Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world-wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Kristin M. Vahle 2/28/2020

Prevalence of human papillomavirus among US females older than recommended age for vaccination by birth cohort, National Health and Nutrition Examination Survey 2003-2016

By

Kristin M. Vahle

Master of Public Health

Global Epidemiology

Dr. Robert A. Bednarczyk

Committee Chair

Dr. Julia W. Gargano

Committee Member

Prevalence of human papillomavirus among US females older than recommended age for vaccination by birth cohort, National Health and Nutrition Examination Survey 2003-2016

By

Kristin M. Vahle

B.Sc., University of Missouri, 2012

Faculty Thesis Advisor: Robert A. Bednarczyk, PhD

An abstract of

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of

Master of Public Health

in Global Epidemiology

2020

Abstract

Prevalence of human papillomavirus among US females older than recommended age for vaccination by birth cohort, National Health and Nutrition Examination Survey 2003-2016

By Kristin M. Vahle

Background: Human papillomavirus (HPV) prevalence among population-based samples of females older than recommended vaccination age has not been studied extensively. Understanding prevalences in these ages could be useful context as females eligible for vaccination advance to these ages. Associations between HPV prevalence and age in cross-sectional surveys could be confounded by cohort differences in HPV exposures. We evaluated HPV prevalences by age overall and by birth cohort and evaluated associations between HPV prevalence and characteristics by birth cohort among females 27-59 year born in 1950-1979 from National Health and Nutrition Examination Survey (NHANES) 2003-2016.

Methods: NHANES data from females with adequate HPV typing results from self-collected cervicovaginal swabs were analyzed. Weighted proportions and 95% confidence intervals (CI) of demographic and behavioral characteristics were measured overall and for 1950-1959, 1960-1969, and 1970-1979 birth cohorts. Weighted prevalences and 95% CIs of any HPV, high-risk HPV, and non-high-risk HPV were estimated by 3-year age groups, overall and by birth cohort. Unadjusted and age-adjusted prevalence ratios and 95% CIs for any HPV and characteristics were estimated by birth cohort with log-binomial regression.

Results: Prevalence was 38.5% for any HPV, 18.1% for HR HPV, and 30.6% for non-HR HPV. Significant declines in prevalence were observed per 3-year age increase for any HPV (APC: -2.86%), HR HPV (APC: -6.40%), and non-HR HPV (APC: -2.02%). Adjusting for age, interaction between age and cohort on prevalence was not significant (p-value > 0.05 for all HPV group types). Associations between most characteristics and any HPV were similar in each cohort after adjusting for age.

Conclusions: We found no evidence of a cohort effect on any HPV, HR HPV, and non-HR HPV as the relationship of prevalence and age did not vary by birth cohort. We also found associations between any HPV prevalence and many characteristics, including marital status, age at sexual debut, number of lifetime partners, and others, did not vary by birth cohort controlling for age; only race/ethnicity varied. Lack of a cohort effect on age-specific prevalence suggests that declines in HPV prevalence with age observed in cross-sectional studies are attributable to differences in age rather than cohort.

Prevalence of human papillomavirus among US females older than recommended age for vaccination by birth cohort, National Health and Nutrition Examination Survey 2003-2016

By

Kristin M. Vahle

B.Sc., University of Missouri, 2012

Faculty Thesis Advisor: Robert A. Bednarczyk, PhD

A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of

Master of Public Health
in Global Epidemiology
2020

Acknowledgements:

Many thanks to my advisors, Dr. Julia W. Gargano and Dr. Robert A. Bednarczyk, as well as the HPV Team at CDC, especially Dr. Lauri Markowitz and Rayleen Lewis, for their mentorship, guidance, and collaboration on this project. Additional thanks to my friends, family, and fellow Rollins students for supporting me throughout my masters' degree.

Table of Contents

Chapter I: Background

HPV overview, natural history, and disease burden

Human papillomavirus (HPV) is the most common sexually transmitted infection (STI); infections with certain non-oncogenic types cause genital warts, and persistent infection with oncogenic types can lead to cancer (1). An estimated 79 million persons globally are infected with HPV, and 14 million persons are newly infected every year (2). HPV-related cancers include cervical, vaginal, vulvar, anal, penile, and oropharyngeal cancers (3). In the US, 33,160 HPV-associated cancers were diagnosed from 2006 to 2010 with 62% of HPV-associated cancers occurring in females (1).

HPV is most commonly transmitted through genital contact, primarily through sexual intercourse, though nonsexual transmission, such as intrapartum transmission, is possible but rare (2). There are over 150 types of HPV that have been identified with approximately 40 types infecting the genital area (4). Most sexually active individuals will acquire at least one type of HPV during their lifetime (3).

Many HPV infections are transient and asymptomatic resolving without intervention in one to two years (5-7). About 70% of persons with new cervical HPV infections clear the infection within a year (5). Yet, persistent HPV infection can lead to HPV-related disease (8). HPV types are classified as high-risk (HR) and non-high-risk (non-HR, sometimes called low-risk) according to their oncogenic potential (9). The International Agency for Research on Cancer classifies 12 HPV types as carcinogenic to humans, HPV 16/18/31/33/35/39/45/51/52/56/58/59 (3). In clinical cervical screenings, commercially available HPV tests include these 12 types and an additional two types, HPV66 and HPV68, which IARC designates as possibly and probably carcinogenic, respectively (1).

Essentially all cervical cancers are attributable to HR HPV types, and HPV16 and 18 cause 70% of all cervical cancers (8, 10). Meanwhile, genital warts are primarily caused by HPV6 and HPV11, which are non-HR types (11).

HPV Vaccination History in United States

In the United States, the Food and Drug Administration (FDA) licenses vaccines and the Advisory Committee on Immunization Practices (ACIP) determines vaccination policy (12). In mid-2006, the first HPV vaccine was licensed by the FDA, a quadrivalent vaccine targeting HPV 6/11/16/18 (12). Since then, routine vaccination for females at age 11 or 12 has been recommended by the ACIP (13). The quadrivalent vaccine originally was recommended for routine use on a 3-dose schedule in females 9-26 years (13). In 2009, the FDA licensed the quadrivalent vaccine for a 3-dose schedule in males 9-26 years and a bivalent vaccine, targeting types 16 and 18, for a 3-dose schedule in females 9-26 years (13). Also in 2009, the ACIP recommended use of bivalent vaccine for females in addition to the quadrivalent vaccine recommendation from 2006 (6, 13). In 2011, the ACIP recommended routine HPV vaccination for males by the quadrivalent vaccine at age 11 or 12 with catch-up until age 21 (13). In 2014, a nonavalent vaccine targeting HPV types 6/11/16/18/31/33/45/52/58 was licensed by the FDA for a 3-dose schedule in males and females (13). In 2015, the ACIP added the nonavalent vaccine to the list of recommended vaccines which then included the nonavalent, quadrivalent, and bivalent vaccine for females and the nonvalent and quadrivalent vaccine for males (13). In 2016, the ACIP recommended a 2-dose series for those initiating vaccination at ages 9-14 years (13). Since late 2016, the nonavalent vaccine has been the only HPV vaccine

distributed in the US (12). In mid-2019, the ACIP updated recommendations for catch-up vaccination to include all persons through age 26 (6). While vaccination after age 26 is not recommended, vaccination among those aged 27 to 45 is permissible through shared decision making between provider and patient (1). HPV vaccination is most effective when administered before HPV exposure, ideally before sexual debut (1).

HPV vaccines are highly effective, safe, and reduce the incidence of HPV infection (6). The quadrivalent and nonavalent vaccines have efficacies greater than 90% against cervical intraepithelial neoplasia grade 2+ among females 15-26 years who had no evidence of past or current HPV infection (3). As of 2016, HPV vaccination coverage has been increasing, yet coverage remains lower than other vaccines recommended for adolescents (13). In 2018, coverage of greater than or equal to 1 dose of HPV vaccine was 68.1% according to the National Immunization Survey-Teen (14). The US vaccination program has resulted in significant declines in vaccine-type HPV prevalence, anogenital warts, and cervical precancers (6). Given the long natural history of HPV infection and HPV-related disease, especially HPV-associated cancers, the full impact of vaccine on total disease burden may not be seen for decades.

HPV Epidemiology

Epidemiologists study detection of HPV DNA in genital swabs and other biologic specimens, interpreted as prevalent HPV infections, to better understand disease risk factors, patterns across populations, natural history of disease, and vaccine impact and effectiveness. While many studies have examined HPV prevalence among young adults for the purpose of evaluating impact of the HPV vaccination program, few US-based

studies have reported HPV prevalence among those older than recommended age for vaccination. Studies on females who are not directly impacted by vaccination are relevant to provide context on underlying patterns and associations of HPV infection in middle and older ages.

Due to type-specific associations with disease, epidemiologists analyze prevalence by different HPV type categories, such as any HPV (e.g. any of the 37 types detected using Linear Array), high-risk HPV (e.g. any of the 14 types detected by clinical HPV tests), and other delineations based on study objective. In the United States, type-specific HPV prevalence has been monitored through the National Health and Nutrition Examination Survey (NHANES) for females since 2003. In 2003-2006, prior to vaccine introduction, the prevalence on any HPV among U.S. females ages 14-59 years was 42.5% (9).

Several demographic and behavioral characteristics are associated with prevalence of HPV. HPV prevalence differs by race and ethnicity; in 2003-2006, the highest prevalence of any HPV in US females 14-59 years was in non-Hispanic blacks (59.2%) followed by Mexican Americans (44.2%) and non-Hispanic whites (38.2%) in the United States (9). Prevalence was significantly higher for those below poverty compared to those above poverty as well in US females, 2003-2006 (9). Higher prevalence was also significantly associated with number of lifetime sex partners, number of sex partners in the past year, age at sexual debut, marital status, and history of genital warts (9). Females ages 18-25 years with one lifetime sex partner had lower prevalence of any HPV (14.3%) compared to those with two lifetime sex partners (22.3%) and those with three or more lifetime sex partners (31.5%) (15). Number of lifetime sex partners has been shown as the main determinant of anogenital HPV infection (3). It has been reported that smoking, use of

oral contraceptives, parity, other sexually transmitted infections, and host susceptibility may influence the risk of HPV acquisition, yet epidemiological evidence is inconsistent for these factors (16, 17).

HPV prevalence varies by age. NHANES data sampled prior to vaccine introduction in the United States, 2003-2006, showed prevalence was highest among those aged 20-24 years at 53.8% (18). Studies of incident HPV infection have shown that first HPV infection usually occurs within a few years of becoming sexually active, and most new HPV infections occur among persons 15-24 years (1).

In de Sanjose and colleague's meta-analysis of global HPV distribution among females with normal cytology, age-specific HPV prevalence was highest in females younger than 25 years and progressively lower at older ages (19). In Smith and colleague's global review of HPV prevalence, the same decrease in prevalence with age was found with prevalence peaking in females 25 years and younger (20). De Sanjose found a second peak in females ages 45 and older in Africa, the Americas, and Europe but not in Asia (19). Franceschi and colleague's study on worldwide age-specific HPV prevalence also observed a second peak in HPV prevalence in females aged 55 and older in multiple counties, but they did not study the United States (21). Whereas Smith found that, globally, counties had inconsistent age patterns for HPV with older ages having a lower, stable, or higher prevalences (20). Smith's study compared their findings to de Sanjose's noting that, while de Sanjose found North America had a second peak in prevalence in females older than 45 years, Smith showed a decline in prevalence with increasing age (19, 20). Another study by Gravitt and colleagues in US females recruited from obstetrics-gynecology clinics in Baltimore found prevalence of any HPV and HR

HPV decreased significantly with increasing age ($P = 0.002$ and $P < 0.01$ for trend, respectively) (22). Using 2003-2006 NHANES data, Hariri and colleagues observed lower HPV prevalences in age groups beyond ages 20-24, though trends were not statistically evaluated (9).

Age-related reductions in HPV prevalence are likely attributable to factors including clearance of infection with time, decrease in risk of incident infection as a result of sexual activity changes, and acquired immunity from previous infections (9). Alternatively, explanations for a second peak in older females could be explained by reactivation due to unknown biological mechanisms in immune response, changes in sex partners in middle age, or specific cohort effects due to sexual attitudes closely relating to social changes (19). Measuring the association between reactivation and age is difficult because there is no molecular marker to detect reactivated latent infection apart from incident infection (22). While there has been speculation that high HPV prevalence at older ages represents changes in sexual behaviors in ages over 50, such as new partnerships indicated by increased divorce rates, Gravitt did not find evidence of this (22). Gravitt hypothesized that, in the United States, a cohort effect may be masking the increase in HPV prevalence in older years seen in some studies due to unique sexual behaviors experienced by different cohorts, such as cohorts who experienced sexual debut at the beginning of the US sexual revolution of the 1960s and 1970s (22).

A birth cohort effect on disease prevalence represents changes that characterize a population born at a specific time point and are independent of the process of aging because birth cohorts age together and experience similar social and historical events at similar ages (23). Estimation by birth cohort has the advantage of controlling for the

similar social, economic, cultural and technological experience of a birth cohort which would affect lifestyle, sexual behaviors, and risk attitudes (24). Most cross-sectional, population-based studies are limited to looking at HPV prevalence by age alone; with this approach, birth cohort effects are not observable. While we found no literature looking at birth cohort effects on HPV prevalence in the United States, Liu and colleagues used NHANES data to evaluate sexual behavior trends by 10-year birth cohorts. Their study found a decline in age at sexual debut for successive 10-year cohorts of females born in 1940-1970 ($P<0.001$, for trend) (25). They also found median number of lifetime sex partners increased among females between 1940-1949 and 1970-1979 birth cohorts ($P<0.001$, for trend), and percent reporting same-sex partners increased among females between successive cohorts ($P<0.001$, for trend) (25).

Most studies evaluating changes in HPV prevalence over time are among young females, especially those age-eligible for vaccination, because monitoring the impact of the HPV vaccination program is an area of high importance. Consequently, little has been published on age-specific HPV prevalence and associations among those older than recommended age for vaccination. Understanding secular patterns in HPV prevalence in middle and older ages could provide useful context for vaccine impact studies in the future as those age-eligible for vaccination reach comparable age. It is important to measure the impact of cohort on age-specific HPV prevalences to separate cohort effects from age effects. Identifying if specific risk factors are influenced by birth cohort and how birth cohort affects the association between HPV and risk factors can further inform understanding of birth cohorts' influence on HPV prevalence.

Chapter II:

Title, Author, Abstract

Title: Prevalence of human papillomavirus among US females older than recommended age for vaccination by birth cohort, National Health and Nutrition Examination Survey 2003-2016

Author: Kristin M. Vahle

Abstract: Background: Human papillomavirus (HPV) prevalence among population-based samples of females older than recommended vaccination age has not been studied extensively. Understanding prevalences in these ages could be useful context as females eligible for vaccination advance to these ages. Associations between HPV prevalence and age in cross-sectional surveys could be confounded by cohort differences in HPV exposures. We evaluated HPV prevalences by age overall and by birth cohort and evaluated associations between HPV prevalence and characteristics by birth cohort among females 27-59 year born in 1950-1979 from National Health and Nutrition Examination Survey (NHANES) 2003-2016.

Methods: NHANES data from females with adequate HPV typing results from self-collected cervicovaginal swabs were analyzed. Weighted proportions and 95% confidence intervals (CI) of demographic and behavioral characteristics were measured overall and for 1950-1959, 1960-1969, and 1970-1979 birth cohorts. Weighted prevalences and 95% CIs of any HPV, high-risk HPV, and non-high-risk HPV were estimated by 3-year age groups, overall and by birth cohort. Unadjusted and age-adjusted prevalence ratios and 95% CIs for any HPV and characteristics were estimated by birth cohort with log-binomial regression.

Results: Prevalence was 38.5% for any HPV, 18.1% for HR HPV, and 30.6% for non-HR HPV. Significant declines in prevalence were observed per 3-year age increase for any HPV (APC: -2.86%), HR HPV (APC: -6.40%), and non-HR HPV (APC: -2.02%). Adjusting for age, interaction between age and cohort on prevalence was not significant (p-value > 0.05 for all HPV group types). Associations between most characteristics and any HPV were similar in each cohort after adjusting for age.

Conclusions: We found no evidence of a cohort effect on any HPV, HR HPV, and non-HR HPV as the relationship of prevalence and age did not vary by birth cohort. We also found associations between any HPV prevalence and many characteristics, including marital status, age at sexual debut, number of lifetime partners, and others, did not vary by birth cohort controlling for age; only race/ethnicity varied. Lack of a cohort effect on age-specific prevalence suggests that declines in HPV prevalence with age observed in cross-sectional studies are attributable to differences in age rather than cohort.

Introduction

Human papillomavirus (HPV) is the most common sexually transmitted infection (26). HPV types that infect the genital tract are classified as high-risk (HR) or non-high-risk (non-HR) according to their oncogenic potential (9, 27). Persistent infection with HR HPV types can lead to cervical, vaginal, vulvar, penile, anal, or oropharyngeal cancer (3). In the United States, each year, there are 33,700 HPV-related cancers including 10,800 cervical cancers (6). In an era of HPV vaccination, which began in 2006 for US females, studies of HPV prevalence in cohorts older than recommended age for vaccination can

provide a baseline for comparison to vaccinated cohorts as these cohorts age into later years (13).

Global reviews by Smith and de Sanjose, and a global study by Franceschi, found the highest HPV prevalence in females by age 25 with lower prevalence at older ages (19, 20). De Sanjose and Franceschi found a second peak in HPV prevalence at older ages in several regions and countries including North America (20, 21). In contrast, Smith's global review found a continual decline with older ages in North America. Gravitt's study of females recruited from Baltimore obstetrics-gynecology clinics also saw a decline in HPV with older age after 25 years (19, 22). HPV prevalence in the United States, as documented through NHANES, varies by age, with 20-24-year-olds having the highest prevalence and comparatively lower prevalences occurring in older age groups (9, 27, 28). In NHANES 2013-2014, prevalence of any HPV was 62.8% in females 20-24 years compared to 32.0% in females 50-59 years (27).

Age-related reductions in HPV prevalence are likely attributable to factors including clearance of infection with time, decreased risk of acquiring infection resulting from fewer new sexual partnerships, and acquired immunity from previous infections (9). Possible explanations for a second peak in older females, if it exists, could include reactivation of latent HPV infections, waning immunity with age, changes in sexual behaviors increasing acquisition risk, and birth cohort effects influencing lifetime risk (19, 22). As Gravitt's study hypothesized, a cohort effect of females with sexual debut before the sexual revolution of the 1960s and 1970s may be masking a second peak in HPV prevalence in older adults due to the unique sexual behaviors experienced by these

cohorts; this could result in the hypothesized true increase in HPV prevalence at older ages not appearing for 10-15 years in the US (22).

This study aims to fill a gap in the understanding of age-specific prevalence of HPV among females who are older than the recommended age for vaccination. Understanding HPV prevalence among these females can provide a needed comparison to interpret future patterns as females age-eligible for recommended vaccination get older. Additionally, analysis by birth cohorts is needed to better describe what contributes to patterns in HPV prevalence. Therefore, we described age-specific prevalence of any HPV, HR HPV, and non-HR HPV in a nationally representative sample of females aged 27-59 years and born in 1950-1979, by 10-year birth cohorts. Subsequently, we evaluated the association between demographic and behavioral characteristics and HPV prevalence by birth cohort to evaluate if cohorts differed in HPV exposures and risk.

Methods

Data Source and Analytic Sample

For this analysis, we used publicly available survey data from seven consecutive NHANES cycles, years 2003-2016. NHANES is an ongoing cross-sectional survey conducted by the National Center for Health Statistics (NCHS) of the Center for Disease Control and Prevention (CDC) (29). Detailed survey methods have been described previously (30, 31). NHANES is a complex, stratified, multistage probability sample of the civilian noninstitutionalized U.S. population. Some groups, such as African Americans and Mexican Americans, are oversampled to provide sufficient sizes for subgroup analysis (32). Consenting participants complete a household interview followed

by a physical examination in a mobile examination center (MEC). Demographic information is ascertained from all participants during household interviews (33). Sexual history information is self-reported by participants 14-59 years using an audio computer assisted self-interview (34). All females 14-59 years who attend the MEC are asked to self-collect a cervicovaginal swab sample. Specimens are tested for 37 HPV types at the CDC using Research Use Only Roche Linear Array Assay (Roche Diagnostics, Indianapolis, Indiana); for specimens positive for HPV52 and HPV33, 35, or 58, an addition quantitative type-specific polymerase chain reaction (PCR) is conducted to determine HPV 52 positivity (35, 36). Laboratory methods are detailed elsewhere (37).

This study used questionnaire and examination data. The average response rate of 2003-2016 household interviews was 74.6% and examination was 71.8%. Self-collected cervicovaginal swabs were reported from 7968 female participants born from 1950-1979 and aged 27-59 at time of survey. Of these, 7902 female participants with valid PCR testing results were included in the analysis.

We assigned age at NHANES participation by subtracting participants' reported age at survey by the second year of the 2-year survey cycle; we used this assigned age to group participants into 10-year birth cohorts. For the primary analysis, cohorts were classified in 10-year groups (born 1950-59, 1960-69, and 1970-79) and age groups were analyzed in 3-year groups (27-29, 30-32, 33-35, 36-38, 39-41, 42-44, 45-47, 48-50, 51-53, 54-56, and 57-59 years).

Categories of HPV types were selected by etiological and clinical relevance representing oncogenic and non-oncogenic classes. Any HPV was defined as positivity for one or more of the 37 HPV types included in the Linear Array assay. High-risk HPV

included the 14 HPV types detected by commercially available cervical cancer screening tests, 16/18/31/33/35/39/45/51/52/56/58/59/66/68. Non-high-risk HPV included the remaining 23 types, 6/11/26/40/42/53/54/55/61/62/64/67/69/70/71/72/73/81/82/83/84/89/IS36.

Demographic and behavioral characteristics that have been associated with HPV prevalence or were hypothesized to vary by birth cohort, and were available for all included NHANES cycles, were selected for analysis. Self-reported race and ethnicity was categorized as non-Hispanic white, non-Hispanic black, Mexican American, and other. Poverty income ratio (PIR) was based on self-reported income, household size, and the state poverty level for the year of data collection; PIR <1 was classified as below poverty (33). Self-reported number of lifetime sex partners included same-sex and opposite-sex partners and was categorized as 0-1, 2-5, 6-9, and ≥10 partners. Self-reported sex partners in the past year was categorized as 0-1 and ≥2 partners. Age at sexual debut was based on self-reported age at first sex and categorized at <16 years old and ≥16 years with those reporting never having sex classified as ≥16 years. History of genital warts, history of cervical cancer and hysterectomy were self-reported. Self-reported smoking status was categorized as ever smoker (≥100 cigarettes in lifetime) and never smoker (<100 cigarettes in lifetime).

Statistical Analysis

All analyses were weighted with the examination sample weights to account for unequal probability of selection and nonresponse, and variances were estimated using methods for complex survey analyses (38, 39). A two-tailed *P*-value was considered statistically significant if < .05. We evaluated all estimates for reliability using criteria of

relative standard error ≤30% and a sample size ≥100 indicating reliability; all estimates presented were reliable. Data management and analyses for this analysis were conducted in SAS 9.4. (SAS Institute, Cary, NC). To be consistent with prior CDC reports on HPV prevalence using NHANES data, all analyses will be repeated using SAS-callable SUDAAN prior to submission for journal publication; slight difference in results, particularly reported confidence intervals, are anticipated.

First, we described demographic and behavioral characteristics of females in the study sample overall and by 10-year birth cohort by estimating frequency distributions and 95% CIs. We used chi-square tests to evaluate if the distribution of demographic and behavioral characteristics varied significantly by cohort.

Then, we estimated prevalence specific to 3-year age groups of any HPV, HR HPV, and non-HR HPV, overall and by 10-year birth cohort. For each HPV type group, we used log-binomial regression to obtain prevalence ratios (PRs) and 95% CIs per 3-year increase in age, overall and by 10-year birth cohort; for these models, 3-year age groups were treated as a continuous variable. To estimate the average percent change (APC) in HPV prevalence with incremental 3-year age, APCs were calculated as (1-PR) × 100%. Using data from all cohorts combined, we tested for interaction between age and cohort in order to evaluate whether the association between 3-year age group and HPV prevalence differed by 10-year birth cohort.

As a sensitivity analysis, the description of prevalence by age and birth cohort was repeated with alternative classifications, including by 4-, 5-, and 10-year birth cohorts and 4-, 5-, and 7-year age groups.

Next, we evaluated whether demographic and behavioral characteristics related to any HPV varied by cohort. We used log-binomial regression of any HPV to estimate unadjusted PRs and age-adjusted PRs stratified by 10-year birth cohort. We adjusted for continuous age in these models to account for the different ages represented in each cohort. To determine if there were cohort differences in associations of any HPV prevalence and demographic and behavioral characteristics, we tested interaction between 10-year birth cohorts and characteristics in log-binomial models adjusted for age among all birth cohorts.

Results

Demographic and behavioral characteristics of study sample

This analysis included 7902 females (ages 27-59 at time of NHANES participation in 2003-2016), including 1942 born in the 1950s (ages 45-59), 2976 born in the 1960s (ages 36-56), and 2984 born in the 1970s (ages 27-44) (Table 1). Overall, 67.0% of the females included in this analysis were non-Hispanic white, 12.6% were non-Hispanic black, 8.4% were Mexican American, and 12.0% were another race/ethnicity. The proportion of females who were non-Hispanic white was lower for those born in the 1970s, 60.3%, compared to those born in the 1950s, 73.1%. Overall, the proportion married or living with a partner was 68.8%, widowed, divorced or separated was 20.5%, and never married was 20.5%. The proportion widowed, divorced or separated decreased from 20.5% for those born in the 1950s to 14.3% for those born in the 1970s; meanwhile the proportion never married increased from 7.2% for those born in the 1950s to 14.8% for those born in the 1970s. Overall, the proportion of participants

with age of sexual debut before age 16 was 24.9%. The cohort with the highest proportion of those with age at sexual debut before 16 years, was those born in the 1970s, 27.7%. In all cohorts, 2-5 of lifetime partners accounted for the highest proportion of females, 38.6% overall. Comparing across successive cohorts the proportion of females with 0-1 and 2-5 lifetime partners decreased while the proportion of those with ≥10 lifetime partners increased. Overall, 1.8% (95% CI: 1.4%, 2.5%) of study sample reported ever receiving a dose of HPV vaccination. Most demographic and behavioral characteristics evaluated differed significantly by cohort, except for history of genital warts and history of cervical cancer; for many of these characteristics, differences may be influenced by the different ages represented.

Age-specific prevalences overall and among birth cohorts

Overall females older than recommended age for vaccination, prevalence was 38.5% for any HPV, 18.1% for HR HPV, and 30.6% for non-HR HPV (Table 2). A total of 10.3% (95% CI: 9.4%, 11.2%) had both HR and non-HR HPV types detected, 21.1% (95% CI: 19.9%, 21.4%) had only one type of HPV detected, and 17.2% (95% CI: 16.3%, 18.5%) had 2 or more HPV types detected. Among all birth cohorts and HPV type groups, HPV prevalence was higher in younger ages compared to older ages. For example, prevalence of any HPV among females born in the 1960s was highest at ages 36-38 years (44.3%) and lower at ages 53-56 years (38.7%).

Prevalence of any HPV declined with age for each cohort (Figure 1). Declines with age for any HPV prevalence were observed for females born in the 1950s (APC per 3-year age group increase of -5.74%, 95% CI: -11.40%, -0.08%), the 1960s, (APC of -2.42%, 95% CI: -6.30%,1.47%), and the 1970s (APC of -4.18%, 95% CI: -7.85%,-

0.51%). The APCs for HR HPV prevalence were negative for all three cohorts per 3-year age increase (Figure 2). The APCs for HR HPV had a greater magnitude of decrease compared to any HPV, with the 1950s cohort having largest APC for HR HPV, -15.17%. Non-HR HPV had a negative APC for the 1970s cohort (APC of -3.84%, 95% CI: -8.14%, 0.45%) and the 1950s (APC of -2.94%, 95% CI: -9.93%, 4.04%) (Figure 3). The 1960s cohort had no association with non-HR HPV with an APC of 0.06% (95% CI: -4.15%, 4.62%).

With data from all three cohorts combined, significant declines in prevalence for any HPV, APC of -2.86% (95% CI: -4.10%,-1.61%), HR HPV, APC of -6.40% (95% CI: -8.44%, -4.35%), and non-HR HPV, APC of -2.02% (95% CI: -3.54%, -0.51%) were observed per 3-year age increase (Figure 4). Depending on the HPV type group examined, some prevalence point estimates were higher for females in their 40s compared to their 30s or 50s, but confidence intervals overlapped in successive age groups (Figure 4, Table 2). The interaction between age and cohort in an age-adjusted log-binomial model on all cohorts was not significant (p-value of 0.66 for any HPV, 0.64 for HR HPV, and 0.48 for non-HR HPV).

Results for alternative classifications of cohort and age group are shown in Appendix I. In general, the pattern of lower prevalence with older age was observed, with variations seen in middle age groups depending on cohort classification.

Associations between any HPV and demographic and behavioral characteristics by birth cohort

Associations between most characteristics and any HPV were similar across the three cohorts after adjusting for age (Table 3). Age-adjusted PRs and 95% CIs estimates

were similar to PRs and 95% CIs from unadjusted models (results not shown). Race/ethnicity was the only characteristic that differed in association across cohorts with a significant interaction between race/ethnicity and cohort (p-value = 0.02). For non-Hispanic blacks compared to non-Hispanic whites, the age-adjusted PR was highest, 1.87, for those born in the 1950s, compared to 1.48, for those born in the 1960s, and 1.46, for those born in the 1970s. Mexican Americans had significantly higher prevalence than non-Hispanic whites, aPR of 1.37, among females born in the 1950s, but these groups did not have significantly different prevalences among females born in the 1960s and the 1970s.

Prevalence was higher for females living below poverty compared to females living above poverty across all three cohorts. For the 1960s and 1970s cohorts, prevalence was significantly lower for those born outside the United States, aPR of 0.86 and 0.81, respectively, while the 1950s cohort did not have a significantly different prevalence, aPR of 1.00. The age-adjusted prevalence for completing high school or obtaining a GED compared to less than high school education was significantly lower in the 1950s cohort, aPR of 0.80, yet in the 1970s cohort prevalence was not significantly different but was higher in magnitude, aPR of 1.13. Prevalences were significantly lower with more than high school education compared to less than high school education for all three cohorts.

Females who were married or living with a partner had significantly lower prevalence for all three cohorts compared to females who were widowed, divorced or separated and females who were never married. The 1960s cohort had the lowest aPRs among all cohorts with an aPR of 1.78 for widowed, divorced, or separated and 1.37 for

never married compared to married or living with partner. Age at sexual debut before 16 years was associated with higher prevalence compared to sexual debut after age 16 across all cohorts. Within each cohort, aPRs for lifetime number of partners increased with each successive categorization of number of partners; the 1950s cohort had an aPR of 2.62 for those with 2-5 partners and an aPR of 3.64 for those with ≥10 partners compared to 0 or 1 partners. The aPR comparing 2 or more partners in the past year to 0 or 1 partners was 2.27 for those born 1950s and 1.78 for those born 1970s.

Both history of genital warts and history of cervical cancer only resulted in significantly higher HPV prevalence in the 1960s cohort, aPRs of 1.40 and 1.26, respectively. Hysterectomy was not significantly associated with HPV prevalence for any cohort. Ever smoking (at least 100 cigarettes in life) was associated with higher prevalence, aPR of 1.42 for the 1950s cohort, 1.43 for the 1960s cohort, and 1.30 for the 1970s cohort.

Discussion

In this analysis of HPV prevalence in females older than recommended age for vaccination, we found that prevalence of any HPV, HR HPV, and non-HR HPV declined significantly per increase in 3-year age group. In our sample, the inverse relationship between HPV types and age did not significantly differ by cohort. Most characteristics, except for race and ethnicity, had similar associations with any HPV prevalence, regardless of birth cohort. Together these findings suggest that the epidemiology of HPV infections in females older than recommended age for vaccination do not vary greatly by cohort.

Among our study population, we found declines in HPV type group prevalences with increasing 3-year age groups, but among individual cohorts our results varied by HPV type groups. We consistently observed an inverse linear relationship between age and HR HPV prevalence across all three cohorts suggesting prevalent HR HPV infections decrease with age unrelated to cohort. Interaction tests of 10-year birth cohorts on the association of prevalence and age were not significant for any HPV, HR HPV, and non-HR HPV indicating the slope of age and prevalence did not differ for by cohort. Thus, our results indicate that age plays a larger role than cohort in determining prevalence for the HPV type groups we tested.

Evidence of a second peak in HPV prevalence in middle or older ages for females has been identified in some global reviews and studies, yet other studies found continually lower HPV prevalence with older age in females (9, 19, 21, 40). Gravitt's study suggested that, in the US, a second peak in HPV prevalence is masked by birth cohort effects (22). In our analysis, declines both overall and in individual cohorts suggested a lack of a second peak in HPV in middle age. Yet, the 1960s cohort had some prevalence point estimates higher for females in their 40s compared to their 30s or 50s depending on the HPV type group examined. These differences could be due to limitations of the data available for analysis or limitations of the age and cohort groupings considered. Yet, our sensitivity analysis of alternative groups for age and cohort also did not conclusively detect a second peak.

Prevalence of any HPV was largest in magnitude because it includes both HR and non-HR HPV; prevalence of non-HR HPV was consistently larger in magnitude than HR HPV, possibly because non-HR HPV comprises of a greater number of types. Prevalence

of HR HPV was similar in magnitude to that observed in Lewis's 2013-2014 NHANES study, but categorization of non-HR HPV differs across studies and is difficult to compare (9, 27, 41). Furthermore, in this sample, the relationship with age is different for non-HR HPV compared to HR HPV with non-HR HPV declining less with age and HR HPV declining more with age. Potential explanations for non-HR HPV remaining more prevalent at older ages include greater persistence or greater likelihood of reactivation. Because HR HPV infections cause cervical disease that can be detected during cervical cancer screening, these infections may be removed during excisional treatment, whereas non-HR infections remain because they do not cause disease. As NHANES only collects data on hysterectomy, and not on treatment of precancerous cervical lesions, we could not test this hypothesis. Sampling could also influence HR and non-HR detection by age; two studies of cervicovaginal HPV found that non-HR HPV types may preferentially infect in the vaginal epithelium while HR HPV types may preferential infect the cervical epithelium (42, 43). Therefore, if non-HR types are more common in the vagina, they might be more commonly detected with self-collected cervicovaginal swabs picking up more vaginal flora.

We found most demographic and behavioral characteristics varied in distribution across the 10-year birth cohorts except for history of genital warts and history of cervical cancer; yet, differences for many of these characteristics may be influenced by the different ages represented in each cohort. Consistent with several NHANES studies, race and ethnicity, poverty, marital status, age at sexual debut, number of lifetime partners, partners in the past year, and history of genital warts, and smoking were related to higher prevalence of any HPV (9, 27, 28, 41). The association between hysterectomy and any

HPV was also examined in our sample, and no association was found, although hysterectomy was uncommon in all cohorts, limiting statistical power.

We found that most many demographic characteristics and behaviors associations with HPV prevalence did not vary by 10-year birth cohort. For example, lifetime number of partners, a well-proven risk factor for HPV, had the highest prevalence for ≥10 partners in the 1970s cohort and the lowest prevalence for ≥10 partners in the 1950s cohort, yet the age-adjusted PRs did not vary significantly across cohort (3, 9). This indicates associations between prevalence and HPV exposures was not confounded by cohort differences for most characteristics. However, associations of race/ethnicity and any HPV significantly varied across cohorts; race/ethnicity also significantly varied in distribution across study sample. This would suggest that cohort confounds the relationship between race/ethnicity prevalence of any HPV. This likely due to factors which race/ethnicity are a proxy for, such as social and racial disparities, varying by birth cohort, rather than race/ethnicity itself.

Strengths and Limitations

We acknowledge several limitations to this evaluation of cohort effects on HPV prevalence. Ideally, each cohort analyzed would have included all ages, 27-59 years, equally so that comparisons across cohorts would not be confounded by age. Our use of this cross-sectional data is limited to cohorts only partially overlapping in ages represented, but these cohorts consistently show no evidence of a cohort effect on HPV prevalence. While our study population is older than the recommended age to experience direct impacts of vaccination, some females, particularly those born in the more recent years, might be affected by herd immunity depending on the demographics of their recent

sexual contacts. Because of this, it is possible that the prevalence of quadrivalent vaccine types, which have been used for the longest period of time in the US, could be lower across a wider range of age cohorts depending on sexual partner mixing in these ages. This is unlikely to affect the broad HPV type categorizations used in this study; reductions in vaccine types observed in prior a NHANES analysis has not translated into significant declines in any HPV or HR HPV (28).

NHANES data is collected from nationally representative samples using consistent methods allowing us to accurately measure HPV prevalence and associations among females aged 27-59 and born in 1950-1979. The strengths of this study include our ability to adapt cross-sectional data to examine cohort effects, which are typically studied using longitudinal data. Previous studies of age-specific HPV prevalence among U.S. population-based samples have used cross-sectional data from only 2-4 years and have not evaluated the influence of birth cohort on HPV prevalence. This alternative use of survey data provides the ability to better understand the trajectory of HPV prevalence in middle and later ages and adds to the body of literature of cohort effects on HPV prevalence.

In conclusion, we found evidence of declining prevalence per successive 3-year age groups overall for any HPV, HR HPV, and non-HR HPV and among individual 10-year birth cohorts for any HPV and HR HPV. As the relationship of prevalence and age did not vary by birth cohort, we found no evidence of a cohort effect on any HPV, HR HPV, and non-HR HPV. Further, we found that, after controlling for age, the associations of any HPV prevalence with most demographic and behavioral characteristics did not vary by birth cohort, although distribution of these characteristics did vary by cohort. This

statistical support for the lack of a cohort effect on age-specific prevalence provides evidence that observed declines in HPV prevalence with age in cross-sectional studies are a function changes with older age rather than a function of cohort differences generated by unique behaviors and demographic factors specific to when a person is born.

References

1. Markowitz LE, Dunne EF, Saraiya M, et al. Human papillomavirus vaccination: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2014;63(RR-05):1-30.
2. D. Heather Watts LAK, King K. Holmes, Deborah Goldman, Jane Kuypers, Nancy B. Kiviat, Denise A. Galloway. Low risk of perinatal transmission of human papillomavirus: Results from a prospective cohort study. Am J Obstet Gynecol 1998;178(2):365-73.
3. IARC. Human Papillomaviruses. (100B):255.
4. Doorbar J, Quint W, Banks L, et al. The biology and life-cycle of human papillomaviruses. Vaccine 2012;30 Suppl 5:F55-70.
5. Ho GYF, Bierman R, Beardsley L, et al. Natural History of Cervicovaginal Papillomavirus Infection in Young Women. N Engl J Med 1998(338):423-8.
6. Meites E, Szilagyi PG, Chesson HW, et al. Human Papillomavirus Vaccination for Adults: Updated Recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep 2019;68(32):698-702.
7. Schiffman M, Castle PE, Jeronimo J, et al. Human papillomavirus and cervical cancer. The Lancet 2007;370(9590):890-907.
8. Forman D, de Martel C, Lacey CJ, et al. Global burden of human papillomavirus and related diseases. Vaccine 2012;30 Suppl 5:F12-23.
9. Hariri S, Unger ER, Sternberg M, et al. Prevalence of genital human papillomavirus among females in the United States, the National Health And Nutrition Examination Survey, 2003-2006. J Infect Dis 2011;204(4):566-73.

10. de Sanjose S, Quint WGV, Alemany L, et al. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. Lancet Oncol 2010;11(11):1048-56.

11. Lacey CJN, Lowndes CM, Shah KV. Chapter 4: Burden and management of non-cancerous HPV-related conditions: HPV-6/11 disease. Vaccine 2006;24(3):S35-S41.

12. Meites E, Kempe A, Markowitz LE. Use of a 2-Dose Schedule for Human Papillomavirus Vaccination - Updated Recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep 2016;65(49):1405-8.

13. Markowitz LE, Gee J, Chesson H, et al. Ten Years of Human Papillomavirus Vaccination in the United States. Academic pediatrics 2018;18(2s):S3-s10.

14. Walker TY, Elam-Evans LD, Yankey D, et al. National, Regional, State, and Selected Local Area Vaccination Coverage Among Adolescents Aged 13–17 Years — United States, 2018. MMWR Morb Mortal Wkly Rep 2019;68(33):718-23.

15. Manhart LE, Holmes KK, Koutsky LA, et al. Human papillomavirus infection among sexually active young women in the United States: Implications for developing a vaccination strategy. Sex Transm Dis 2006;33(8):502-8.

16. Burchell AN, Winer RL, de Sanjose S, et al. Chapter 6: Epidemiology and transmission dynamics of genital HPV infection. Vaccine 2006;24 Suppl 3:S3/52-61.

17. Moscicki AB, Schiffman M, Burchell A, et al. Updating the natural history of human papillomavirus and anogenital cancers. Vaccine 2012;30 Suppl 5:F24-33.

18. Dunne EF, Sternberg M, Markowitz LE, et al. Human papillomavirus (HPV) 6, 11, 16, and 18 prevalence among females in the United States--National Health And Nutrition Examination Survey, 2003-2006: opportunity to measure HPV vaccine impact? J Infect Dis 2011;204(4):562-5.

19. de Sanjosé S, Diaz M, Castellsagué X, et al. Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: a meta-analysis. The Lancet Infectious Diseases 2007;7(7):453-9.

20. Smith JS, Melendy A, Rana RK, et al. Age-specific prevalence of infection with human papillomavirus in females: a global review. The Journal of adolescent health : official publication of the Society for Adolescent Medicine 2008;43(4 Suppl):S5-25, S.e1-41.

21. Franceschi S, Herrero R, Clifford GM, et al. Variations in the age-specific curves of human papillomavirus prevalence in women worldwide. Int J Cancer 2006;119(11):2677-84.

22. Patti E. Gravitt AFR, Michelle I. Silver, Morgan A. Marks, Kathryn Chang, Anne E. Burke, and Raphael P. Viscidi. A Cohort Effect of the Sexual Revolution May Be Masking an Increase in Human Papillomavirus Detection at Menopause in the United States. The Journal of infectious diseases 2013;207:272–80.

23. An R, Xiang X. Age-period-cohort analyses of obesity prevalence in US adults. Public Health 2016;141:163-9.

24. Komlos J, Brabec M. The trend of BMI values of US adults by deciles, birth cohorts 1882-1986 stratified by gender and ethnicity. Econ Hum Biol 2011;9(3):234-50.

25. Liu G, Hariri S, Bradley H, et al. Trends and patterns of sexual behaviors among adolescents and adults aged 14 to 59 years, United States. Sex Transm Dis 2015;42(1):20-6.

26. Satterwhite CL, Torrone E, Meites E, et al. Sexually transmitted infections among US women and men: prevalence and incidence estimates, 2008. Sex Transm Dis 2013;40(3):187-93.

27. Lewis RM, Markowitz LE, Gargano JW, et al. Prevalence of Genital Human Papillomavirus Among Sexually Experienced Males and Females Aged 14-59 Years, United States, 2013-2014. J Infect Dis 2018;217(6):869-77.

28. McClung NM, Lewis RM, Gargano JW, et al. Declines in Vaccine-Type Human Papillomavirus Prevalence in Females Across Racial/Ethnic Groups: Data From a National Survey. The Journal of adolescent health : official publication of the Society for Adolescent Medicine 2019;65(6):715-22.

29. Center for Disease Control and Prevention. National Health and Examination Survey: Overview. Hyattsville, MD: National Center for Health Statistics, 2020.

30. Center for Disease Control and Prevention. National Health and Examination Survey: interviewer procedures manual. Hyattsville, MD: Center for Disease Control and Prevention, 2016.

31. Center for Disease Control and Prevention. National Health and Examination survey: MEC interviews procedures manual. Hyattsville, MD: National Center for Health Statistics, 2016.

32. CL J, SM D, VL B, et al. National health and nutrition examination survey: sample design, 2011-2014. Vital Health Stat 2014;2(162):1-33.

33. National Center for Health Statistics. National Health and Examination Survey: 2015-2016 Data, Documentation, Codebook and Frequencies, demographic variables and sample weights. Hyattsville, MD: National Center for Health Statistics 2017.

34. National Center for Health Statistics. National Health and Examination Survey: 2015-2016 Data Documentation, Codebook, and Frequencies, sexual behavior. . Hyattsville, MD: National Center for Health Statistics, 2017.

35. National Center for Health Statistics. National Health and Examination Survey: 2005-2006 Data Documentation, Codebook, and Frequencies, human papillomavirus DNA – vaginal swab: digene hybrid capture and roche linear array. Hyattsville, MD: National Center for Health Statistics 2010.

36. Onyekwuluje J, Steinau M, Swan D, et al. A real-time PCR assay for HPV52 detection and viral load quantification. Clin Lab 2012;58(1-2):61-6.

37. National Center for Health Statistics. National Health and Examination Survey: 2005-2006 HPV Vaginal Swab Linear Array, laboratory procedure manual. .

38. Johnson CL, Paulose-Ram R, Ogden CL, et al. National Health and Nutrition Examination Survey: Analytic Guidelines, 1999–2010. National Center for Health Statistics. Vital Health Stat 2013;2.

39. Hale JJ, Thompson DM, Darden PM. Calculating Subset Weighted Analysis Using PROC SURVEYFREQ and GENMOD. SAS Global Forum 2013 2013.

40. Smith JS, Gilbert PA, Melendy A, et al. Age-specific prevalence of human papillomavirus infection in males: a global review. The Journal of adolescent health : official publication of the Society for Adolescent Medicine 2011;48(6):540-52.

41. Hirth JM, Kuo YF, Starkey JM, et al. Regional variations in human papillomavirus prevalence across time in NHANES (2003-2014). Vaccine 2019;37(30):4040-6.

42. Castle PE, Rodriguez AC, Porras C, et al. A comparison of cervical and vaginal human papillomavirus. Sex Transm Dis 2007;34(11):849-55.

43. D'Souza G, Burk RD, Zhong Y, et al. Cervicovaginal human papillomavirus (HPV)-infection before and after hysterectomy: evidence of different tissue tropism for oncogenic and nononcogenic HPV types in a cohort of HIV-positive and HIV-negative women. Int J Cancer 2012;131(6):1472-8.

44. Zietkowiak W, Zimna K, Sroka Ł, et al. Frequency of HPV infection of the uterine cervix among perimenopausal women in Wielkopolska Region. Ginekol Pol 2002;73(11):939-44.

45. Lindau ST, Drum ML, Gaumer E, et al. Prevalence of high-risk human papillomavirus among older women. Obstet Gynecol 2008;112(5):979-89.

Tables

Table 1: Distribution of demographic and behavioral characteristics overall and by birth cohort among females older than recommended age for vaccination, NHANES 2003-2016

Characteristic	Total (n = 7902) Age-range (27-59)	Birth Cohort 1950-1959 (n = 1942) Age-range (45-59)	1960-1969 (n = 2976) Age-range (36-56)	1970-1979 (n = 2984) Age-range (27-44)	Pr > Chi Sq*
	Weighted % (95% CI)				
Race/ethnicity					<.0001
Non-Hispanic white	67.0 (64.0, 69.9)	73.1 (69.5, 76.7)	68.5 (65.2, 71.8)	60.3 (56.8, 63.8)	
Non-Hispanic black	12.6 (11.0, 14.2)	12.3 (10.2, 14.4)	12.2 (10.5, 13.8)	13.3 (11.4, 15.3)	
Mexican American	8.4 (7.1, 9.8)	5.4 (4.1, 6.7)	7.4 (6.0, 8.9)	12.0 (10.2, 13.8)	
Other	12.0 (10.7, 13.3)	9.2 (7.5, 10.9)	11.9 (10.3, 13.6)	14.4 (12.5, 16.3)	
Poverty Status					<.0001
Living below poverty	86.3 (85.0, 87.7)	89.6 (88.0, 91.2)	86.2 (84.4, 87.9)	83.9 (82.2, 85.7)	
Living above poverty	13.7 (12.3, 15.0)	10.4 (8.8, 12.0)	13.8 (12.1, 15.6)	16.1 (14.3, 17.8)	
Country of Birth					<.0001
US	82.4 (80.6, 84.1)	87.2 (85.1, 89.3)	83.0 (80.6, 85.3)	77.8 (75.3, 80.3)	
Other	17.6 (15.9, 19.4)	12.8 (10.7, 14.9)	17.0 (14.7, 19.4)	22.2 (19.7, 24.7)	
Education					<.05
Less than high school	14.8 (13.5, 16.1)	13.5 (11.9, 15.2)	15.3 (13.5, 17.2)	15.3 (13.6, 17.0)	
High school graduate/GED	20.4 (19.1, 21.6)	23.3 (20.7, 26.0)	21.1 (18.8, 23.3)	17.2 (15.6, 18.8)	
More than high school	64.8 (62.8, 66.8)	63.1 (59.8, 66.4)	63.6 (60.6, 66.6)	67.5 (65.1, 69.9)	
Marital status					<.0001
Married/living with partner	68.7 (67.3, 70.1)	67.6 (64.8, 70.4)	67.5 (65.2, 69.9)	70.9 (68.7, 73.0)	
Widowed/ Divorced/Separated	20.5 (19.3, 21.7)	25.2 (22.9, 27.4)	22.7 (20.8, 24.6)	14.3 (12.6, 16.1)	
Never married	10.8 (9.8, 11.8)	7.2 (5.6, 8.7)	9.8 (8.4, 11.2)	14.8 (13.1, 16.5)	
Age at Sexual Debut					<.0001
Age ≥16 years	77.2 (75.9, 78.6)	83.6 (81.9, 85.4)	76.7 (74.5, 78.9)	72.3 (70.0, 74.6)	
Age <16 years	22.8 (21.4, 24.1)	16.4 (14.6, 18.1)	23.3 (21.1, 25.5)	27.7 (25.4, 30.0)	
Number of Lifetime Partners					<.0001
0-1	17.4 (16.3, 18.6)	20.8 (18.2, 23.4)	15.6 (14.1, 17.2)	16.7 (14.9, 18.5)	
2-5	38.6 (37.2, 40.0)	43.3 (40.4, 46.2)	39.5 (37.1, 41.9)	33.5 (30.8, 36.2)	
6-9	16.9 (15.7, 18.1)	16.1 (13.8, 18.4)	16.8 (15.1, 18.6)	17.6 (15.9, 19.4)	
≥10	27.1 (25.6, 28.5)	19.7 (17.3, 22.2)	28.0 (25.8, 30.2)	32.1 (29.7, 34.6)	
Partners in past year					<.0001
0-1	91.3 (90.5, 92.1)	95.2 (93.9, 96.4)	91.5 (90.3, 92.8)	87.8 (86.2, 89.3)	
≥2	8.7 (7.9, 9.5)	4.8 (3.6, 6.1)	8.5 (7.2, 9.7)	12.2 (10.7, 13.8)	
History of genital warts diagnosis					0.11
No	92.3 (91.4, 93.2)	93.5 (91.9, 95.1)	91.3 (89.8, 92.9)	92.4 (91.2, 93.6)	
Yes	7.7 (6.8, 8.6)	6.5 (4.9, 8.1)	8.7 (7.1, 10.2)	7.6 (6.4, 8.8)	
History of cervical cancer					0.87
No	97.9 (97.5, 98.3)	97.8 (97.1, 98.6)	98.1 (97.4, 98.8)	97.9 (97.1, 98.6)	
Yes	2.1 (1.7, 2.5)	2.2 (1.4, 2.9)	1.9 (1.2, 2.6)	2.1 (1.4, 2.9)	
Hysterectomy					<.0001
No	78.9 (77.4, 80.5)	69.2 (66.2, 72.2)	76.1 (73.5, 78.6)	91.5 (89.9, 93.2)	
Yes	21.1 (19.5, 22.6)	30.8 (27.8, 33.8)	23.9 (21.4, 26.5)	8.5 (6.8, 10.1)	
Smoking (at least 100 cigarettes in life)					<.0001
Ever Smoker	58.4 (56.9, 59.8)	55.5 (52.4, 58.6)	56.1 (53.6, 58.5)	63.2 (61.1, 65.4)	
Never Smoker	41.6 (40.2, 43.1)	44.5 (41.4, 47.6)	43.9 (41.5, 46.4)	36.8 (34.6, 38.9)	

* Rao-Scott Chi Square Test comparing proportion distribution of characteristics by 10-year birth cohort

Table 2: Age-specific prevalences of any HPV, high-risk HPV, and non-high-risk HPV in females older than recommended age for vaccination, NHANES 2003-2016

		Birth Cohort		
	Total (n = 7902) Age-range (27-59)	1950-1959 (n = 1942) Age-range (45-59)	1960-69 (n = 2976) Age-range (36-56)	1970-79 (n = 2984) Age-range (27-44)
HPV type and Age Group	Weighted % (95% CI)			
Overall				
Any HPV	38.5 (37.0, 40.0)	35.1 (32.2, 38.0)	38.8 (36.5, 41.1)	40.9 (38.5, 43.3)
High-risk HPV	18.1 (17.0, 19.3)	16.1 (14.1, 18.2)	17.3 (15.5, 19.1)	20.7 (18.8, 22.5)
Non-high-risk HPV	30.6 (29.4, 31.9)	28.0 (25.3, 30.6)	31.4 (29.2, 33.6)	31.9 (29.8, 34.1)
27-29 years				
Any HPV	49.9 (44.8, 55.0)			49.9 (44.8, 55.0)
High-risk HPV	25.5 (18.1, 32.8)			25.5 (18.1, 32.8)
Non-high-risk HPV	39.0 (33.5, 44.4)			39.0 (33.5, 44.4)
30-32 years				
Any HPV	42.8 (37.4, 48.3)			42.8 (37.4, 48.3)
High-risk HPV	25.5 (20.6, 30.5)			25.5 (20.6, 30.5)
Non-high-risk HPV	32.7 (27.4, 38.0)			32.7 (27.4, 38.0)
33-35 years				
Any HPV	43.5 (38.7, 48.3)			43.4 (38.3, 48.5)
High-risk HPV	23.2 (19.6, 26.8)			22.8 (19.1, 26.4)
Non-high-risk HPV	34.5 (29.6, 39.3)			34.0 (28.8, 39.2)
36-38 years				
Any HPV	37.6 (33.9, 41.4)		44.3 (35.9, 52.6)	35.5 (31.2, 39.9)
High-risk HPV	19.9 (17.2, 22.5)		25.5 (18.7, 32.2)	18.1 (15.3, 20.9)
Non-high-risk HPV	29.6 (26.1, 33.0)		34.1 (27.1, 41.2)	28.1 (24.1, 32.2)
39-41 years				
Any HPV	37.5 (33.8, 41.1)		35.6 (30.5, 40.7)	39.1 (34.2, 44.0)
High-risk HPV	19.1 (16.2, 21.9)		19.3 (15.4, 23.2)	18.8 (14.5, 23.1)
Non-high-risk HPV	28.1 (24.9, 31.4)		26.8 (22.1, 31.4)	29.3 (25.0, 33.7)
42-44 years				
Any HPV	41.6 (37.5, 45.8)		42.3 (37.5, 47.1)	40.3 (32.4, 48.1)
High-risk HPV	15.7 (12.9, 18.4)		15.1 (11.8, 18.4)	16.9 (11.8, 21.9)
Non-high-risk HPV	34.0 (30.2, 37.7)		34.3 (29.7, 38.87)	33.4 (26.9, 39.9)
45-47 years				
Any HPV	40.8 (37.0, 44.6)	41.9 (32.9, 50.9)	40.4 (36.1, 44.8)	
High-risk HPV	21.0 (17.5, 24.5)	23.9 (14.9, 32.9)	21.2 (17.4, 25.1)	
Non-high-risk HPV	31.3 (27.6, 35.0)	33.6 (25.6, 41.5)	30.8 (26.2, 35.4)	
48-50 years				
Any HPV	35.8 (32.1, 39.5)	39.1 (34.2, 43.9)	34.1 (28.9, 39.2)	
High-risk HPV	15.0 (12.2, 17.8)	19.6 (14.3, 24.9)	12.6 (9.4, 15.8)	
Non-high-risk HPV	28.7 (25.2, 32.1)	27.5 (23.0, 32.1)	29.2 (24.5, 34.0)	
51-53 years				
Any HPV	35.9 (30.9, 40.9)	34.9 (29.2, 40.7)	37.3 (28.6, 46.0)	
High-risk HPV	15.6 (12.5, 18.6)	16.2 (12.2, 20.2)	14.6 (10.0, 19.2)	
Non-high-risk HPV	30.2 (25.0, 35.1)	29.1 (23.2, 35.0)	31.6 (22.7, 40.5)	
54-56 years				
Any HPV	33.9 (29.8, 38.0)	32.5 (27.7, 37.3)	38.7 (31.2, 46.3)	
High-risk HPV	15.2 (12.0, 18.4)	15.5 (11.8, 19.2)	14.1 (7.6, 20.5)	
Non-high-risk HPV	27.1 (23.4, 30.9)	24.6 (20.3, 28.8)	36.1 (28.8, 43.4)	
57-59 years				
Any HPV	33.8 (28.5, 39.1)	33.8 (28.5, 39.1)		
High-risk HPV	12.3 (8.7, 15.8)	12.3 (8.7, 15.9)		
Non-high-risk HPV	29.1 (24.1, 34.1)	29.1 (24.1, 34.1)		

Table 3: Prevalence of any HPV and prevalence ratios by demographic and behavioral characteristics stratified by birth cohort, among females older than recommended age for vaccination, NHANES 2003-2016

	Birth Cohort						
	1950-1959 (n = 1942) Age-range (45-59)		1960-69 (n = 2976) Age-range (36-56)		1970-79 (n = 2984) Age-range (27-44)		
Characteristic	Weighted % (95% CI)	Age-adjusted PR (95% CI)	Weighted % (95% CI)	Age-adjusted PR (95% CI)	Weighted % (95% CI)	Age-adjusted PR (95% CI)	P-value for interaction*
Race/ethnicity							0.02
Non-Hispanic white	30.7 (27.2, 34.1)	Ref	36.6 (33.3, 39.8)	Ref	39.1 (35.6, 42.6)	Ref	
Non-Hispanic black	58.0 (53.3, 62.7)	1.87 (1.65, 2.12)	54.2 (50.1, 58.2)	1.48 (1.31, 1.66)	57.2 (52.5, 62.0)	1.46 (1.30, 1.64)	
Mexican American	42.4 (35.5, 49.3)	1.37 (1.15, 1.63)	38.2 (32.6, 43.7)	1.04 (0.89, 1.22)	38.1 (34.1, 42.1)	0.98 (0.85, 1.12)	
Other	35.7 (28.8, 42.6)	1.17 (0.92, 1.48)	36.4 (31.1, 41.6)	1.00 (0.84, 1.20)	35.6 (30.5, 40.7)	0.92 (0.78, 1.09)	
Poverty Status							0.15
Living below poverty	32.7 (29.6, 35.7)	Ref	36.4 (33.7, 39.0)	Ref	38.4 (35.5, 41.2)	Ref	
Living above poverty	55.3 (49.5, 61.0)	1.68 (1.45, 1.95)	52.2 (47.3, 57.2)	1.43 (1.27, 1.60)	53.9 (49.3, 58.6)	1.40 (1.24, 1.57)	
Country of Birth							0.20
US	35.1 (31.9, 38.4)	Ref	39.8 (36.9, 42.6)	Ref	42.8 (39.9, 45.7)	Ref	
Other	35.1 (29.9, 40.3)	1.00 (0.83, 1.22)	34.0 (29.6, 38.3)	0.86 (0.74, 0.99)	34.3 (30.4, 38.2)	0.81 (0.71, 0.91)	
Education							0.06
Less than high school	44.5 (37.8, 51.3)	Ref	46.3 (41.0, 51.6)	Ref	44.6 (39.9, 49.2)	Ref	
High school graduate/GED	35.5 (29.6, 41.4)	0.80 (0.66, 0.98)	42.8 (38.1, 47.5)	0.92 (0.80, 1.07)	50.9 (46.0, 55.8)	1.13 (0.99, 1.28)	
More than high school	33.0 (29.2, 36.7)	0.75 (0.62, 0.91)	35.7 (32.8, 38.6)	0.77 (0.68, 0.88)	37.5 (34.6, 40.5)	0.84 (0.74, 0.95)	
Marital status							0.71
Married/living with partner	28.3 (25.0, 31.6)	Ref	32.0 (29.2, 34.8)	Ref	33.6 (30.9, 36.3)	Ref	
Widowed/ Divorced/Separated	51.0 (45.9, 56.1)	1.80 (1.57, 2.07)	56.6 (51.7, 61.5)	1.78 (1.57, 2.02)	66.0 (61.0, 71.0)	1.99 (1.78, 2.22)	
Never married	42.4 (31.9, 52.9)	1.49 (1.13, 1.98)	44.1 (38.2, 50.0)	1.38 (1.17, 1.62)	51.5 (46.6, 56.4)	1.50 (1.33, 1.70)	
Age at Sexual Debut							0.51
Age ≥16 years	32.3 (29.1, 35.5)	Ref	36.1 (33.2, 39.0)	Ref	37.0 (34.3, 39.8)	Ref	
Age <16 years	48.2 (40.3, 56.1)	1.49 (1.26, 1.77)	47.6 (42.8, 52.4)	1.31 (1.16, 1.49)	52.2 (47.7, 56.7)	1.41 (1.26, 1.57)	

Characteristic	Birth Cohort 1950-1959 (n = 1942) Age-range (45-59) Weighted % (95% CI)	Age-adjusted PR (95% CI)	1960-69 (n = 2976) Age-range (36-56) Weighted % (95% CI)	Age-adjusted PR (95% CI)	1970-79 (n = 2984) Age-range (27-44) Weighted % (95% CI)	Age-adjusted PR (95% CI)	P-value for interaction*
Number of Lifetime Partners							0.79
0-1	13.5 (9.5, 17.4)	Ref	14.1 (10.8, 17.4)	Ref	Ref	Ref	
2-5	35.5 (30.9, 40.1)	2.62 (1.93, 3.57)	35.6 (32.5, 38.7)	2.53 (1.95, 3.29)	2.26 (1.75, 2.92)	2.27 (1.76, 2.93)	
6-9	41.9 (34.7, 49.1)	3.08 (2.19, 4.32)	47.9 (41.8, 54.0)	3.40 (2.65, 4.37)	2.71 (2.11, 3.47)	2.73 (2.14, 3.50)	
≥10	49.5 (42.4, 56.7)	3.64 (2.66, 4.98)	51.1 (46.1, 56.2)	3.60 (2.79, 4.66)	3.20 (2.54, 4.03)	3.20 (2.54, 4.03)	
Partners in past year							0.06
0-1	32.7 (26.9, 35.9)	Ref	36.3 (33.8, 38.7)	Ref	Ref	Ref	
≥2	75.3 (64.8, 86.2)	2.27 (1.91, 2.69)	65.2 (56.0, 74.5)	1.79 (1.55, 2.06)	1.80 (1.58, 2.04)	1.78 (1.57, 2.03)	
History of genital warts diagnosis							0.79
No	33.5 (30.4, 36.5)	Ref	37.7 (35.0, 40.3)	Ref	Ref	Ref	
Yes	52.8 (39.4, 66.1)	1.55 (1.17, 2.04)	52.6 (44.2, 61.1)	1. 40 (1.17,1.68)	1.39 (1.16, 1.66)	1.40 (1.17, 1.67)	
History of cervical cancer							0.57
No	34.6 (31.7, 37.5)	Ref	38.6 (36.3, 40.9)	Ref	Ref	Ref	
Yes	57.1 (38.9, 75.4)	1.64 (1.18, 2.28)	48.7 (29.9, 67.5)	1.26 (0.85, 1.86)	1.31 (0.94, 1.80)	1.32 (0.97, 1.80)	
Hysterectomy							0.79
No	35.0 (31.5, 38.5)	Ref	37.4 (34.4, 40.4)	Ref	Ref	Ref	
Yes	35.3 (29.1, 41.5)	0.99 (0.82, 1.19)	39.4 (32.9, 45.9)	1.06 (0.90, 1.25)	1.08 (0.84, 1.39)	1.10 (0.85, 1.42)	
Smoking (at least 100 cigarettes in life)							0.34
Ever Smoker	29.4 (26.1, 32.8)	Ref	32.6 (30.0, 35.2)	Ref	Ref	Ref	
Never Smoker	42.2 (37.2, 47.1)	1.42 (1.20, 1.67)	46.7 (43.0, 50.4)	1.43 (1.29, 1.59)	1.30 (1.17, 1.45)	1.30 (1.17, 1.45)	

*p-value for test of interaction between 10-year birth cohort and characteristics in log-binomial models adjusted for continuous age

Figures

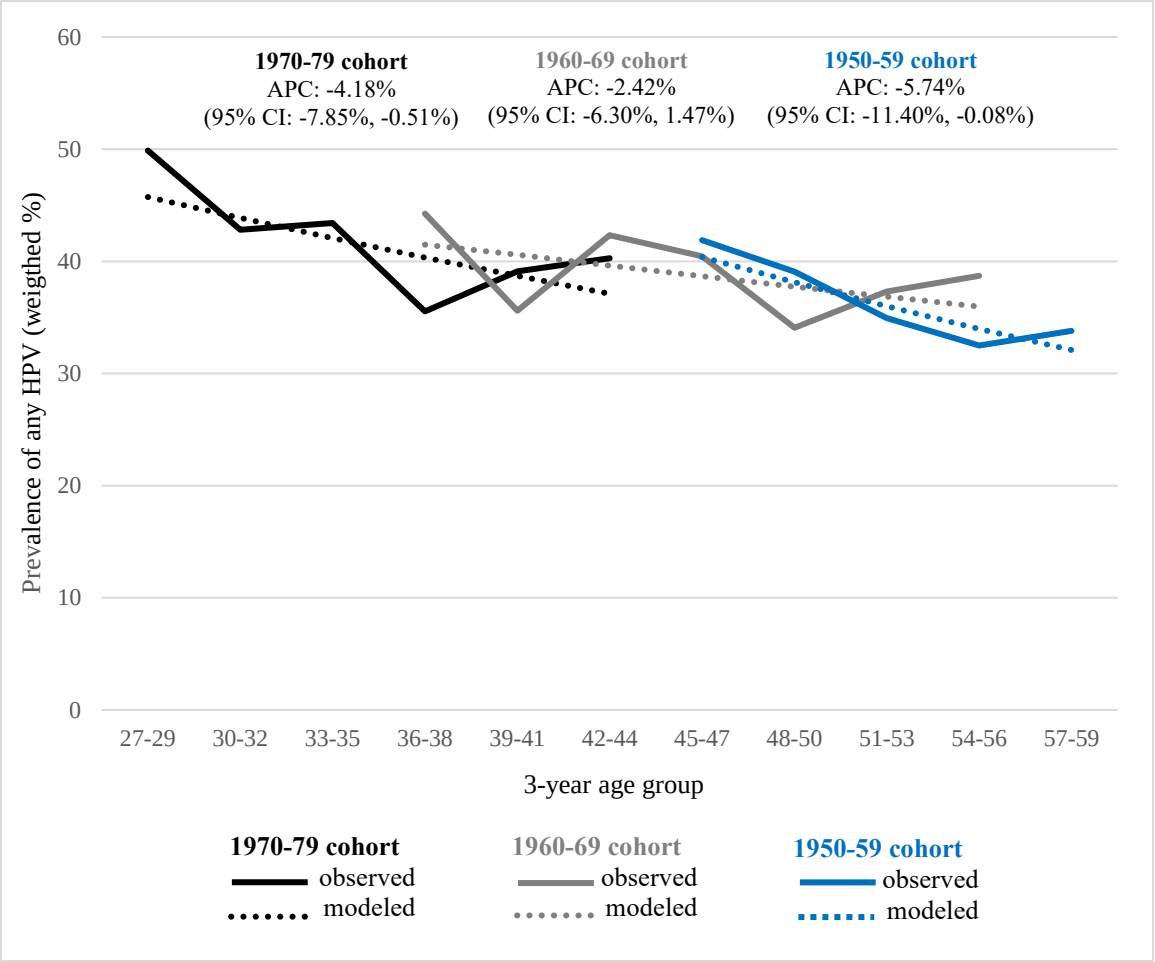


Figure 1: Prevalence and modeled linear relationship of any HPV and 3-year age group by birth cohort among females older than recommended age for vaccination, NHANES 2003-2016

APC, average percent change per 3-year increment

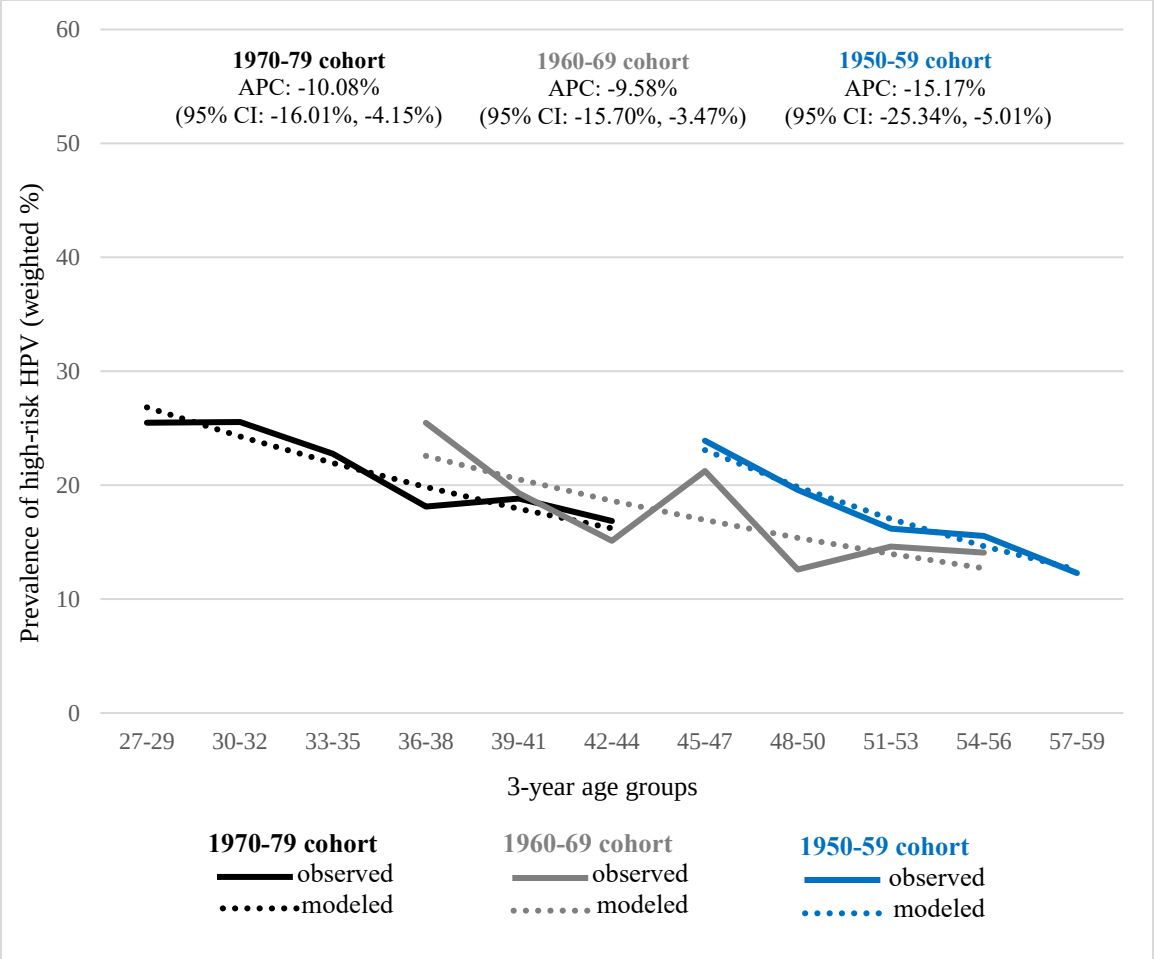


Figure 2: Prevalence and modeled linear relationship of high-risk HPV and 3-year age groups by birth cohort among females older than recommended age for vaccination, NHANES 2003-2016

APC, average percent change per 3-year increment

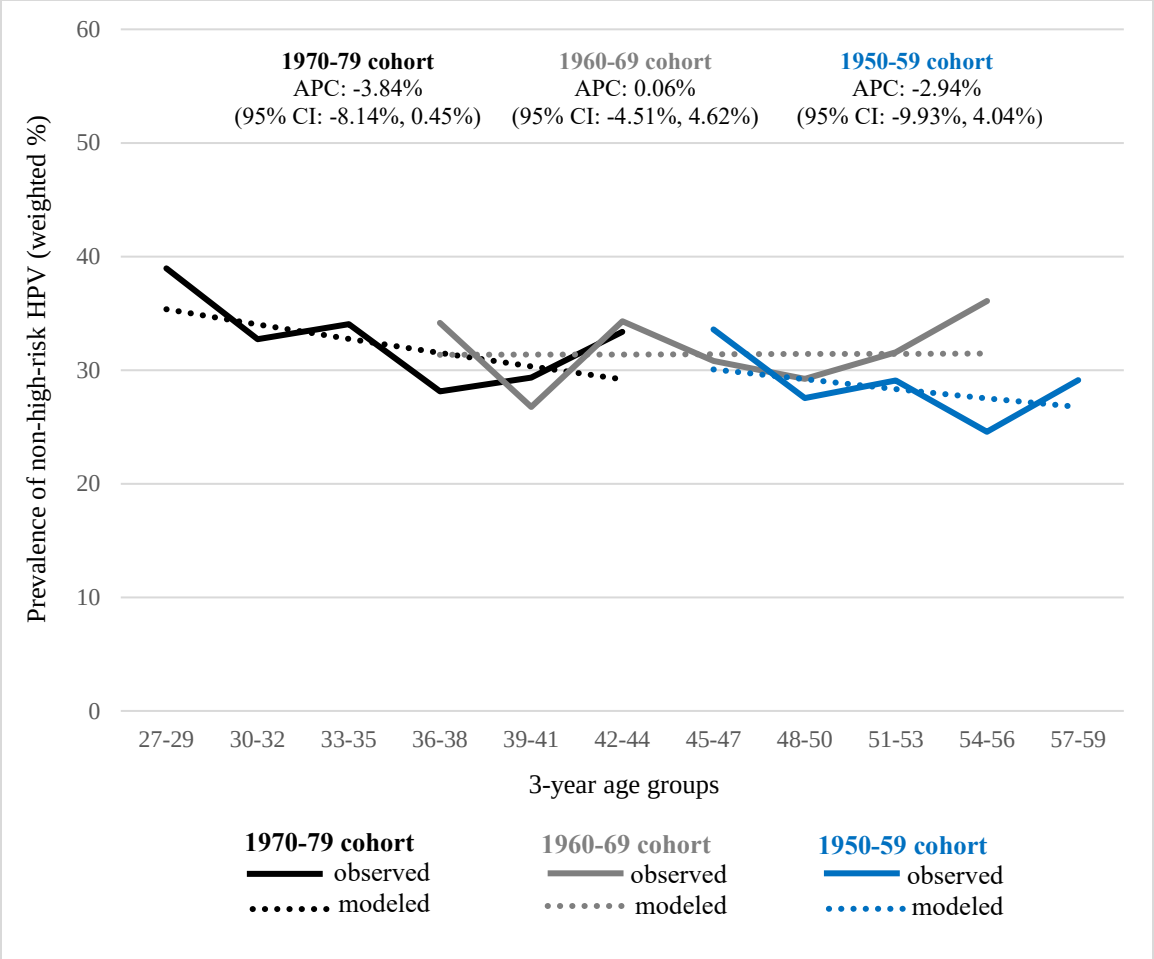


Figure 3: Prevalence and modeled linear relationship of non-high-risk HPV by birth cohort among females older than recommended age for vaccination, NHANES 2003-2016

APC, average percent change per 3-year increment

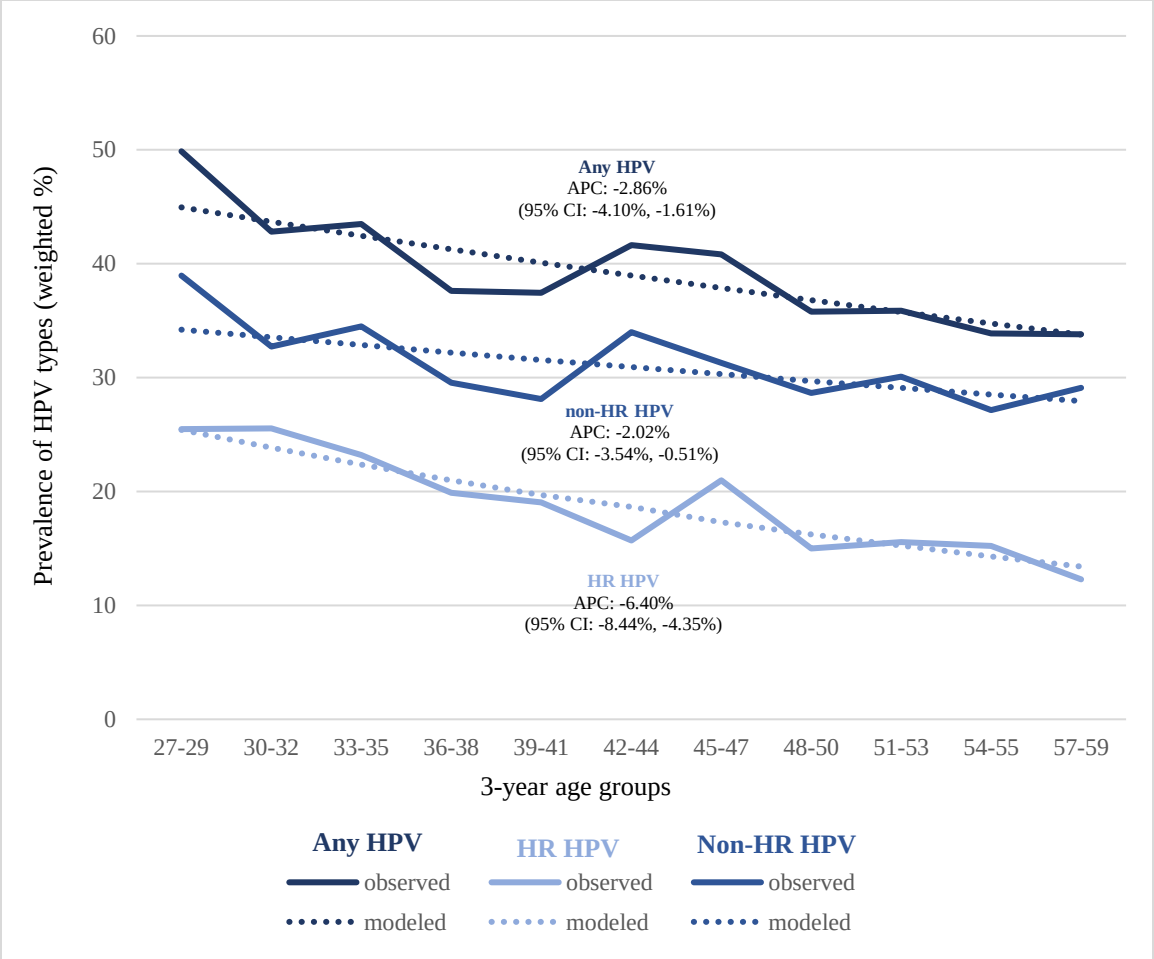


Figure 4: Prevalence and modeled linear relationship between HPV type groups prevalence and 3-year age groups among older than recommended age for vaccination, NHANES 2003-2016

APC, average percent change per 3-year increment

Chapter III: Summary, Public Health Implications, Possible Future Directions

Summary

In this analysis on a nationally representative sample of females ages 27-59 born in 1950-1979, we found that HPV prevalence declined with age in all birth cohorts, and age-adjusted associations of any HPV with most characteristics did not vary by birth cohort. We found evidence to support declines in prevalence with successive 3-year age groups overall for any HPV, HR HPV, and non-HR HPV and among individual 10-year birth cohorts for any HPV and HR HPV. Our study suggests that age plays a larger role in HPV prevalence than cohort.

Public Health Implications

Evaluating patterns in HPV prevalence among those older than recommended age for vaccination provides a needed context for interpretation of trends seen in cohorts of females eligible for vaccination as they age into these older age groups. Statistical support for the lack of a cohort effect on age-specific prevalence allows researchers to confidently conclude that declines with age are in fact a function of age rather than masking cohort differences generated by unique behaviors and demographic specific to when a person is born.

Possible Future Directions

This data can help inform the direction of future studies on HPV prevalence. First, as more years of NHANES data are collected and released, expansions of the study of

age-specific HPV prevalence by cohort can be conducted. While our data allow insight into the association between age and HPV prevalence in different birth cohorts, future years of data will include data on additional ages for the 1960s and 1970s cohort; this could solidify patterns observed by allowing analysis of more complete cohorts. Of consideration is that in the future more females in these age groups may be vaccinated, given the individual clinical decision-making that is part of the current vaccine recommendations for those over age 27. Also, in the future, many vaccinated females in NHANES data will be vaccinated with the nonvalent vaccine, which will affect type distribution, especially for HR HPV type groups; it will be many years before cohorts vaccinated with routine vaccinate by the nonvalent vaccine reach these age groups.

Second, a cohort study of on HPV prevalence among females of all ages would be ideal to observe trends and associations. A study specifically designed to collect longitudinal data on a cohort would provide evidence to better answer if there is a cohort effect on HPV prevalence. Ideally a cohort study would be conducted on a nationally representative sample, but this is often not feasible.

Additionally, our study cannot make conclusions on HPV prevalence at ages older than 59. A Polish study found HPV prevalence to be lower at age 78 compared to age 56, and a US study found HR HPV prevalence in females 57-85 to be nearly identical to females 50-59, but there still little published data on HPV prevalence in US population-based samples of older females, especially females older than 60 (44, 45). If one wants to provide conclusive evidence on a second peak in HPV prevalence at older ages, it would be best to study HPV in ages beyond 59 years.

Appendix I: HPV prevalence using alternative classification of age and cohort

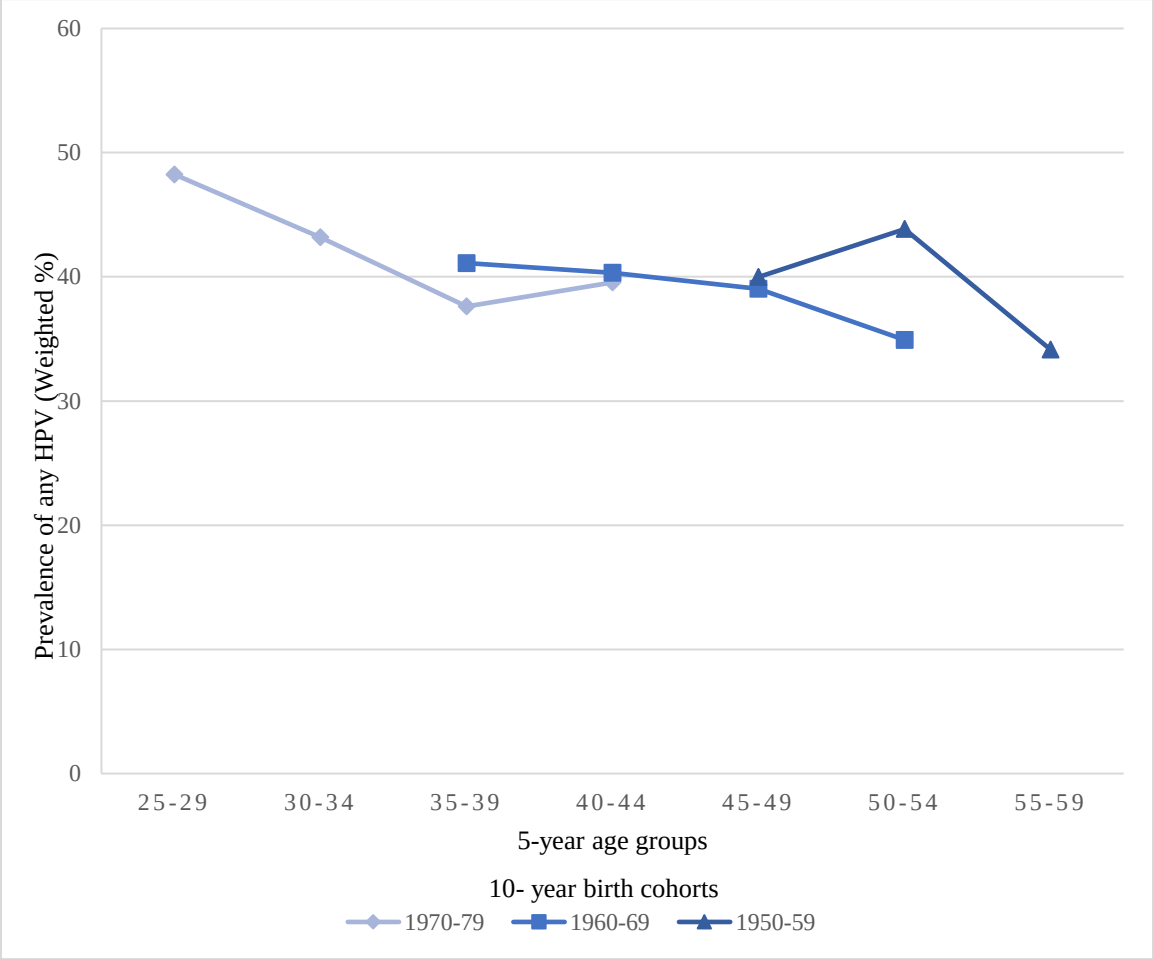


Figure A1: Prevalence of any HPV by 5-year age groups and 10-year birth cohorts among older than recommended age for vaccination, NHANES 2003-2016

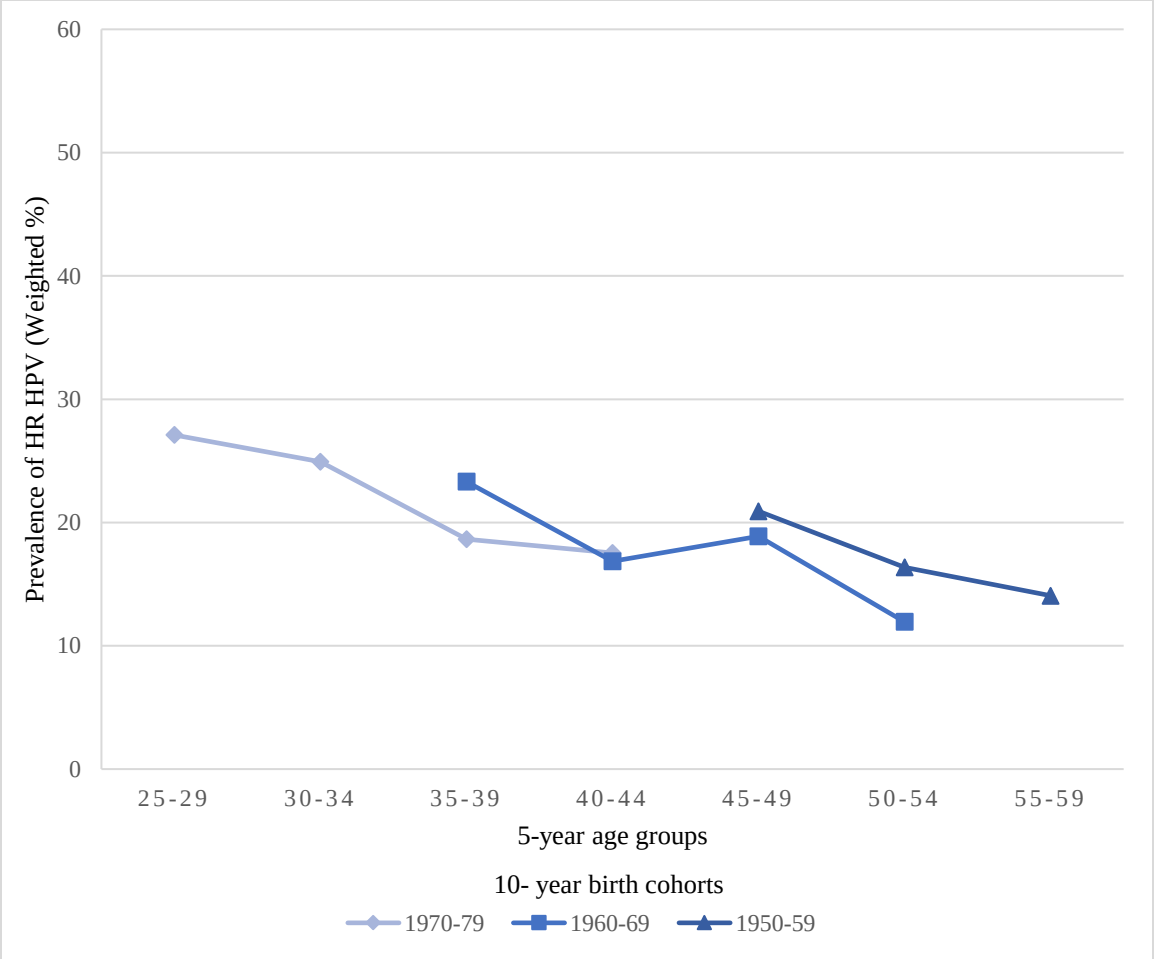


Figure A2: Prevalence of HR HPV by 5-year age groups and 10-year birth cohorts among older than recommended age for vaccination, NHANES 2003-2016

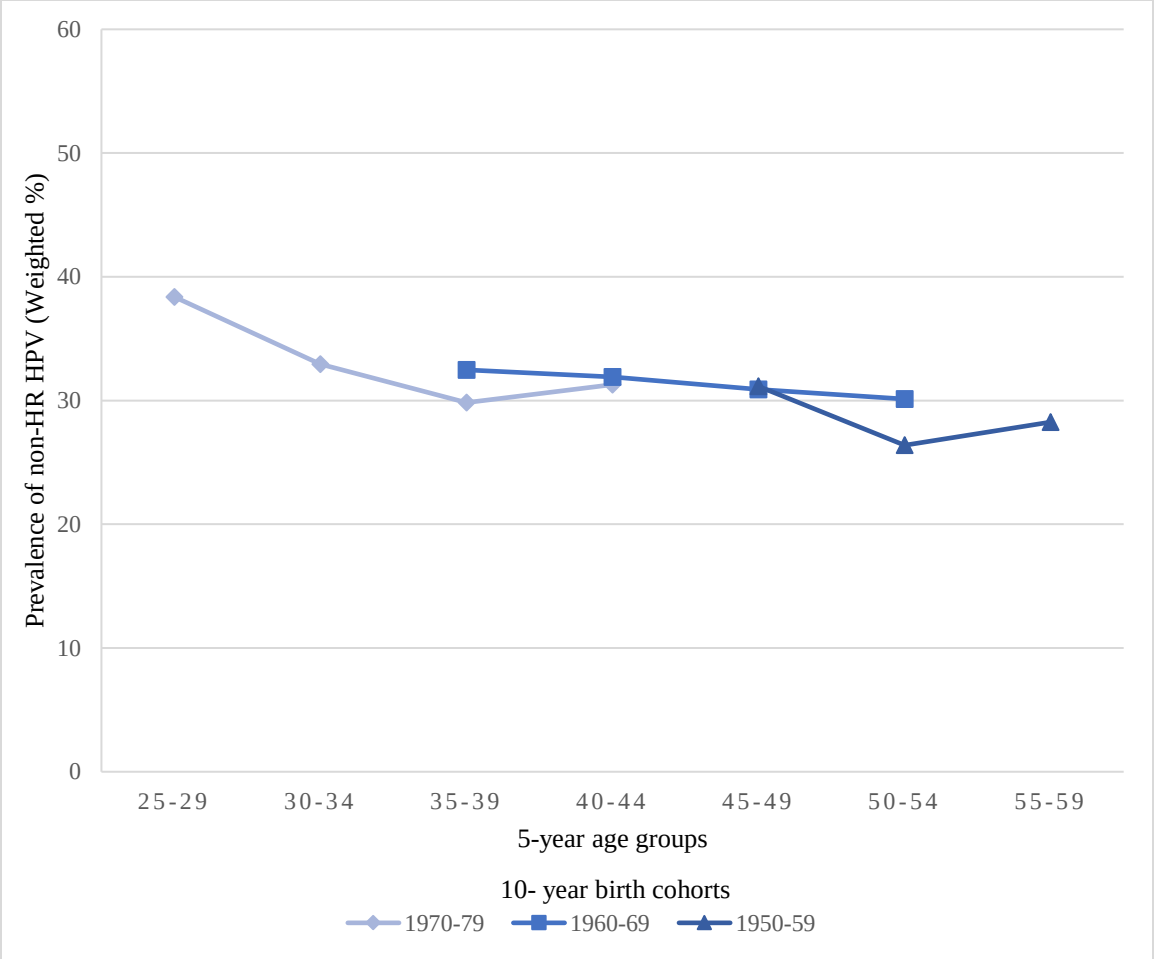


Figure A3: Prevalence of non-HR HPV by 5-year age groups and 10-year birth cohorts among older than recommended age for vaccination, NHANES 2003-2016

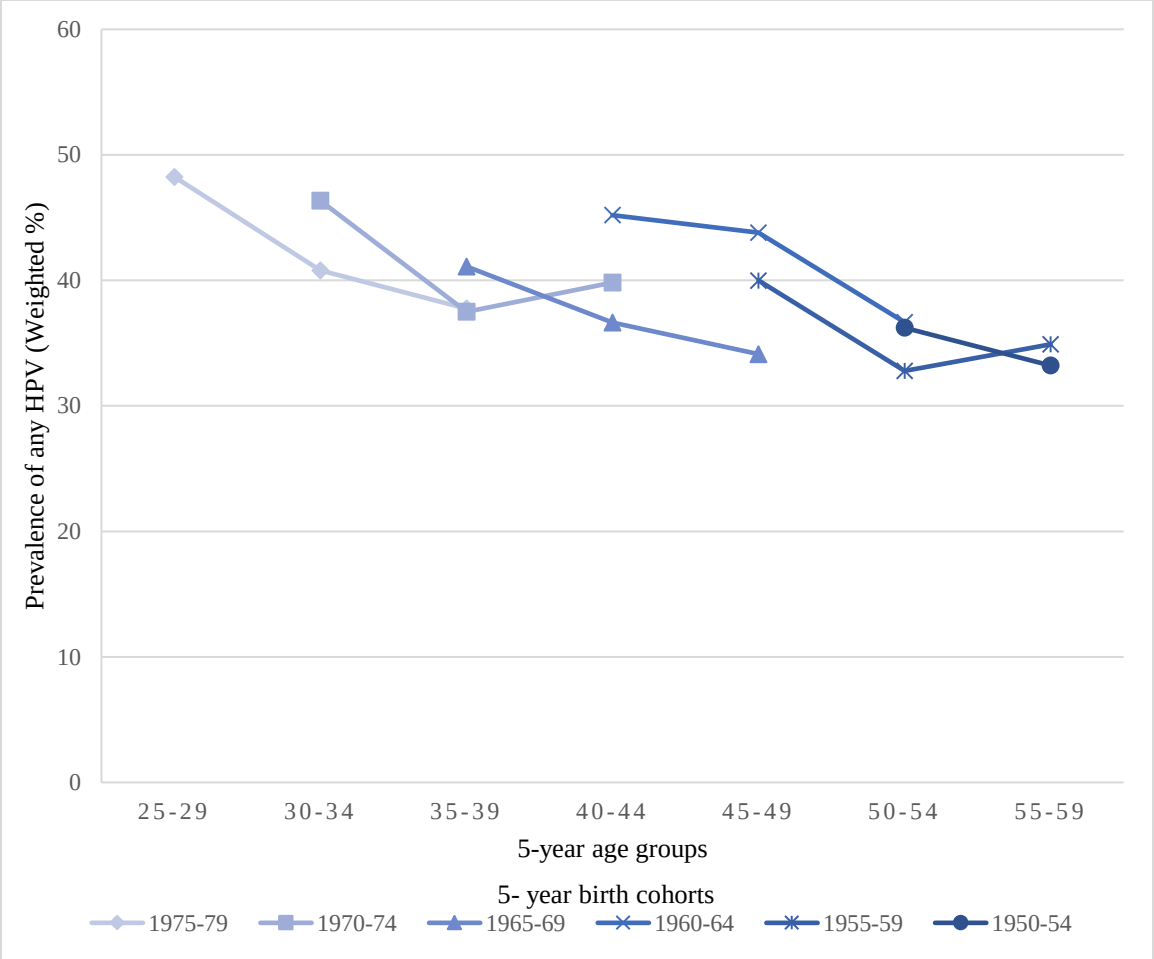


Figure A4: Prevalence of any HPV by 5-year age groups and 5-year birth cohorts among older than recommended age for vaccination, NHANES 2003-2016

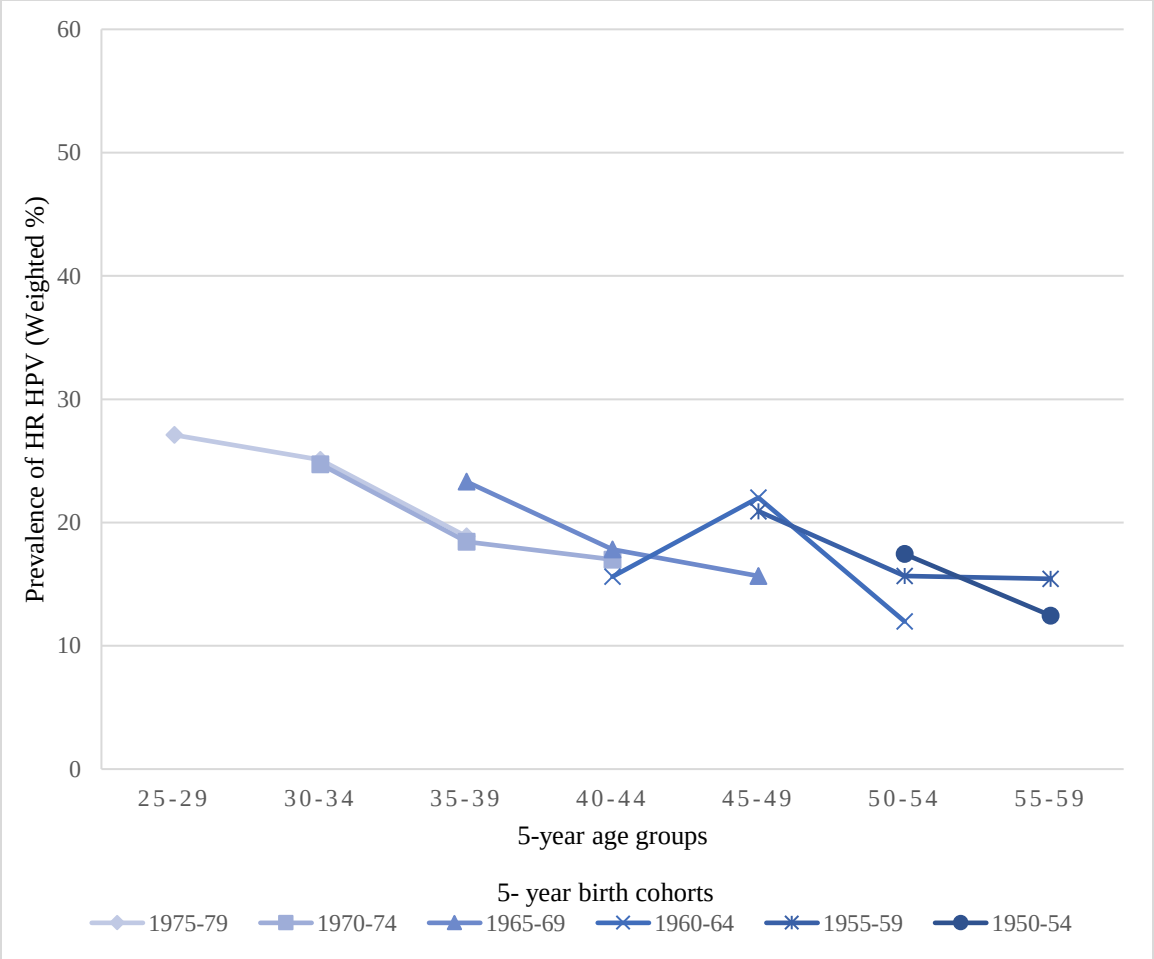
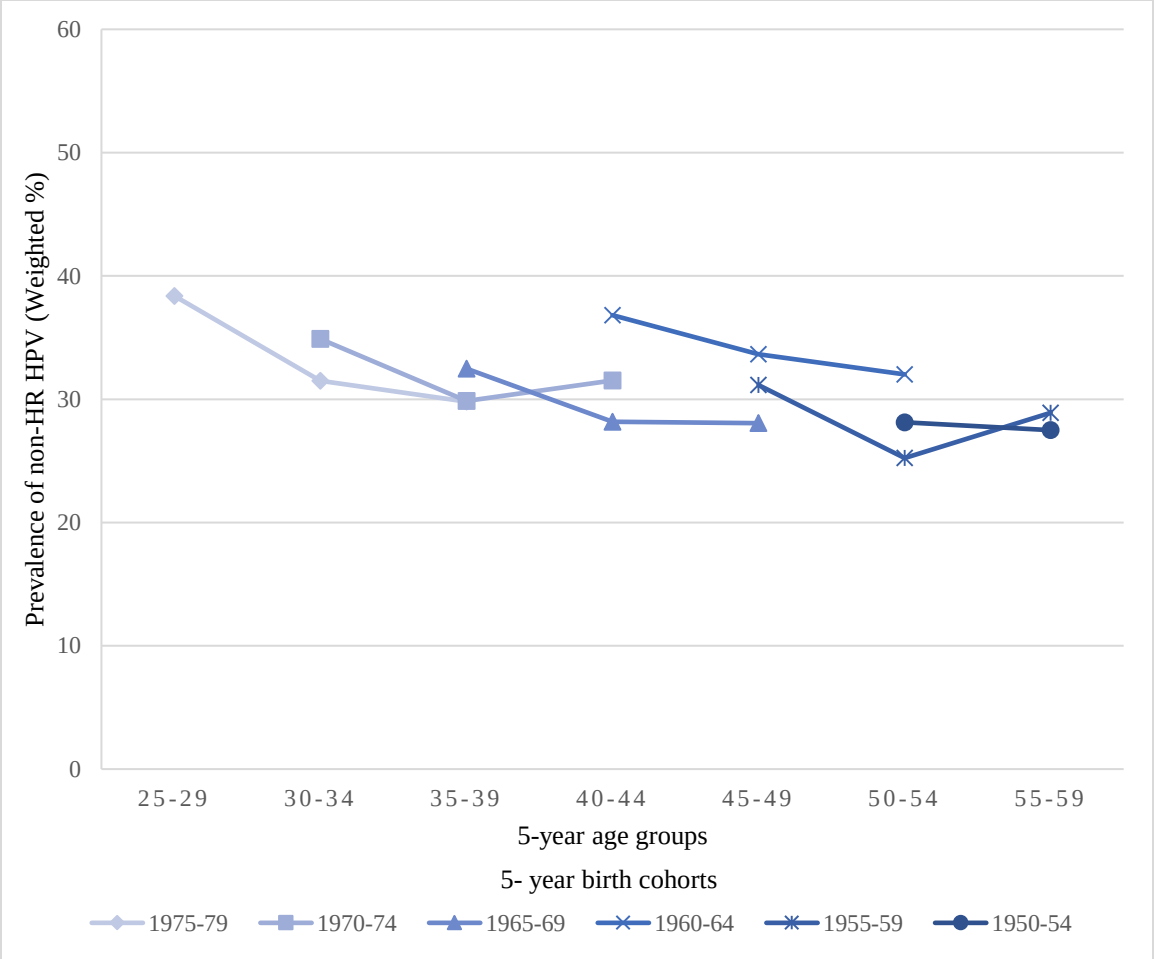


Figure A5: Prevalence of HR HPV by 5-year age groups and 5-year birth cohorts among older than recommended age for vaccination, NHANES 2003-2016



Figures A6: Prevalence of non-HR HPV by 5-year age groups and 5-year birth cohorts among older than recommended age for vaccination, NHANES 2003-2016

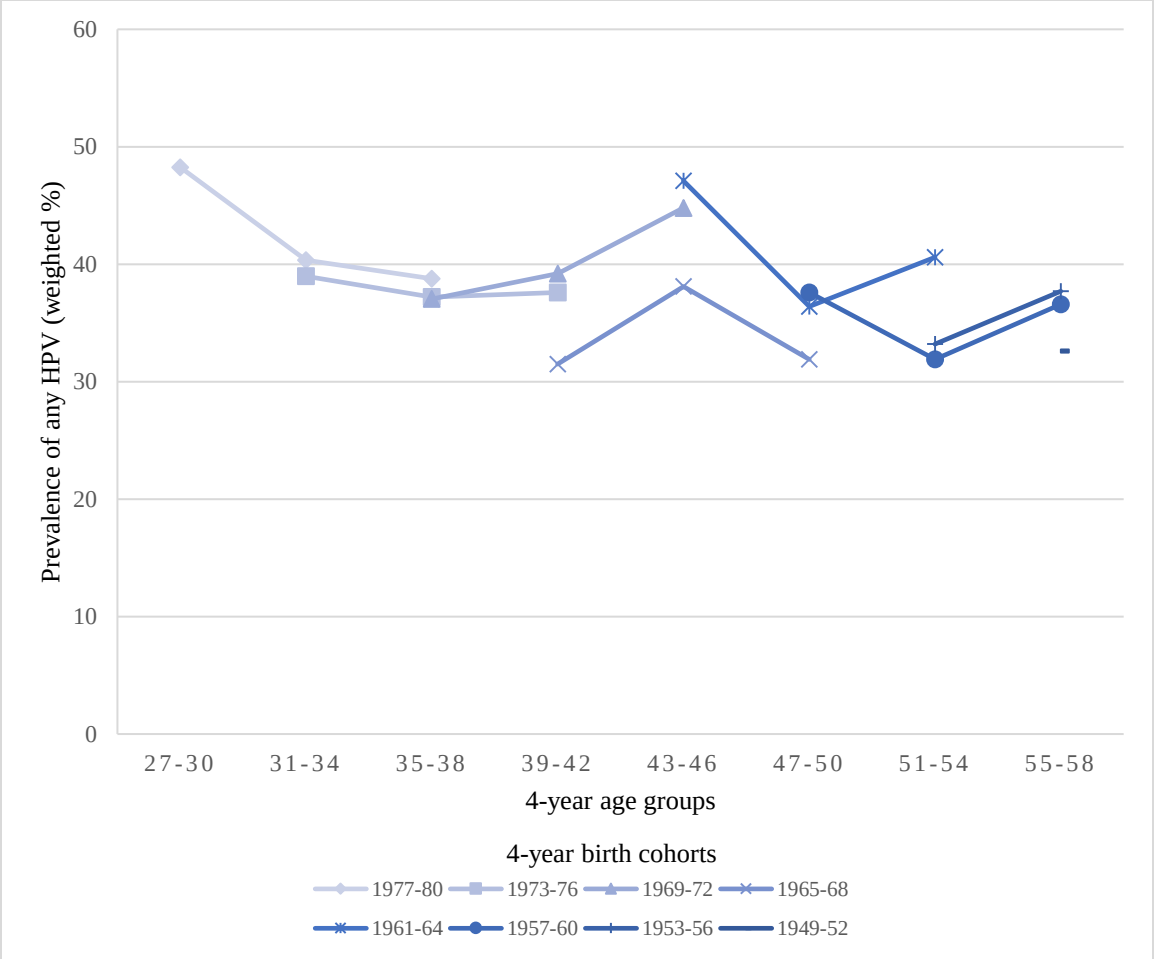


Figure A7: Prevalence of any HPV by 4-year age groups and 4-year birth cohorts among older than recommended age for vaccination, NHANES 2003-2016

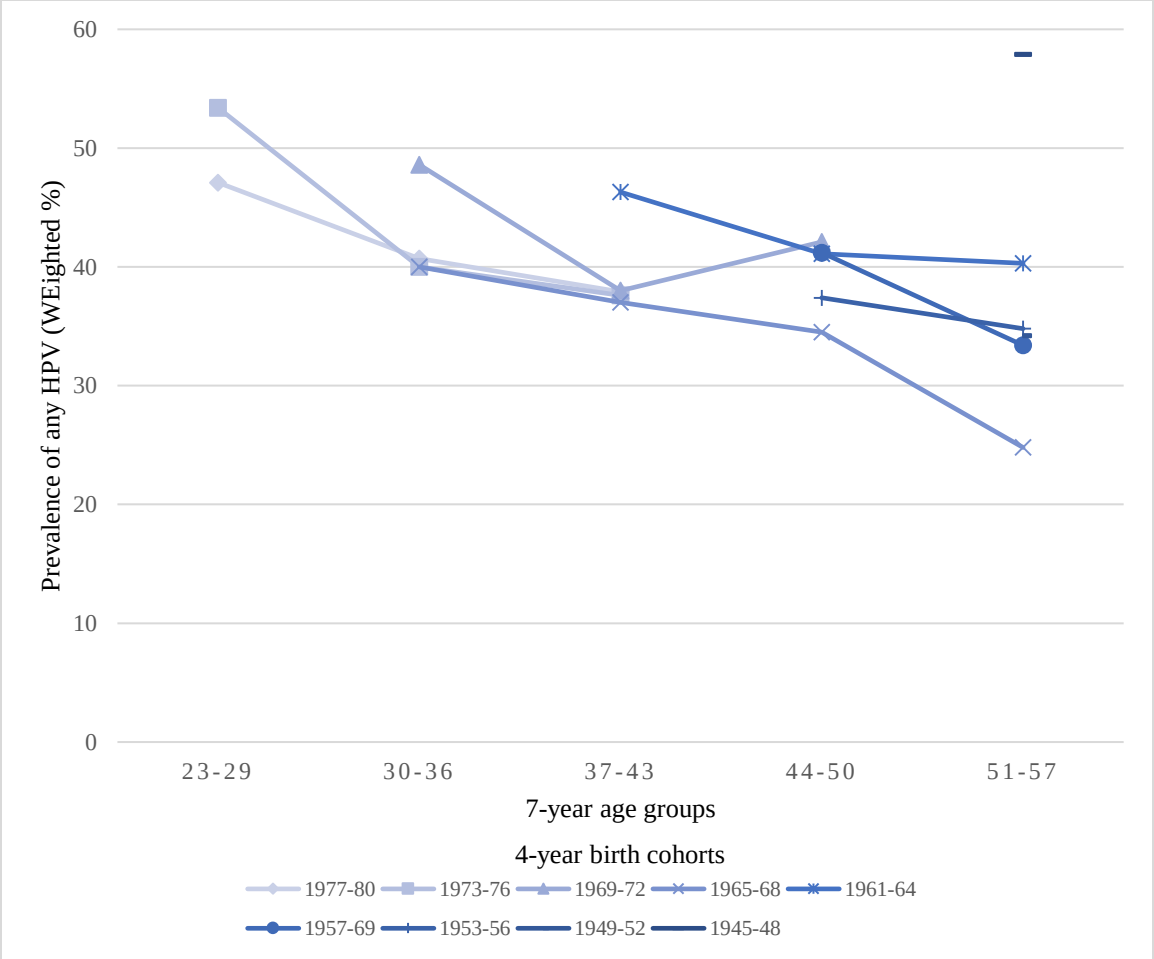


Figure A8: Prevalence of any HPV by 7-year age groups and 4-year birth cohorts among older than recommended age for vaccination, NHANES 2003-2016

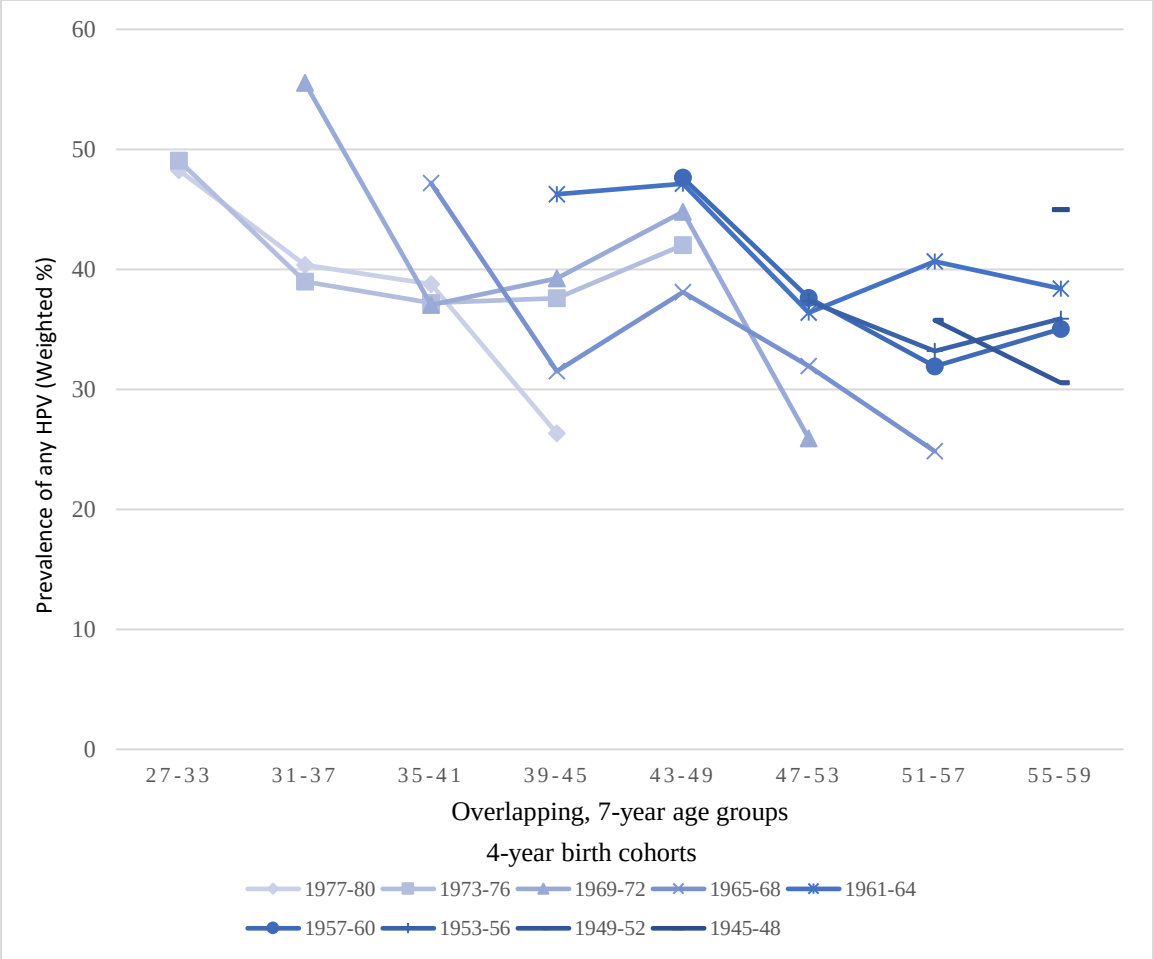


Figure A9: Prevalence of any HPV by overlapping 7-year age groups and 4-year birth cohorts among older than recommended age for vaccination, NHANES 2003-2016