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Cancers Associated with Human Papillomavirus, Illinois, 2008-2012

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INTRODUCTION

Human papillomavirus (HPV) has been shown to have a causal role in nearly all cervical cancers and in many vaginal, vulvar, penile, anal, and oropharyngeal cancers.[1] An individual's own immune system will clear most HPV infections within one-two years. However, some infections do persist and can result in pre-cancer or cancer. In Illinois, public health prevention of cervical cancer includes both secondary prevention through cervical cancer screening and primary prevention through the HPV vaccination. Three vaccines (bivalent, quadrivalent and 9-valent) are available to protect against HPV types 16 and 18, which are found in 70% of cervical cancers. HPV type 16 is the most common HPV type and is found in the five other sites often associated with HPV.[2] Incidence rates of HPV-associated cancers, those cancers at specific anatomic sites and with specific cell types in which HPV DNA is frequently found, were examined by utilizing the Illinois State Cancer Registry (ISCR) data from 2008 through 2012.

METHODS

Cancer incidence data was analyzed for all Illinois residents on cancers diagnosed between 2008 and 2012. ISCR has attained the North American Association of Central Cancer Registries Gold certification for the past 17 years (1996-2012) and is a Centers for Disease Control and Prevention (CDC) - National Program of Cancer Registries "Registry of Excellence". Temporal trends in HPV-associated cancer were examined by site for 2003 through 2012. The case definition of HPV-associated cancers was guided by published consensus around the anatomic sites (cervix, vagina, vulva, penis, anus, and oropharynx) and the cell types (carcinoma of the cervix and squamous cell carcinoma in the other sites) in which HPV DNA is frequently found. All cases were microscopically confirmed. The definition of oropharynx in this analysis was narrowed further to specific sites where HPV DNA is most likely to be found: base of tongue, tonsils and "other oropharynx".[3] See Table 1 in the Appendix for a complete listing of ICD-O-3 codes used in selecting cases for analysis.

Cancer data were analyzed by sex, age, race, and Hispanic ethnicity. Race categories included white, black, and other (Asian/Pacific Islander, American Indian or Native Alaskan, and other and unknown race). Totals include other and unknown races. American Indian and Native Alaskan data were enhanced through data linkage with Indian Health Service administrative records. The Hispanic ethnic category included persons identified as being Hispanic in the ISCR data or by use of the Hispanic identification algorithm.[4] Age-adjusted rates were calculated per 100,000 persons in SEER Stat and were standardized to the 2000 U.S. Standard population.[5] Significant differences between rates were noted at the $p<0.05$ level. Because ISCR does not routinely collect information on HPV status and since HPV-associated cancers are defined by cell type and specific anatomic site, the data contained in this report might include cancers not caused by HPV.

The true number of cancer cases that are due to HPV cannot be accurately estimated and this analysis does not attempt to provide that information. Rather it provides information on cancers at sites that are believed to be primarily HPV associated. Table 2 displays estimates of the percent of cases by site that are attributable to HPV for the U.S. and then applies them to observed HPV-associated cases in Illinois. For this analysis the number of HPV-associated cancers was multiplied by the percentage of

each cancer type found attributable to HPV based on genotyping studies at a national level. To be clear, the numbers of HPV-attributable cancers are estimates based upon available information in literature at the time this report was written.

RESULTS

Overall, there were 7,997 HPV-associated cancers diagnosed in Illinois residents during 2008-2012 (11.7 per 100,000 people): 4,939 among females (13.9) and 3,058 among males (9.3). The total number of HPV-related cancers accounted for 4.8% of all cancer diagnoses in 2008-2012: 3.0% among females and 1.8% among males. Oropharyngeal cancer was the most common of the HPV-associated sites with 3,035 cases during 2008-2012 (2,444 in males and 591 in females). Cervical cancer was the second most common during the time period with 2,671 cases. Males experienced a rate of oropharyngeal cancer (7.3 per 100,000) over 4 times that of females (1.6). The rate of anal cancer was higher in females (1.8) than in males (1.2) with the exception of blacks where the rate in black males (2.3) was higher than black females (1.6). Black females exhibited higher rates of cervical carcinoma (12.1) compared to white women (7.1). Hispanic females displayed a higher rate of cervical carcinoma (10.6) compared to Non-Hispanic females (7.7). The other race grouping (Asian, Pacific Islander, American Indian, Native Alaskan, other, and unknown races) displayed lower rates than whites and blacks in all HPV-associated sites, except for cervical carcinoma.

Multiplying the number of HPV-associated cancers by the percent attributable to HPV[6], it is estimated that during 2008-2012 6,070 cancers attributable to HPV occurred in Illinois residents, including 4,100 in females and 1,970 in males. Cervical and oropharyngeal cancers were the most common of these with an estimated 2,560 and 1,910 Illinois cases respectively during 2008-2012. Table 2 displays estimates for HPV-attributable cancers for all HPV-associated sites.

Ten-year trends for HPV-associated sites by gender in Illinois are presented in Figures 1 and 2. Outside of oral cancer in males and cervical cancer, the trends for the remaining HPV-associated sites in both males and females were quite flat and exhibited little change over the time period. However, HPV-associated oral cancer in males increased significantly from 5.5 per 100,000 in 2003 to 7.2 per 100,000 in 2012. Conversely, HPV-associated cervical cancer rates dropped significantly from 9.2 per 100,000 to 6.7 per 100,000. Examination of male HPV-associated oropharyngeal cancer showed relatively flat trends for black men and men of other races. White men displayed a significant increase in incidence rates over the time period rising from 5.3 cases per 100,000 in 2003 to 7.5 per 100,000 in 2012 (42% increase, Figure 3). The rate of 7.5 per 100,000 in 2012 for white men was higher than that of both black and other race males. Figure 4 shows that HPV-associated cervical cancer rates declined for all racial groups during the time period with significant declines seen in both white (23% decline) and black women (37% decline).

DISCUSSION

This analysis shows that 4,939 HPV-associated cancers occurred in Illinois women between 2008-2012, making these cancers, as an aggregate group, similar in magnitude to melanoma among females. In Illinois males, the burden was smaller with 3,058 HPV-associated cancers, making these numbers roughly equivalent to those of liver cancer in males during 2008-2012. An important primary prevention method aimed at HPV-associated cancers is the use of an HPV vaccine. Three vaccines

(bivalent, quadrivalent, and 9-valent) are available to protect against HPV 16 and 18; the types of HPV that are associated with cervical and other anogenital cancers as well as some oropharyngeal cancers. These vaccines have been shown to be effective in preventing cervical pre-cancer; quadrivalent and 9-valent vaccines have been show to prevent vaginal, vulvar, and anal pre-cancer. Because HPV 16 is responsible for the majority of non-cervical cancers caused by HPV, it is possible that the vaccines may also protect against other non-cervical HPV-associated cancers.

The CDC Advisory Committee on Immunization Practices (ACIP) recommends, "routine HPV vaccination be initiated at age 11 or 12 years. The vaccination series can be started beginning at age 9 years. Vaccination is also recommended for females aged 13 through 26 years and for males aged 13 through 21 years who have not been vaccinated previously or who have not completed the 3-dose series. Males aged 22 through 26 years may be vaccinated (vaccination is also recommended through age 26 years for men who have sex with men and for immunocompromised persons (including those with HIV infection) if not vaccinated previously). Vaccination of females is recommended with bivalent, quadrivalent, or 9-valent vaccines. Vaccination of males is recommended with the quadrivalent or 9-valent HPV vaccine types." The National Immunization Survey estimated that, in 2013, 33.8% of Illinois females (37.6% U.S.) and 16.5% of males (13.9% U.S.) aged 13-17 had received three doses of HPV vaccine.[7]

Most cases of cervical cancer are preventable with regular screening for pre-cancerous lesions (e.g. Papanicolau test) and follow up of abnormal results. According to the Illinois Behavioral Risk Factor Surveillance System, in 2012, 91.5% of Illinois women over the age of 18 have had a Pap test. The U.S. Preventive Services Task Force recommends cervical cancer screening for women 21 to 65 years old. A Pap test should be performed once every three years or, for women over 30, screening with a Pap test and HPV DNA test every 5 years is another option.[8] Non-cervical cancer sites included in the HPV-associated definition do not have approved screening programs; therefore HPV vaccines are important prevention tools to reduce the incidence of the cancers.

The reason for differences in the rates of non-cervical HPV-associated cancers by race and ethnicity are not clear but might be explained by differences in screening practices, demographics, tobacco use, or other factors that influence HPV infection or persistence. HPV-associated oropharyngeal cancers, while defined narrowly, might be attributable to variations in smoking and alcohol use rather than, or in combination with, HPV infection. Studies around the interaction between smoking, alcohol and HPV infections have been uncertain.[9]

This report is limited in at least three ways. First, not all cancers termed "HPV-associated" reflect actual HPV infections, and the numbers judged to be HPV-attributable are in fact estimates. Uncertainties are inherent in these estimates and in the numbers that were calculated or projected based on these estimates. This may be particularly true for age- and race/ethnicity-specific breakdowns where a same estimate was applied across sub-groups. Second, data from the Illinois State Cancer Registry are subject to rigorous reporting requirements and require multiple steps in collecting and preparing the data for public use. Because of this stringent quality control the most recent data are several years old. And finally, ISCR does not typically collect information on HPV status or other risk

factors such as smoking or alcohol use that may have a role in the development of HPV-associated tumors.

Of the 7,997 cancers that occurred in 2008-2012 at anatomic sites associated with HPV, approximately 6,070 can be attributed to HPV and might have been prevented through the use of an HPV vaccine. Ongoing surveillance of HPV-associated cancers using a high quality population-based registry is necessary to monitor trends in incidence that may result from increasing use of HPV vaccines in Illinois, changes in cervical cancer screening practices, and changes in behaviors that influence HPV infection, persistence, and progression to pre-cancer.

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APPENDIX

TABLE 1: Definitions for Site and Histology*

Site	ICD-O-3 Site Code	ICD-O-3 Histology Code
Cervix Uteri	C53	All carcinomas
Endo Cervix	C53.0	
Exocervix	C53.1	
Overlapping lesion of cervix uteri	C53.8	
Cervix Uteri	C53.9	
Vagina	C52	Squamous cell carcinoma
Vagina, NOS	C52.9	
Vulva	C51	Squamous cell carcinoma
Labium majus	C51.0	
Labium minus	C51.1	
Clitoris	C51.2	
Overlapping lesion of vulva	C51.8	
Vulva, NOS	C51.9	
Anus, anal canal and anorectum	C21	Squamous cell carcinoma
Anus, NOS	C21.0	
Anal canal	C21.1	
Cloacogenic zone	C21.2	
Overlapping lesion of anus, anal canal, and anorectum	C21.8	
Rectum	C20.9	
Penis	C60	Squamous cell carcinoma
Prepuce (foreskin)	C60.0	
Glans penis	C60.1	
Body of penis	C60.2	
Overlapping lesion of penis	C60.8	
Penis, NOS	C60.9	
Base of tongue and lingual tonsil		Squamous cell carcinoma
Base of tongue, NOS	C01.9	
Lingual tonsil	C02.4	
Tonsil (including Waldeyer ring)		Squamous cell carcinoma
Tonsillar fossa	C09.0	
Tonsillar pillar	C09.1	
Overlapping lesion of tonsil	C09.8	
Tonsil , NOS	C09.9	
Waldeyer ring	C14.2	
Other oropharynx, potentially HPV-associated		Squamous cell carcinoma
Overlapping lesion of tongue	C02.8	
Lateral wall of oropharynx	C10.2	
Overlapping lesion of oropharynx	C10.8	
Oropharynx, NOS	C10.9	
Pharynx, NOS	C14.0	
Overlapping lesion of lip, oral cavity, and pharynx	C14.8	

ICD-O-3, International Classification of Diseases for Oncology, 3rd Edtion; NOS, not otherwise specified

**Watson M, Saraiya M, Ahmed F, et al. Using population-based cancer registry data to assess the burden of human papillomavirus-associated cancers in the United States: overview of methods. Cancer 2008;113:2841-54.*

All carcinomas defined as ICD-O-3 histology codes 8010-8671, 8940-8941.

Squamous cell carcinomas defined as ICD-O-3 histology codes 8050-8084, 8120-8131

TABLE 2: Estimated number of cancers attributable to human papillomavirus by site and gender, Illinois, 2008-2012

Site	% U.S. Estimate Attributable to HPV**		Observed Cases in Illinois*	Estimated Number Attributable to HPV in Illinois***	
	%	*CI Range*	*#*	*#*	*CI Range*
Cervix	96	(95-97)	2,671	2,560	(2,537-2,591)
Vulva	51	(37-65)	800	410	(296-520)
Vagina	64	(43-82)	185	120	(80-152)
Penis	36	(26-47)	235	80	(61-110)
Oral					
male	63	(50-75)	2,444	1,540	(1,222-1,833)
female	63	(50-75)	591	370	(296-443)
Anus					
male	93	(86-97)	379	350	(326-368)
female	93	(86-97)	692	640	(595-671)
TOTAL			7,997	6,070	

** Source: Illinois State Cancer Registry, data as of November 2014*

** Source: Gillison ML, Chaturvedi AK, Lowy DR, HPV Prophylactic vaccines and the potential prevention of non-cervical cancers in both men and women. Cancer 2008; 113(10 Suppl):3036-46.

*** Estimates were obtained by multiplying the HPV-associated cancer counts by the percentage of each cancer attributable to HPV. Estimates were rounded to the nearest 10.

HPV-Human papillomavirus CI- 95% Confidence Interval

TABLE 3: HPV Associated Age-Adjusted Cancer Rates per 100,000 by site, age, race/ethnicity, Illinois, 2008-2012

	Cervical Carcinoma			Vaginal and Vulvar Squamous Cell Carcinoma			Penile Squamous Cell Carcinoma		
CHARACTERISTIC	**RATE**	**95% CI**	**COUNT**	**RATE**	**95% CI**	**COUNT**	**RATE**	**95% CI**	**COUNT**
Illinois	7.9	7.6-8.2	2,671	2.6	2.5-2.8	985	0.8	0.7-0.9	235
Age Group									
0-19	0.0	0.0-0.1	1	0.0		0	0.0	0	0
20-29	2.9	2.4-3.4	130	0.1	0.0-0.2	4	0.0	0.0-0.1	1
30-39	10.2	9.3-11.3	435	0.9	0.7-1.3	39	0.2	0.1-0.3	7
40-49	15.3	14.2-16.5	698	2.2	1.8-2.7	105	0.5	0.3-0.8	24
50-59	14.1	13.0-15.2	627	4.7	4.1-5.4	209	0.8	0.6-1.2	36
60-69	13.6	12.3-15.0	417	6.0	5.1-6.9	181	1.9	1.4-2.5	52
70-79	12.3	10.8-14.0	228	10.9	9.5-12.6	202	4.1	3.1-5.3	58
80+	9.1	7.6-10.7	135	15.8	13.9-17.9	245	6.9	5.2-8.9	57
Race									
White (referent)	7.1	6.8-7.5	1,916	2.7	2.5-2.9	833	0.8	0.7-0.9	201
Black	12.1*	11.1-13.1	609	2.6	2.2-3.1	131	0.8	0.5-1.2	28
Other	7.9	6.6-9.4	146	1.3*	0.8-2.0	21	0.5	0.1-1.0	6
Ethnicity									
Non-Hispanic (referent)	7.7	7.4-8.0	2,306	2.7	2.5-2.9	933	0.8	0.7-0.9	207
Hispanic	10.6*	9.4-11.8	365	2.6	1.9-3.4	52	1.0	0.6-1.6	28

Sources: Illinois State Cancer Registry, data as of November 2014; U.S. Bureau of Census Population Estimates Program, intercensal and Vintage 2013 bridged single-race estimates

HPV-Human Papillomavirus

* Rate significantly different from referent group

TABLE 3 (cont.): HPV Associated Age-Adjusted Cancer Rates per 100,000 by site, age, race/ethnicity, Illinois, 2008-2012

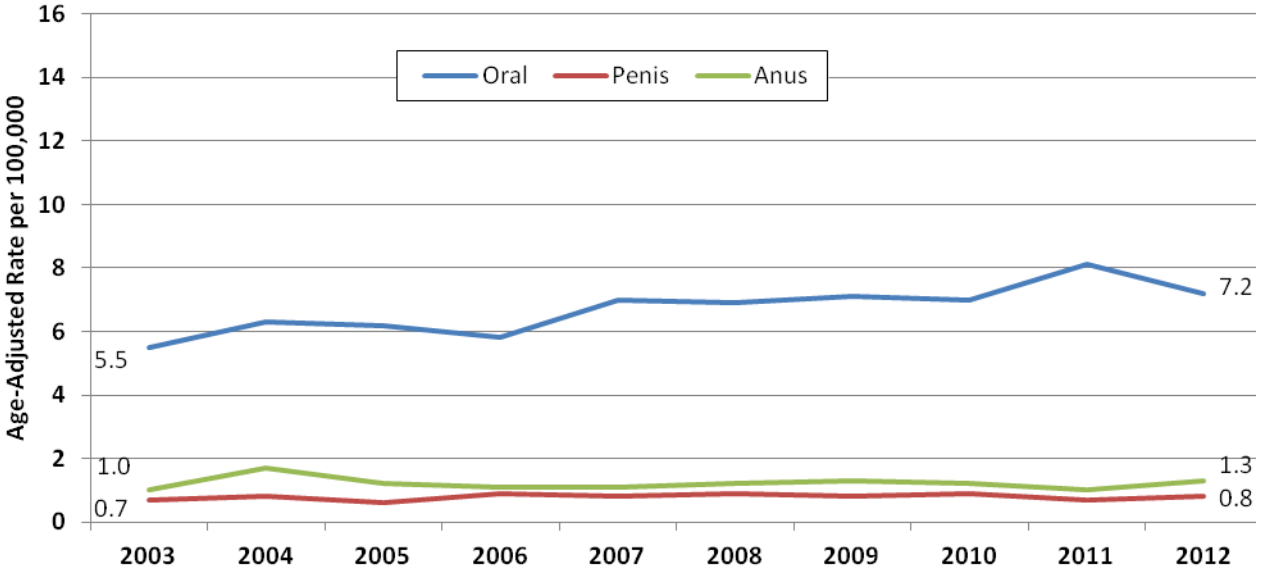
	Anal Squamous Cell Carcinoma						Oropharyngeal Squamous Cell Carcinoma					
	MALE			FEMALE			MALE			FEMALE		
CHARACTERISTIC	**RATE**	**95% CI**	**COUNT**	**RATE**	**95% CI**	**COUNT**	**RATE**	**95% CI**	**COUNT**	**RATE**	**95% CI**	**COUNT**
Illinois	1.2	1.1-1.3	379	1.8	1.7-2.0	692	7.3	7.0-7.6	2,444	1.6	1.5-1.7	591
Age Group												
0-19	0.0	0	0	0.0	0	0	0.0	0.0-0.1	1	0.0	0	0
20-29	0.1	0.0-0.2	4	0.0	0.0-0.1	0	0.1	0.0-0.2	4	0.0	0.0-0.1	1
30-39	0.5	0.3-0.8	22	0.5	0.3-0.7	20	0.7	0.5-1.1	31	0.2	0.1-0.4	9
40-49	1.9	1.5-2.4	87	1.9	1.5-2.4	91	6.7	6.0-7.5	312	1.6	1.2-2.0	75
50-59	2.6	2.1-3.1	111	4.8	4.2-5.5	216	22.4	21.0-23.9	955	3.6	3.0-4.2	159
60-69	2.9	2.3-3.7	80	5.7	4.8-6.6	173	26.2	24.3-28.1	718	6.3	5.5-7.3	192
70-79	3.1	2.2-4.1	44	5.6	4.6-6.8	104	22.1	19.8-24.7	323	5.4	4.4-6.6	100
80+	3.7	2.5-5.3	31	5.8	4.6-7.1	88	11.9	9.7-14.5	100	3.7	2.8-4.8	55
Race												
White (referent)	1.1	0.9-1.2	278	2.0	1.8-2.1	602	7.5	7.2-7.8	2,110	1.6	1.5-1.8	491
Black	2.3*	1.9-2.9	94	1.6	1.2-2.0	80	6.9	6.1-7.8	277	1.6	1.3-2.0	86
Other	0.5	0.2-1.0	7	0.6*	0.3-1.2	10	4.1*	3.0-5.4	57	0.7*	0.4-1.3	14
Ethnicity												
Non-Hispanic (referent)	1.3	1.1-1.4	358	1.9	1.7-2.0	653	7.6	7.3-8.0	2,343	1.7	1.5-1.8	572
Hispanic	0.7	0.4-1.1	21	1.5	1.0-2.1	39	3.5	2.8-4.3	101	0.7	0.4-1.1	19

Sources: Illinois State Cancer Registry, data as of November 2014; U.S. Bureau of Census Population Estimates Program, intercensal and Vintage 2013 bridged single-race population estimates

HPV-Human Papillomavirus

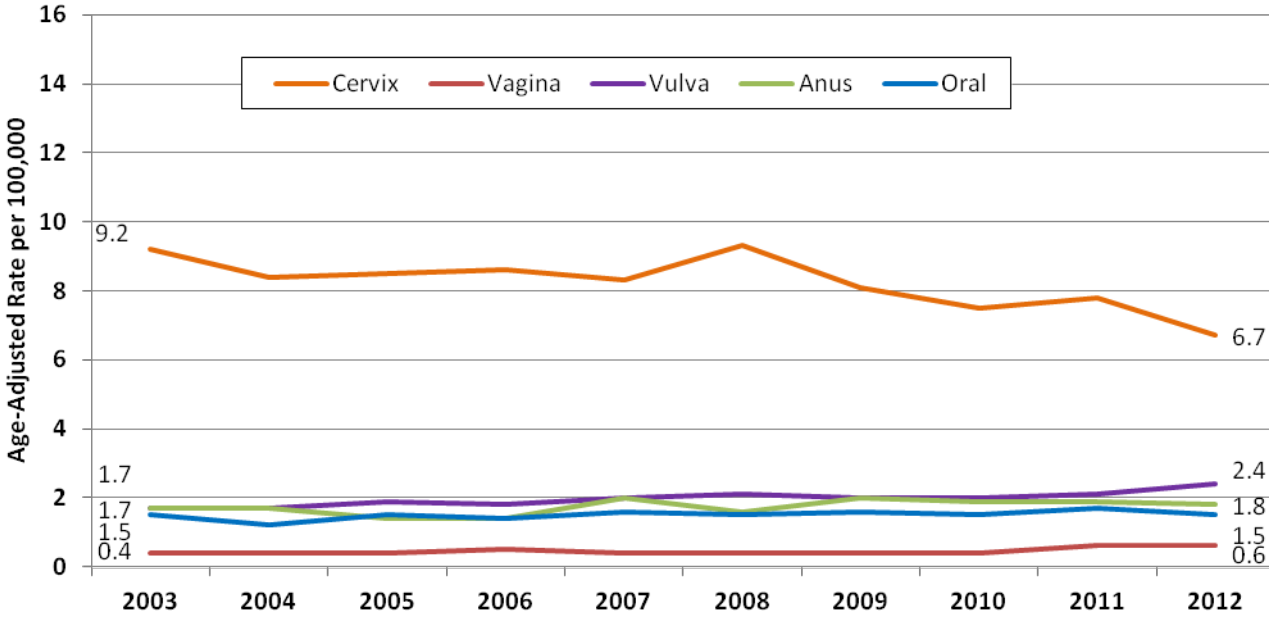
* Rate significantly different from referent group

Figure 1: Human Papillomavirus Associated Cancer Incidence in Illinois Males by Site, 2003-2012



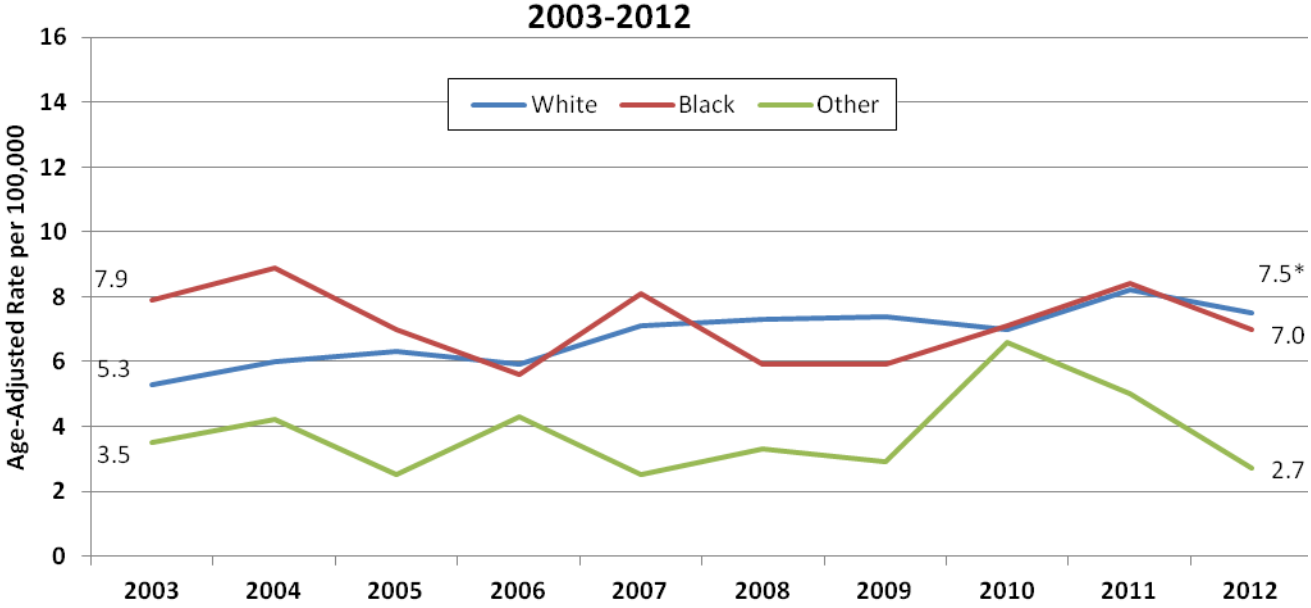
Source: Illinois State Cancer Registry, data as of November 2014 ; HPV-Human Papillomavirus
** Rate significantly different compared to 2003*
***HPV-associated cancers are as defined in: Watson M, Saraiya M, Ahmed F, et al. Using population-based cancer registry data to assess the burden of human papillomavirus-associated cancers in the United States: overview of methods. Cancer 2008; 113:2841-54.*

Figure 2: Human Papillomavirus Associated Cancer Incidence in Illinois Females by Site, 2003-2012



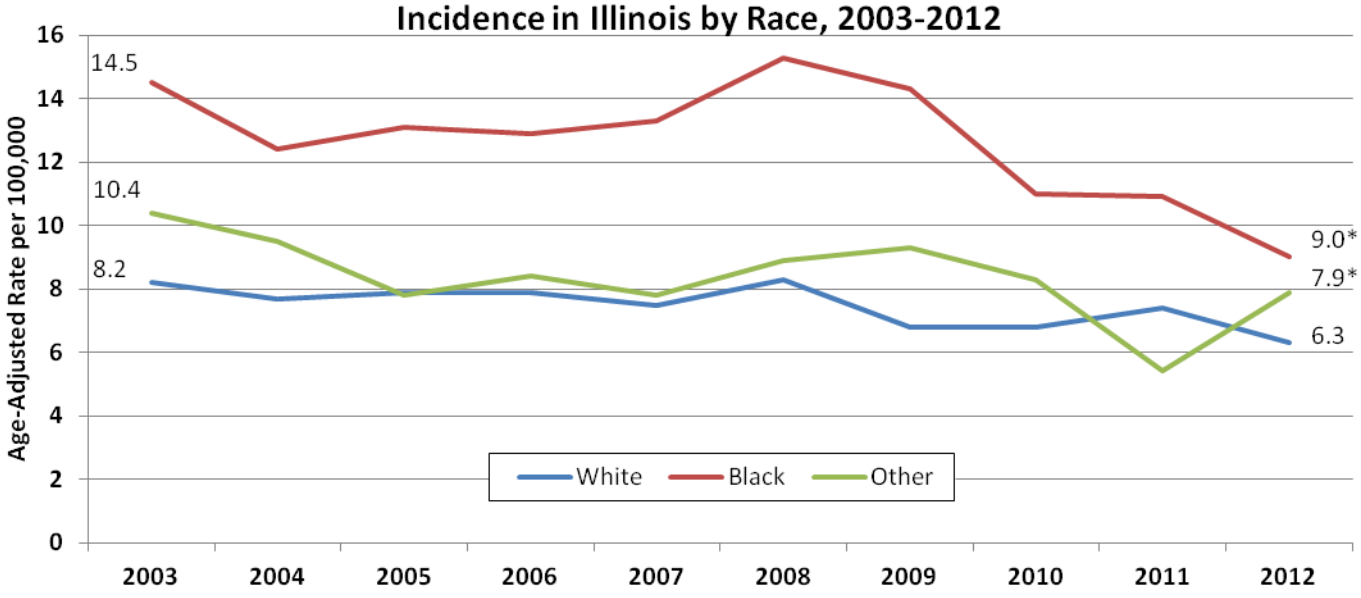
Source: Illinois State Cancer Registry, data as of November 2014 ; HPV-Human Papillomavirus
** Rate significantly different compared to 2003*
***HPV-associated cancers are as defined in: Watson M, Saraiya M, Ahmed F, et al. Using population-based cancer registry data to assess the burden of human papillomavirus-associated cancers in the United States: overview of methods. Cancer 2008; 113:2841-54.*

Figure 3: Human Papillomavirus (HPV) Associated** Oropharyngeal Cancer Incidence in Illinois Males by Race, 2003-2012



Source: Illinois State Cancer Registry, data as of November 2014; HPV-Human Papillomavirus
** Rate significantly different compared to 2003*
***HPV-associated cancers are as defined in: Watson M, Saraiya M, Ahmed F, et al. Using population-based cancer registry data to assess the burden of human papillomavirus-associated cancers in the United States: overview of methods. Cancer 2008; 113:2841-54.*

Figure 4: Human Papillomavirus (HPV) Associated** Cervical Cancer Incidence in Illinois by Race, 2003-2012



Source: Illinois State Cancer Registry, data as of November 2014; HPV-Human Papillomavirus
** Rate significantly different compared to 2003*
***HPV-associated cancers are as defined in: Watson M, Saraiya M, Ahmed F, et al. Using population-based cancer registry data to assess the burden of human papillomavirus-associated cancers in the United States: overview of methods. Cancer 2008; 113:2841-54.*