-adeno). We included all cases diagnosed among residents of the nine cancer registry areas (SEER-9) during 1978–2007. SEER-9 includes five states (Connecticut, Hawaii, Iowa, New Mexico, and Utah) and the areas of Detroit, Michigan; San Francisco, California; Seattle-Puget Sound, Washington; and Atlanta, Georgia and includes approximately 10% of the U.S. population. Information on expanded racial/ethnic groups began to be collected in 1992 and at the same time the SEER Program also expanded to include 13 cancer registry areas (SEER-13), which

represent nearly 14% of the U.S. population and include the SEER-9 cancer registry areas; Los Angeles and San Jose, California; rural Georgia; and the Alaska Native Tumor Registry. Incidence data were derived from the Incidence-SEER-9 and SEER-13 Registries Research Data released April 2011 (updated October 28, 2011) based on the November 2010 submission.^{11, 12}

Since 2001, the SEER Program has classified histology and topography information according to the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3).¹³ Tumors classified prior to 2001 using earlier versions of ICD-O have been centrally recoded to ICD-O-3. We included all cases of microscopically confirmed, malignant or invasive (behavior code /3) and preinvasive (behavior code /2) squamous cell (ICD-O-3 morphology codes M-8050-8084), basaloid (M-8123), and cloacogenic (M-8124) tumors of potentially HPV-related sites: cervix (ICD-O-3 topography codes C53.0-53.9), vagina (C52.9), vulva (C51.0-51.9), penis (C60.0-60.9), anus (C21.0-21.8), and, as previously defined,¹⁰ H&N (base of tongue, C01.9; lingual tonsil, C02.4; tonsil, C09.0-09.9; oropharynx, C10.0-10.9; and Waldeyer's ring, C14.2). Because of the known association with HPV, we also separately evaluated IRs of adenomatous neoplasms (M-8140-8490) of the cervix (cervix-adeno). The SEER Program only required collection of information on preinvasive tumors of the cervix through 1995 and preinvasive tumors of the penis through 2000; therefore data in our study were limited to 1978–1995 for preinvasive cervical tumors and 1978–2000 for preinvasive penile tumors.

We calculated age-adjusted IRs, IR ratios (IRRs), and 95% confidence intervals (CIs) using SEER*Stat software (version 7.0.4). All IRs were age-adjusted to the 2000 U.S. population and expressed per 1-million person-years. IRs were calculated according to gender, age, race (SEER-9: whites, blacks, other/unspecified; SEER-13: non-Hispanic whites, blacks, Hispanic whites, Asian/Pacific Islanders (APIs), other/unspecified), and calendar year.

Age-specific IRs were calculated for eight age groups (<15, 15–24, 25–34, 35–44, 45–54, 55–64, 65–74, 75+ years), age-adjusted within age group, and depicted on a log-linear scale as previously described.¹⁴ Age-adjusted temporal trends were estimated for six 5-year calendar year periods (1978–1982, 1983–1987, 1988–1992, 1993–1997, 1998–2002, and 2003–2007) and depicted on a log-linear scale such that a slope of 10 degrees portrays a rate change of 1% per year.¹⁴ For preinvasive cervical and penile tumors, IRs were calculated for four (1978–1982, 1983–1987, 1988–1992, 1993–1995) and five (1978–1982, 1983–1987, 1988–1992, 1993–1997, and 1998–2000) calendar year periods, respectively. Temporal trends were calculated overall and according to age or racial/ethnic groups. Annual percent change (APC) and significance testing were calculated using the weighted least squares method. According to the convention of the SEER Program, IRs associated with fewer than 16 cases are not presented, and only curves with 3 or more consecutive points are presented.

Results

Among females, the IRs for preinvasive neoplasms were highest for cervix-squamous (IR=264.4 per 1-million female-years), vulva (IR=30.1), and vagina (IR=5.8), whereas IRs for invasive neoplasms were highest for cervix-squamous (IR=77.3), vulva (IR=16.1),

cervix-adeno (IR=14.6), and H&N sites (IR=12.8) (Table 1). Among males, preinvasive tumor IRs of the penis (IR=5.0 per 1-million male-years) and anus (IR=4.1) exceeded that of H&N sites (IR=0.5). In contrast, the incidence of invasive neoplasms of H&N sites (IR=43.6) far exceeded that for cancers of the penis (IR=7.9) and anus (IR=7.7). Overall IRs for preinvasive tumors were significantly higher than for invasive tumors for cervix-squamous (IRR=3.42), vulva (IRR=1.87), and vagina (IRR=1.19), whereas for all other sites, the IRs for invasive neoplasms were significantly higher than for preinvasive tumors. Across all sites, preinvasive-to-invasive IRRs decreased with advancing age (data not shown). Preinvasive tumors of H&N sites were exceedingly rare among all age groups and all racial/ethnic groups, with IRs only 1–2% those of invasive tumors.

Age-specific IR patterns for preinvasive neoplasms generally increased rapidly at young ages and then plateaued or even decreased at older ages, with the exception of preinvasive neoplasms of the penis that increased progressively with advancing age (Figure 1). A prominent peak in incidence with subsequent decline was apparent for preinvasive neoplasms of cervix-squamous (peak age 25–34 years), cervix-adeno (peak age 35–44 years), vulva (peak age 45–54 years), and anus (males) (peak age 35–44 years). IRs for invasive neoplasms of cervix-squamous, cervix-adeno, anus (males, females), and H&N sites (males, females) rose exponentially at younger ages and plateaued or decreased at older ages. In contrast, IRs for invasive neoplasms of vagina, vulva, and penis increased progressively with age.

The IRs for preinvasive neoplasms increased rapidly over time for cervix-squamous, (APC=6.9; 1978–1995), vagina (APC=5.6; 1978–2007), and penis (APC=3.1; 1978–2000), and decreased for invasive neoplasms at these sites between 1978–2007 (APC=–2.6, –1.7, and –1.1, respectively) (Figure 2). The IRs increased more prominently for preinvasive than invasive tumors for cervix-adeno, vulva, and anus (males, females). The H&N IRs for invasive tumors rose among males while declining modestly among females.

With the exception of H&N sites, preinvasive tumor IRs for cervix-squamous, cervix-adeno, vagina, vulva, penis, and anus (males, females) rose over time among all evaluable age groups, with little variation in the rates of increase within each site (Figure 3). Incidence patterns of invasive tumors were more varied, with IRs declining or stable for squamous cancers of the cervix-squamous, vagina, penis, and H&N (females). Overall, the IRs rose for vulvar cancers among women (45–64 years), H&N cancers among men especially those aged 25–64 years, and for anal cancers among men and women.

Temporal patterns for preinvasive and invasive tumors for most sites generally followed similar patterns among racial/ethnic groups (Figure 4). The notable exceptions to this were the IRs for H&N cancers which increased among white males, changed little among white females, and decreased among blacks of both genders, Hispanic white males, and APIs.

Discussion

This is among the first studies to comprehensively describe preinvasive and invasive carcinoma IRs at sites most frequently associated with HPV infection. Except for H&N

sites, we describe a significant rise in incidence of preinvasive tumors of cervix-squamous, cervix-adeno, vagina, vulva, penis, and anus (males, females), with the most rapid increases noted for anal tumors among both sexes. The observed increases in IRs of preinvasive tumors were apparent across all evaluable age groups and racial/ethnic groups. Contrary to the decline in IRs observed for cancers of cervix-squamous, vagina, and penis, invasive H&N IRs among males and anal tumor IRs among males and females and most age and racial/ethnic groups continued to increase significantly over time.

Although national screening guidelines for HPV-related sites are limited to cervical cancer, it is plausible that visualized abnormalities at other anogenital sites would be detected in women undergoing cervical cancer screening, thereby potentially influencing preinvasive and invasive IRs at non-cervical sites. The peak incidence of preinvasive squamous cervical neoplasms between ages 25–34 years is notably younger than for preinvasive tumors of vagina, vulva, and anus. This finding suggests a longer latency and/or later detection for these non-cervical neoplasms, likely due to the absence of formal screening measures, thereby necessitating sufficient time for larger and/or symptomatic lesions to develop. Cervical and anal carcinoma age-specific IRs rose rapidly at younger ages and plateaued at older ages, suggesting that relevant exposures occur earlier in life and/or rates are affected by early detection and treatment of precursor lesions at younger ages. In contrast, IRs for invasive carcinoma of the vagina and vulva increased progressively with advancing age, a pattern well described for the multi-step model of carcinogenesis, with progressive accumulation of genetic damage over time. The potential role of other, non-HPV-related etiologies is suggested by the smaller fraction of vaginal and vulvar cancers that are associated with HPV than cervical and anal cancers.³

Similar to our findings, previous SEER-based reports of penile cancer describe a decreasing incidence over time.^{15, 16} This temporal trend is similar to that in some,^{17, 18} but not all,^{18, 19} international cancer registry studies. The risk of penile cancer is significantly increased in individuals with AIDS, with risk rising over time since AIDS diagnosis and remaining approximately 5-times higher than in the general population during the era of highly active antiretroviral therapy.²⁰ The rising incidence of preinvasive squamous penile neoplasms we report is consistent with findings from other SEER-based (1973–1998)²¹ and European (1989–2006) studies.¹⁹ A similar increase in incidence of preinvasive penile lesions among individuals with AIDS has been reported in the U.S.²² The continued rise in incidence with advancing age suggests that other risk factors may contribute to preinvasive disease at older ages. Indeed penile cancer has only partially been attributed to HPV infection, with other factors also considered etiologically relevant.²³

The more rapid increases in preinvasive anal tumors among males than females during 1978–2007 has resulted in IRs among males that are more than twice those among females overall. While increasing HPV exposure may account for the exponential rise of preinvasive anal neoplasm IRs over time, the rise may also be attributed to improved recognition and reporting of preinvasive lesions since the description of anal intraepithelial neoplasia (AIN) in 1985 and AIN grading in 1986.²⁴ Invasive anal cancer is one of the few cancer sites that predominate among women.^{5, 25} We found that the female predominance of invasive anal cancer was apparent overall, at ages < 45 years, and among all racial/ethnic groups except

blacks. Risk factors for anal cancer include HIV infection and sexual practices associated with increased HPV transmission; however, the role of HIV in rising anal cancer IRs appears limited to males.²⁶ Although anal cancer is not an AIDS-defining malignancy, in the U.S. individuals with HIV have a 29-fold increased risk of anal cancer compared to the general population.²⁷ The early-onset peak in incidence of preinvasive anal neoplasms among males (35–44 years) may reflect increased awareness and early detection among high-risk populations. Between 1991–1995 and 2001–2005 the burden of anal cancer increased by more than 7-fold among HIV-infected individuals,²⁷ suggesting that the incidence of this cancer is unaffected by highly active antiretroviral therapy.²⁰ Recent reports of decreased prevalence of HPV among women²⁸ and men who have sex with men²⁹ undergoing HPV vaccination, and decreased recurrence of high-grade AIN among HPV-vaccinated men who have sex with men³⁰ suggest that IRs of preinvasive and invasive neoplasms of the anus may decrease in the future. Although anal cancer screening among high-risk populations has been advocated by some,³¹ the natural history and rate of progression of AIN to carcinoma may differ from cervical disease, and therefore extrapolation of screening modalities for cervical cancer to anal cancer may be inappropriate.³²

In contrast to the other sites described, preinvasive tumors of the H&N were rare. In a recent study using a “pap-test equivalent”, oropharyngeal squamous cell carcinoma but not tonsillar dysplasia was detected among individuals with tonsillar or oral HPV infection.³³ The inability to detect squamous epithelial dysplasia may have been due to tonsillar cancers arising from deep within the tonsillar crypts in areas relatively inaccessible to this type of screening.³³ This finding suggests that pap testing at this site may be of limited value as a screening modality. This is of particular concern given that by 2020, without intervention, the number of HPV-associated oropharyngeal cancers are estimated to exceed the number of cervical cancers.³⁴ Our findings of invasive H&N cancers confirm those reported by others,^{10, 35} with a notable rise in IRs among males.

The strength of our study is the population-based analysis that avoids biases associated with clinical series. Limitations include the absence of a centralized pathology review and lack of information on HPV tumor status. Nevertheless, prior studies using SEER Program data have demonstrated distinct incidence patterns for presumed HPV-related and HPV-unrelated oral squamous cancers.^{10, 35} In addition, we cannot exclude the possibility of underreporting of cases to the cancer registries, particularly for neoplasms diagnosed in an outpatient setting and for preinvasive disease, for which there may be less awareness of reporting requirements. Nevertheless, our data represent conservative estimates of disease burden.

In summary, we describe age and temporal patterns for preinvasive and invasive neoplasms of the major sites known to be associated with HPV infection in the pre-vaccination era. In particular, the exponential rise in IRs of anal tumors among men and women and H&N carcinomas among males supports an urgent need for prevention efforts. While it is difficult to disentangle the influence of screening/early detection and other non-HPV risk factors that vary by age, gender, race/ethnicity, and sexual preference, ultimately a slowing/reversal of the upward trend in the incidence of preinvasive and subsequently of invasive tumors, would support a vaccination effect. Unfortunately recent data indicate that in the two years

following the licensure of the HPV vaccine in the U.S., only 15.2% of females 11–26 years of age reported HPV vaccination initiation, of which 37.2% completed the series of vaccines.³⁶ Provided that there is widespread adherence to HPV vaccination guidelines, monitoring HPV disease trends, age patterns, and cohort effects in the post-HPV vaccination era will enable assessment of the effectiveness of this public health intervention and underscores the importance of continuing data collection on preinvasive and invasive tumors at disease sites where this remains feasible.

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Figure 1.

Age-specific incidence rates of preinvasive and invasive adenomatous tumors of the cervix and squamous cell tumors of the cervix, vagina, vulva, penis, anus, and potentially HPV-related head and neck sites (H&N) diagnosed in SEER-9 during 1978–2007 by gender.

Figure 2. Age-adjusted trends of preinvasive and invasive adenomatous tumors of the cervix and squamous cell tumors of the cervix, vagina, vulva, penis, anus, and potentially HPV-related head and neck sites (H&N) diagnosed in SEER-9 during 1978–2007 by gender.

Figure 3.

Age-adjusted trends of preinvasive and invasive adenomatous tumors of the cervix and squamous cell tumors of the cervix, vagina, vulva, penis, anus, and potentially HPV-related head and neck (H&N) sites diagnosed in SEER-9 during 1978–2007 by gender and age group. *Note:* There were too few cases of H&N tumors among males and females to plot.

Figure 4.

Age-adjusted trends of preinvasive and invasive adenomatous tumors of the cervix and squamous cell tumors of the cervix, vagina, vulva, penis, anus, and potentially HPV-related head and neck (H&N) sites by gender diagnosed in SEER-9 during 1978–2007 for whites and blacks and in SEER-13 during 1992–2007 for Hispanics (white) and Asian/Pacific Islanders (APIs). *Note:* There were too few cases of H&N tumors among females to plot.

Table 1

Gender-specific age-adjusted incidence rates, incidence rate ratios, and annual percent change of preinvasive and invasive adenomatous neoplasms of cervix and squamous cell neoplasms of cervix, vagina, vulva, penis, anus, and presumed human papillomavirus (HPV)-related head and neck sites diagnosed in nine cancer registry areas of the Surveillance, Epidemiology and End Results Program, 1978–2007*

Preinvasive		Invasive		Preinvasive:invasive		Preinvasive		Invasive	
No.	IR	No.	IR	IRR (95% CI)	APC (95% CI)	APC (95% CI)	APC (95% CI)	APC (95% CI)	APC (95% CI)
Cervix (1978–1995)									
<i>Squamous histology</i>									
Females	60,665	264.4	15,677	77.3	3.42 (3.36, 3.48)	6.9 (4.8, 9.1)	–2.2 (–2.6, –1.8)		
<i>Adenomatous histology</i>									
Females	1,307	6.3	2,918	14.6	0.43 (0.40, 0.46)	13.7 (12.2, 15.3)	2.2 (1.3, 3.1)		
Vagina (1978–2007)									
Females	2,158	5.8	1,867	4.9	1.19 (1.12, 1.27)	5.6 (4.7, 6.6)	–1.7 (–2.2, –1.1)		
Vulva (1978–2007)									
Females	11,048	30.1	6,107	16.1	1.87 (1.81, 1.93)	4.0 (3.3, 4.6)	0.6 (0.2, 1.0)		
Penis (1978–2000)									
Males	1,136	5.0	1,610	7.9	0.64 (0.59, 0.69)	3.1 (2.1, 4.1)	–1.2 (–2.1, –0.2)		
Anus (1978–2007)									
Males	1,402	4.1	2,449	7.7	0.53 (0.49, 0.57)	16.0 (13.5, 18.5)	3.6 (3.0, 4.2)		
Females	545	1.5	4,087	11.0	0.14 (0.13, 0.15)	7.3 (5.6, 9.0)	2.3 (1.8, 2.8)		
Potentially HPV-related head and neck (1978–2007)									
Males	150	0.5	13,864	43.6	0.01 (0.01, 0.01)	0.1 (–1.9, 2.1)	1.5 (1.2, 1.9)		
Females	89	0.2	4,792	12.8	0.02 (0.01, 0.02)	#	–1.1 (–1.5, –0.7)		

Abbreviations: No., number of cases; IR, incidence rate; IRR, IR ratio; CI, confidence interval; APC, annual percent change; #, APC is not calculated for sites with at least one annual rate of zero.

* Incidence rates are age-adjusted to the 2000 U.S. standard population and expressed per 1-million person-years. IRRs are based on unrounded rates. Data for preinvasive and invasive cervical and penile tumors are limited to calendar years 1978–1995 and 1978–2000, respectively, so that preinvasive-to-invasive IRRs are comparable. APC values are significant ($P < 0.05$) if the 95% CI excludes zero.