EXAMINING GEOGRAPHIC DIFFERENCES IN HPV-ASSOCIATED CANCER AMONG WOMEN AND MEN, ADOLESCENT HPV VACCINE UPTAKE, AND STATE IMMUNIZATION POLICY

by

PARAN PORDELL

(Under the Direction of Mark H. Ebell)

ABSTRACT

Human papillomavirus (HPV) is the most common sexually transmitted infection (STI) in the United States. Each year, over 46,000 cancers are attributable to HPV types that can be prevented by the current vaccine, and almost 56% of these cancers are diagnosed among women. Additionally, adolescent HPV vaccine coverage remains below 60 percent in the U.S. The study purpose was to better understand the impact of rurality on HPV-associated cancers among women and men and the impact of state immunization policies on adolescent HPV vaccine uptake. CDC National Program of Cancer Registries and NCI Surveillance, Epidemiology, and End Results 2008-2018 program data was used to calculate mean age-adjusted incidence rates and incidence rate ratios for all HPV-associated and six site-specific cancers. Bivariate and multivariate regression analyses were performed using negative binomial models. The qualitative study explored the policy environment and process in states that passed HPV vaccine school mandate legislation and assessed HPV and cancer risk knowledge, attitudes, beliefs, and perceptions among state stakeholders.

Quantitative study findings demonstrated an association between rurality and elevated penile and vulvar cancer incidence after adjustment for confounders. Economic status was independently associated with increased all HPV-associated, cervical, vulvar, oropharyngeal, and anal cancer. A lower county PCP rate was associated with increased cervical cancer incidence. Policy stakeholders described parent, healthcare professional, and state as intersecting at three roles essential to adolescent vaccine uptake: as educator, public health advocate, and vaccine champion. Stakeholders cited Department of Health (DOH) leadership and changing existing DOH rules or regulations as major facilitators to HPV vaccine policy introduction. Participants identified opposition from anti-vaccine groups and a lengthy regulatory review and approval process as barriers to policy introduction. Quantitative findings illustrate the independent association between socioeconomic status and increased HPV-associated and site-specific cancers. Additional behavioral studies are warranted to examine the root causes of sexual risk behavior, poor access to health care, and vaccine and cancer screening hesitancy in rural and urban populations. Parents, healthcare professionals, and the state can collectively use their influence and shared responsibilities as vaccine advocate, educator, and champion to improve state vaccination rates post-COVID-19.

INDEX WORDS: HPV, Human papillomavirus, HPV-associated cancer, Rural health, Adolescent vaccine uptake, Vaccine policy, Mixed methods, Cancer incidence, Social determinants of health, Social ecological model

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DEDICATION

In loving memory of Parvin Zahedi Pordell (1937-2001)

This dissertation is dedicated to all individuals impacted by HPV-associated cancer: Survivors, those who lost their lives due to a cancer diagnosis, their families, and caregivers. It is also dedicated to clinicians, community health workers, researchers, public health professionals, and policymakers committed to reducing geographic, gender-based, and racial/ethnic health disparities among women, men, and adolescents through cancer prevention, early detection, and treatment.

"Success is not a goal to reach or a finish line to cross. It is a system to improve, an endless process to refine."
- James Clear

"Yesterday I was clever, so I wanted to change the world. Today I am wise, so I am changing myself."
-Rumi

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ACRONYMS

ACS American Community Survey

AMA American Medical Association

AHRF Area Health Resource Files

ARC Appalachian Regional Commission

CDC Centers for Disease Control and Prevention

DNA Deoxyribonucleic acid

FIPS Federal Information Processing System

HRSA Health Resources and Services Administration

HPV Human papillomavirus

NCI National Cancer Institute

NPCR National Program of Cancer Registries

MSA Metropolitan Statistical Area

RUCC Rural Urban County Code

SEER Surveillance, Epidemiology, and End Results Program

SEM Social Ecological Model

USDA United States Department of Agriculture

VIF Variance Inflation Factor

CHAPTER 1

INTRODUCTION

Statement of the Problem

Human papillomavirus (HPV) is the most common sexually transmitted infection (STI) in the United States and causes approximately 14 million new infections among males and females annually (CDC, 2017). Persistent HPV infection with high-risk subtypes is associated with an increased risk of cancer. Senkomago et al. (2019) note that each year over 32,000 cancers are attributable to HPV types that can be prevented by the current vaccine, and about 59% of these cancers are diagnosed among women. The International Classification of Diseases for Oncology, 3rd Edition (IACR, 2021; Viens et al., 2016) defines HPV-associated cancers as invasive cancers at anogenital or oropharyngeal sites (cervical adenocarcinoma and squamous cell carcinoma (SCC); vaginal, vulvar, penile, anal, and oropharyngeal SCC) with squamous or glandular cell types containing HPV DNA.

Two doses of 9-valent HPV (9vHPV) vaccine administered before the onset of sexual activity in adolescents (age 11 or 12 years) can reduce the risk of acquiring HPV-associated cancers caused by seven high-risk HPV types (HPV type 16, 18, 31, 33, 45, 52, and 58) later in life (CDC, 2017; Huh et al., 2017, Jemal et al., 2013; Kjaer et al., 2020). Lei and colleagues (2020) conducted a registry-based cohort study in Sweden of over 1.67 million 10-30-year-old females who received or did not receive the HPV quadrivalent vaccine to examine the

association between HPV vaccination and cervical cancer risk and found that vaccinated women had a significantly lower risk of acquiring invasive cervical cancer. Women who initiated HPV quadrivalent vaccine before 17 years of age had a cumulative incidence of 4 cases per 100,000 11 years later while unvaccinated women had a cumulative incidence of 94 cases per 100,000 by age 30 (Lei et al., 2020). The Swedish HPV study findings are consistent with previous studies that showed vaccination against HPV prior to sexual debut (11-12 years) reduces the risk of genital warts and cervical pre-cancers (Herweijer et al., 2017; Level et al., 2013; Silverberg et al., 2018).

Furthermore, in the study directed by Lei et al., cervical cancer incidence rate ratios among women vaccinated before age 17 years and between 17 and 30 years of age were very low at 0.12 (95% CI, 0.00- 0.34) and 0.47 (95% CI, 0.27-0.75), respectively (2020). In 2017, the incidence rate for HPV-associated cancer among women was 13.7/100,000, with cervical cancer comprising the highest overall incidence (7.1/100,000) (CDC USCS, 2020). In the same year, the rate of new HPV-associated cancers among men was 11/100,000, with oropharyngeal cancer accounting for most of these cancers (8.9/100,000) (CDC USCS, 2020).

Behavioral risk factors such as low HPV vaccine uptake, high-risk sexual activity, and inadequate cervical cancer screening may contribute to increased HPV-associated cancer incidence and later stage at diagnosis among women and men residing in rural versus urban areas (Brisson et al., 2013; CDC, 2019; Drolet et al., 2013; Viens et al., 2016; Walker et al., 2019; Yu et al., 2019; Zahnd et al., 2018). These risk factors are more pronounced among rural women and men, which increases their vulnerability to HPV infection exposure and a subsequent cancer diagnosis. While prior studies investigated differences in HPV-associated cancer incidence by

socioeconomic status, age, race, ethnicity, gender, and cancer type, very few studies included community level variables such as health care access, insurance status, some college education, and economic status to examine rural-urban differences in HPV-associated cancer incidence for all HPV-associated cancers among women and men.

Furthermore, there is a paucity of research focused on evaluating the relationship between HPV vaccine uptake and state immunization policy (Benard et al., 2008; Reiter et al., 2013; Viens et al., 2016; Yu et al., 2019; Zahnd et al., 2019). To date, no studies have used combined data from the Centers for Disease Control and Prevention's (CDC) National Program of Cancer Registries (NPCR) and the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) Program cancer registry, which represents all reportable cancer cases in the U.S. (50 states, D.C., and Puerto Rico), to examine the role of rural-urban residence on cancer incidence for all HPV-associated cancers in women and men (CDC, 2018; NCI, 2019).

Research Purpose, Aims, Questions, and Hypotheses

The project's overall purpose was to better understand the impact of rurality on HPV-associated cancers among women and men and the impact of state immunization policies on adolescent HPV vaccine uptake. The project study aims were to: (1) determine the association between geographic status (rural vs. urban) and HPV-associated cancer incidence among U.S. women and men aged 20 years and older; (2) explore the policy environment, process, and stakeholder involvement in states that passed HPV vaccine legislation as part of immunization policy; and (3) assess HPV and cancer risk knowledge, attitudes, beliefs, and perceptions among state stakeholders and how this may impact rejection or passage of HPV vaccine legislation.

The populations of interest for the quantitative study component included women and men aged 20 years and older because the incidence rates of HPV-associated cancer among individuals aged 19 years and under are very low (if cancer case count is 6 or less cases per year, the data is suppressed in the NPCR/SEER registry data set) and some HPV-associated cancers take several years (10-20 years) to advance from pre-cancer to cancer (CDC DCPC, 2019; CDC USCS, 2020; NCI, 2021). The group of interest for the qualitative study component (focuses on HPV vaccine uptake and immunization policy) consisted of 13-17-year-old adolescents because the National Immunization Program-Teen (NIP-Teen) data set includes state data for these age ranges. NIP-Teen notes that measuring HPV vaccination coverage within this age group allows time for adolescents who initiated the vaccine series to complete it and captures vital vaccination data for adolescents who were immunized against HPV at older ages (CDC, 2018). Table 1.1 maps the study aims to the research questions and hypotheses.

Study aim 1 corresponded to research question 1 and hypothesis 1, which focused on the quantitative study component. Study aims and questions 2 and 3 and hypotheses 2 and 3 related to the qualitative study component comprised of stakeholder in-depth interviews and policy analysis.

Table 1.1.

Study Aims, Research Questions, and Hypotheses

Study Aims	Research Questions	Hypotheses
1. Determine the association between geographic status (rural vs. urban) and HPV-associated cancer incidence among U.S. women and men aged 20 years and older.	1. How does HPV-associated cancer incidence among U.S. women and men aged 20 years and older differ by urban versus rural residence, and if so, for which HPV-associated cancers?	1. Rural residence among women and men aged 20 years and older is associated with a higher incidence of HPV-associated cancers.
2. Explore the policy environment, process, and stakeholder involvement in states that passed HPV vaccine legislation as part of immunization policy. 3. Assess HPV and cancer risk knowledge, attitudes, beliefs, and perceptions among state stakeholders and how this may impact rejection or passage of HPV vaccine legislation.	2. What were the circumstances, processes, and contexts for the development and passage of HPV vaccine state legislation in Hawaii and Rhode Island? 3. How do the knowledge, attitudes, beliefs, and perceptions of state stakeholders about HPV and cancer risk affect passage or rejection of HPV vaccine legislation in CA, GA, HI, MA, and RI?	2. Adopting state HPV vaccine policy increases adolescent vaccine uptake and access to HPV vaccination, which significantly reduces the risk of acquiring HPV-associated cancer later in life among males and females 3. Stakeholders who are aware of the link between HPV infection and cancer risk are more likely to advocate for inclusion and passage of state HPV immunization legislation.

Social Ecological Model, HPV-associated Cancer Conceptual Model, and Constructivist Paradigm as Study Frameworks

The social ecological perspective on health promotion by McLeroy et al. (1988) is based on the notion that behavior is shaped by certain factors including 1) individual factors; 2) interpersonal processes and primary groups; 3) community factors; and 4) societal or structural level factors. The Social Ecological Model provided an appropriate theoretical framework for this mixed methods study because empowered and sustainable change is necessary at individual, interpersonal, community, and structural levels to promote cancer prevention and a reduction in rural HPV-associated cancer disparities among women and men (Frieden, 2010). The interconnected nature of components such as individual knowledge and behavior, social networks and family, school, church, and access to health care as well as geographic location, culture, employment, economic development, and state immunization policy exemplifies the multifaceted relationships between behavior, spheres of influence, and environment (Glanz, 2016; McLeroy et al., 1988). Please see Figure 1.1 for the HPV-Associated Cancers in Women and Men Social Ecological Model.

At the individual level, knowledge, attitudes, behavior, and socioeconomic status represent the primary factors that increase HPV infection and associated cancer risk among men and women aged 20 years and older (Mohammed et al., 2018). At the interpersonal level, lack of access to or lack of health care professionals available within rural areas who provide cancer prevention and screening services may increase HPV-associated cancer risk and may decrease the likelihood of obtaining a physician recommendation for adolescent immunization against HPV (Bailey et al., 2016; Mohammed et al., 2018; Ojeaga et al., 2017).

Family and social networks may promote health-seeking behavior through knowledge sharing and support or increase a woman or man's cancer risk due to a lack of knowledge about HPV or engaging in and promoting risk-taking behavior (e.g., smoking, drug use, excessive alcohol use, sex with multiple partners, unprotected sexual activity). Employers affect cancer risk by providing health care benefits for workers and their families and allowing female workers to take time off to get screened for cervical cancer.

Employers may or may not allow parents to take time off work to take their adolescents to get vaccinated for HPV, provide their employees with paid leave to schedule routine health care and cancer screening appointments, or provide onsite access to health care via a mobile or temporary health clinic (Malone et al., 2020; Vamos et al., 2018). At the community level, lack of public transportation options may impede access to care and reliable transportation options may facilitate access to rural women's and men's health care visits (Syed et al., 2013; Vais et al., 2019). Churches, schools, and community centers serve as venues for health promotion and education as well as potential sites for wellness visits and free immunization and cancer screening services (Kaul, 2019; Lahijani et al., 2021). However, based on conservative political or traditional spiritual beliefs, churches and schools may impede adolescent HPV vaccine uptake (Galbraith et al., 2016; Shelton et al., 2013).

Adequate access to health clinics and hospitals helps women and men in rural areas receive care that may prevent HPV-associated cancer or detect cancer at its earliest stage (Rodriguez et al., 2018). At the structural level, geography, culture and traditional norms, government, economic development, and state immunization policy affect HPV-associated cancer risk among women and men.

These factors can facilitate or deter health and wellness among rural populations. In addition to the Social Ecological Model as a theoretical framework for the study, a conceptual model created by Brisson and colleagues (2013), which consists of sociodemographic characteristics, behavioral risk factors, and HPV-related components was adapted to develop the conceptual model for the quantitative part of the study.

The model (Figure 1.2) was ideal for the study design and research questions because it shows the relationship between sociodemographic characteristics, behavior and health care access (low HPV vaccine uptake, high-risk sexual activity, low cancer screening, delays in seeking care), and risk for persistent HPV infection with cancer-causing DNA types, which increases HPV-associated cancer incidence and later stage at cancer diagnosis among women and men residing in rural areas (Brisson et al., 2013). Drolet et al. (2013) used an iteration of this framework to explore sociodemographic inequalities in sexual activity and cervical cancer screening among women and implications for the successful uptake of the HPV vaccine. The conceptual model consisted of individual and community-level characteristics, behavior, HPV infection, and late stage at diagnosis and HPV-associated cancer outcomes. The qualitative study component consisted of a policy content analysis that focused on three state immunization policies (CA, GA, and MA) without a school HPV vaccine mandate and two state policies (HI, RI) that contained HPV immunization requirements, including school entry mandates.

I chose 3-5 of the following criteria to evaluate each policy: cost; efficacy; equity; political feasibility; administrative feasibility; liberty/freedom; or sustainability. A constructivist paradigm guided the qualitative study component (Table 1.2).

Methodology

I conducted a 12-month study using a convergent, parallel mixed methods design to answer research questions and test hypotheses. Incorporating this design allowed me to compare findings from quantitative and qualitative data sources, collect some of the qualitative and quantitative data simultaneously, and analyze results within the 12-month timeframe (Wisdom and Creswell, 2013). I used a cross-sectional study design for the quantitative part of my study. CDC NPCR and NCI SEER Cancer Registry data from 2008-2018 served as the primary data sources for the secondary analysis, which also included an economic status composite variable.

Additionally, county level public use data was acquired from the County Health Rankings and Roadmaps website (https://www.countyhealthrankings.org/), which included data from U.S. Health Research and Services Administration (HRSA) Area Health Resources Files (AHRF) and U.S. Census for county level primary care physicians rate, percent uninsured, and percent some college variables. The qualitative study component consisted of 13 in-depth interviews with state immunization policy stakeholders and a content analysis of five state immunization policies.

Delimitations and Assumptions

The quantitative study sample consisted of women and men aged 20 years and older diagnosed with HPV-associated cancer from 2008 through 2018. The qualitative study sample included 13 state stakeholders (health department staff from cancer and immunization programs, cancer control coalition members, primary care health professionals, and staff from academic and advocacy organizations) from five states (CA, GA, HI, MA, RI) who resided in the state for at least two years and held their current professional position for at least two years or served in a volunteer or professional role related to HPV vaccine within the last five years. I conducted all in-depth interviews virtually through MS Teams.

Study assumptions included:

(1) State stakeholders would be available to participate in interviews during the chosen timeframe (October-December 2021).

(2) Interview responses from study participants would accurately reflect their professional opinions.

(3) In-depth interview study participants would answer interview questions openly and honestly.

(4) The principal investigator would recruit at least 1-2 representatives from all five states for the stakeholder interviews.

(5) The combined cancer incidence data set from CDC NPCR and NCI SEER contained data from at least 48 states for the timeframe of interest (2008-2018).

Study Significance and Public Health Implications

This study added to the existing research on rural-urban differences and HPV-associated cancer among women and men within the cancer research community and validated prior findings. It also filled a research gap since the quantitative data analysis included individual variables such as age, sex, race/ethnicity, area of residence, and sociodemographic variables at the county level (percent some college, percent uninsured, primary care physicians rate, and economic status). By including individual and community-level characteristics, the study was able to examine associations between multiple variables to assess rural-urban differences in HPV-associated cancer among women and men instead of focusing on age, sex, and race/ethnicity exclusively. Findings will hopefully uncover the myriad and inter-related factors which impact HPV-associated health outcomes in rural areas.

Additionally, I analyzed the most recent HPV vaccine policies from five states, which generated policy recommendations that may provide the necessary evidence to motivate stakeholders to revisit and revise state immunization legislation to include the HPV vaccine. Since social determinants of health, reducing chronic disease disparities, and improving access to care are national and state public health priorities, conducting this study will inform and target cancer prevention and screening programs, including planning and implementation of adolescent HPV immunization programs in rural areas.

Organization of the Study

The remainder of the study is organized into five chapters (with references included after each chapter) and appendices. Chapter 2 presents a review of the literature, which provides background on HPV-associated cancers, including morbidity, mortality, incidence, and cancer trends; differences in HPV-associated cancer by age, sex, race/ethnicity, and geography; four of the main drivers that increase HPV-associated cancer risk: behaviors, lack of vaccination, health care access, and knowledge about HPV. Chapter two concludes with a section devoted to HPV vaccination policy, previous analyses, and adolescent vaccination coverage in the five states of interest. Chapter three includes manuscript one, which focuses on the research aims, methods, analysis, and findings from HPV vaccine policy in-depth interviews with 13 stakeholders.

Chapter four focuses on manuscript two, which consists of the quantitative study rationale, methods, data analyses, and study findings. Chapter 5 contains the study summary, discussion, public health implications, study strengths and limitations, the study's contribution to the HPV-associated cancer and vaccine policy body of knowledge, and future research recommendations.

The study concludes with chapter 6 which ties HPV vaccine policy and HPV-associated cancer burden together and includes implications and recommendations. The remaining dissertation sections consist of the appendices.

Definition of Terms

I will use the following terms frequently throughout dissertation chapters 1-6.

Cancer - A collection of related diseases where some of the body's cells begin to divide without stopping and spread into surrounding tissues. Cancer can begin almost anywhere in the body.

Cancer incidence - New cancer cases per 100,000 population (incidence rate).

Cancer stage at diagnosis - Cancer stage refers to the extent of a diagnosed cancer and is based on factors such as how large the tumor is and if it has spread to other organs, tissues.

Distant cancer stage - Cancer has spread to distant parts of the body.

Health disparities - Gaps in health or health determinants between segments of the population. Examples are differences in disease rates, risky behaviors, receipt of preventive vaccinations like HPV vaccine by race or ethnicity, income level, gender.

Human Papillomavirus (HPV) - A virus that can cause abnormal tissue growth (e.g., warts) and other changes to cells. Persistent infection with certain types of HPV may cause cervical, anal, vaginal, vulvar, penile, and oropharyngeal cancers. HPV spreads by skin-to-skin contact, including through oral, vaginal, or anal sex. Low risk viral strains (6,11) cause genital warts while high-risk strains (type 16, 18, 31, 33, 45, 52, and 58) cause cancer.

HPV-associated cancer - An HPV-associated cancer is a specific cellular type of cancer that is diagnosed in a part of the body where HPV is often found. These parts of the body include the cervix, vagina, vulva, penis, anus, rectum, and oropharynx (back of the throat, including the base of the tongue and tonsils)

HPV-attributable cancer - A cancer that is probably caused by HPV. Centers for Disease Control and Prevention (CDC) studies use population-based data from cancer tissue to estimate the percentage of cancers that are probably caused by HPV.

HPV vaccine initiation - when an adolescent or adult receives at least one dose of HPV vaccine.

HPV vaccine uptake - Initiation and completion of HPV vaccine recommended doses (based on age at initiation).

HPV vaccine up to date - Receipt of two doses of HPV vaccine six months apart before age 15.

Localized cancer stage - Cancer is limited to the place where it started (e.g., cervix), with no sign that it has spread.

Metropolitan statistical area - A Metro area containing a core urban area of 50,000 or more population.

NPCR - Established by Congress in 1992, The Centers for Disease Control and Prevention's (CDC) National Program of Cancer Registries (NPCR) collects data on cancer occurrence (including type, extent, and location of the cancer), the type of initial treatment, and cancer outcomes. NPCR supports 46 states, the District of Columbia, Puerto Rico, the U.S. Pacific Island Jurisdictions, and the U.S. Virgin Islands. This cancer data represents all reported cancer cases in the U.S.

Non-metropolitan statistical area - All counties that are not part of a Metropolitan Statistical Area (MSA) are considered rural.

Parallel, Convergent Mixed Methods Design - A contemporary approach that involves the simultaneous collection of qualitative and quantitative data followed by the combination and comparisons of these multiple data sources.

Regional cancer stage - Cancer has spread to nearby lymph nodes, tissues, or organs.

Rural - A geographic area designation that is below a specific population threshold, such as less than 2,500 people or less than 20,000 people, for example. Rural populations consistently show

lower education and income levels than the overall U.S. population, regardless of how they are defined, and experience barriers to health care access.

SEER Program - Funded since 1973, The National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) Program provides U.S. cancer incidence and survival data from population-based cancer registries covering about 35% of the U.S. population. Data are reported from 19 U.S. geographic areas.

State vaccine policy - State laws that require specific immunizations for students to receive (e.g., Measles, Tdap, Meningitis, HPV, etc.) prior to school entry. These laws may also include medical, spiritual, or personal exemption clauses, funding allocation for immunization programs, vaccine supply, insurance program coverage requirements, and requirements to collect immunization data as part of ongoing surveillance.

Unknown cancer stage - There is not enough information to figure out the stage.

Urban - The U.S. Census defines urban in two ways: Urbanized areas where 50,000 or more people live, and urban clusters of at least 2,500 and less than 50,000 people (U.S. Census, 2020).

Vaccine bundling - Recommending and administering multiple vaccines at the same based on age such as Tdap, HPV, and meningococcal vaccines in adolescents.

Table 1.2.

Theoretical Constructivist Questions and Relevant Postulates
(Adapted from Maykut and Morehouse, 1984; Wilson, 1999; Sage, n.d.)

Questions	Postulates of Constructivism (subjectivism)
1. How does the world work? What is the nature of reality? (Ontology)	1. There are multiple, socially constructed realities forming an interconnected whole
2. What is the nature of knowledge and relationship between the knower and what is known? (Epistemology)	2. The knower and known are interdependent; values are made explicit; created findings
3. What role do values play in understanding the world? (Axiology)	3. Values mediate and shape what is understood; balanced representation of views; participants' awareness; community rapport
4. Are causal linkages possible?	4. Events shape each other. There are multi-directional relationships
5. What is the possibility of generalization?	5. Only tentative explanations for one time and place are possible
6. Human nature	6. Voluntarism
7. Methodology (Approach to systematic inquiry)	7. Idiographic

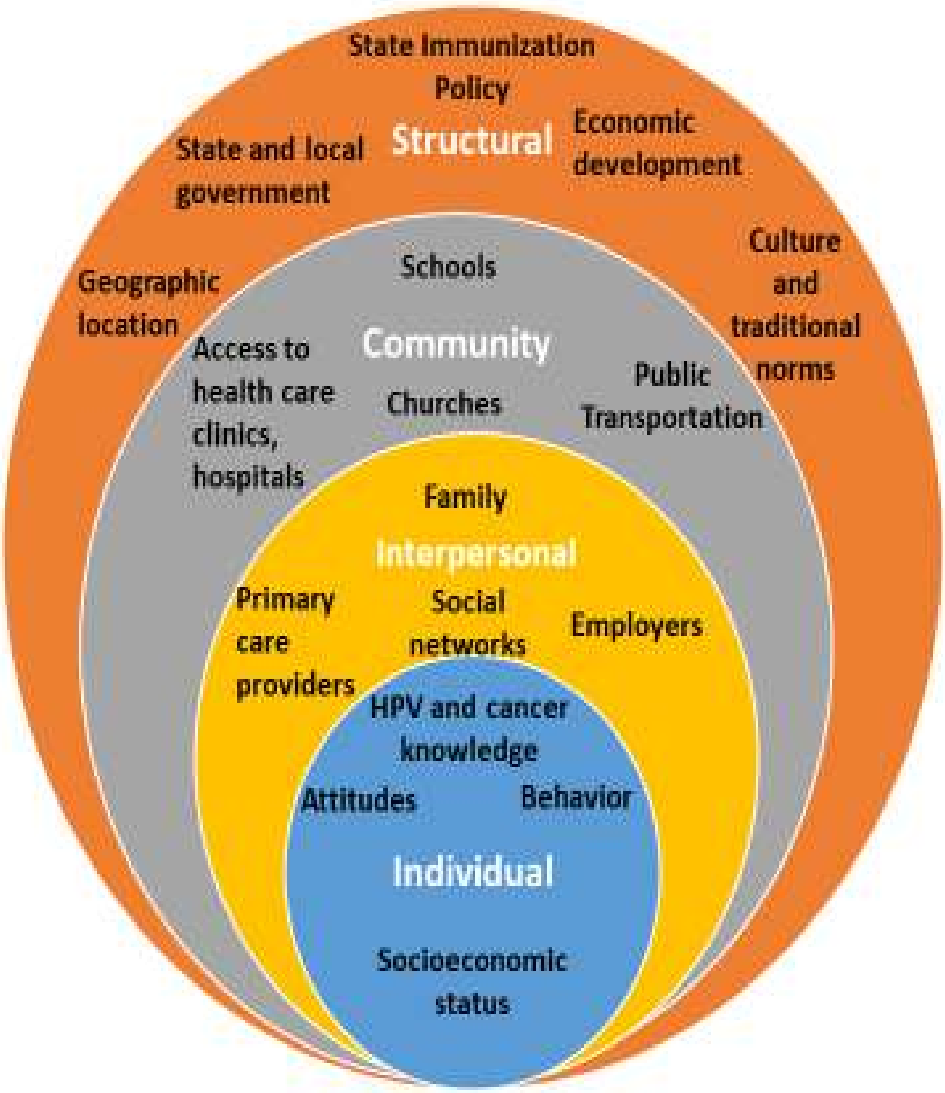

Figure 1.1. *HPV-Associated Cancers in Women and Men Social Ecological Model* (McLeroy et al., 1988)

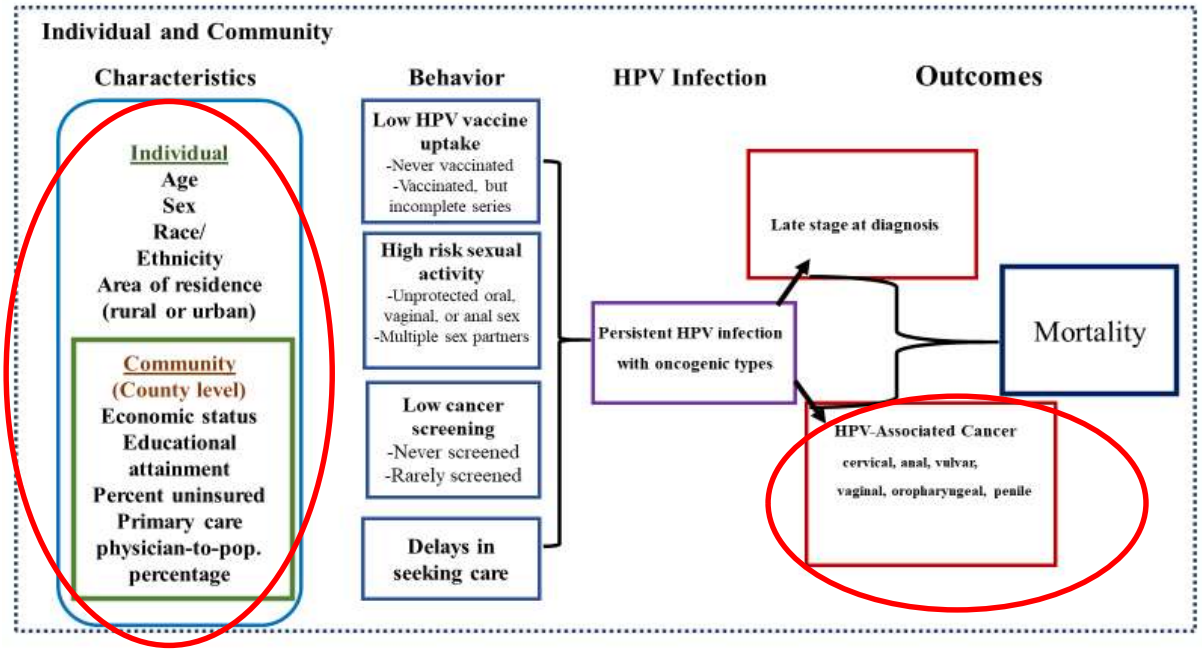

Figure 1.2. *Rural-Urban Differences in HPV-associated Cancer among U.S. Women and Men Conceptual Model* (Adapted from Brisson et al, 2013)

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CHAPTER 2

LITERATURE REVIEW

Overview

This chapter provides a comprehensive synthesis of the existing literature on individual and community level variables that may impact incidence of HPV-associated cancers. Individual variables include age, sex, race/ethnicity, and area of residence. Community level variables consist of economic status, educational attainment (percent some college), percent uninsured, and primary care physicians rate. Behaviors such as high-risk sexual activity, low HPV vaccine uptake, and low cancer screening represent cancer risk factors and are also explored in this chapter followed by a discussion of HPV vaccine legislation.

Epidemiology and Etiology of HPV

Human papillomavirus (HPV) infection causes significant morbidity and mortality in the U.S., causing cancer in about 43,999 individuals each year and an estimated 19,000 deaths in 2021(Senkomago et al., 2019; NCI SEER, 2021a). HPV is a circular double-stranded, non-enveloped DNA virus that infiltrates the body by infecting the cutaneous or mucosal epithelium through skin-to-skin sexual contact (de Sanjose et al., 2018; Dunne and Park, 2013; Longworth and Laimins, 2004; Stanley et al., 2012). HPV is transmitted through vaginal, anal, and oral sex and infection takes place in some males and females shortly after sexual debut (de Sanjose et al., 2018; Dunne and Park, 2013). The risk of acquiring HPV infection increases with an increasing number of lifetime sexual partners.

The prevalence of HPV infection is quite high and reaches its apex among women in their early to mid-twenties (de Sanjose et al., 2018; Hariri et al., 2011). HPV infection among men follows a different trajectory, as prevalence starts increasing around age 18 years and steadily increases through age 65 (Giuliano et al., 2008; Liu et al., 2014; Smith et al., 2011). More than 40 types of HPV DNA infect the anus and genital organs (CDC, 2020a; CDC 2020b; Dunne et al., 2006), and these are categorized as oncogenic (high-risk) and non-oncogenic (low-risk) based on their likelihood to cause cancer. In most cases, HPV infections are transient, and the body clears the virus within 1-2 years after initial infection (de Sanjose et al., 2018; Dunne and Park, 2013).

Low-risk HPV types (non-oncogenic: 6, 11, 42, 43, 44, 54, 61, 70, 72, and 81) are linked to recurrent respiratory papillomatosis (RRP) and anogenital warts. High-risk oncogenic HPV types (16, 18, 31, 33, 45, 52, and 58) may cause persistent infections in females and males, which result in mucosal cell changes and lesions, and may progress to pre-cancer and HPV-associated cancer (anal, cervical, oropharyngeal, penile, vaginal, and vulvar cancer) (de Sanjose et al, 2018; Dunne and Park, 2013; Longworth and Laimins, 2004; Wheeler, 2008). HPV types 16 and 18 are implicated in approximately 63% of all HPV-associated cancers, more than 70% of cervical and oropharyngeal cancers, and almost all anal cancers in the U.S. (Parkin and Bray, 2006; Saraiya et al., 2015; Viens et al., 2016). HPV-associated cancer also increases the risk for secondary HPV-associated cancers: men and women diagnosed with HPV-associated vulvo-vaginal or anal cancer as their primary cancer have a ten-fold higher risk of obtaining a second cancer at either site (Gilbert et al., 2019).

HPV-Associated Cancer Incidence and Mortality

HPV-Associated Cancer Indicence by Age

Certain female and male age groups are particularly vulnerable to HPV-associated cancer. Benard and colleagues (2007) analyzed 1989-2001 NPCR/SEER cancer registry data and concluded that 35-49-year-old women who lived in rural areas had the highest cervical cancer incidence rates after adjusting for poverty and race (35-39-year-olds: 17.5, 95% CI 16.0-19.0); 40-44-year-olds: 17.7, 95% CI 16.2-19.2, 45-49-year-olds: 17.2, 95% CI 15.7-18.8). According to national cancer registry data, new cervical carcinoma cases were highest among 40-44-year-old women (15.4/100,000) in 2015 (CDC USCS, 2020; Van Dyne et al., 2018). Between 2013-2017, cervical carcinoma incidence remained highest among 40-49-year-old females while cervical cancer was diagnosed most often among 35-44-year-old women (22.8% of cases) and 45-54-year-old women (22.4% of cases), respectively, based on 2014-2018 NCI SEER cancer surveillance data (2021).

During the same timeframe, national cancer registry data demonstrate that cervical cancer deaths occurred among 55-64-year-old women most frequently followed by 45-54-year-olds. However, oropharyngeal cancer among men and women impacted an older age group. NPCR/SEER combined registry data for 2013-2017 concluded that 60-69-year-old males experienced the highest oropharyngeal cancer rates while a study using 2013-2014 data from the SEER HPV status database (n = 12,000 patients) discovered similar findings; 60-64-year-old men had the highest incidence of oropharyngeal cancer (13.6/100,000, 95% CI 12.8-14.3) (CDC USCS, 2021; Mahal et al., 2019). It is worth noting that 70-79-year-old women (6.2/100,000) experienced the highest incidence rate of oropharyngeal cancer from 2008-2012, based on national cancer registry data, but in 2015, women ten years younger had the highest disease

burden (60-69-year-olds: 5.8/100,000) (Van Dyne et al., 2018; Viens et al., 2016). Furthermore, Ellington and colleagues (2020) looked at oropharyngeal cancer incidence trends using NPCR/SEER cancer registry data and found that between 2007-2016, oral cavity and pharynx cancer incidence increased among 60-69-year-olds by 1.3% annually; the same cancers declined among 20-49-year-olds.

Additionally, based on 2001-2011 NPCR/SEER data representing 59% of the U.S. population, Razzaghi et al. (2018) concluded that oropharyngeal cancer 10-year survival rates decreased by increasing age (≥ 60 years: 49.1% survival rate vs. 73.4% survival rate among < 40-year-olds) and later stage at diagnosis (regional and distant stages) with the greatest percent reduction in survival among males and females diagnosed at distant stage (female: 29.9%, 95% CI 27.6-32.2; male: 30.9%, 95% CI 29.5-32.4).

NCI SEER cancer surveillance data from 2013-2017 show that anal cancer incidence was highest among 50-59-year-old men and 60-69-year-old females, respectively (CDC USCS, 2021). Deshmukh et al. (2019) examined incidence and mortality trends from 2001-2015 and 2001-2016, respectively, using the US Cancer Statistics (NPCR/SEER combined data) dataset and concluded that anal SCC increased 2.7% each year with the biggest increases in incidence among individuals 50 years of age and older (50-59 years, 3.45, 95% CI 3.40-3.50; 60-69 years, 4.17, 95% CI 4.10-4.23; 70 years and older, 4.21, 95% CI 4.14-4.27). Moreover, during the same timeframe, the study team found that anal SCC diagnosed at distant stage was two times higher and anal SCC diagnosed at regional and distant stages increased by 14% among men and 13% among women, respectively. Earlier studies that examined cancer registry data found that anal SCC incidence from the late seventies through 2010 significantly increased among men and women (Nelson et al., 2013; Shiels et al., 2015).

Additionally, anal cancer mortality rates increased by about 3% per year from 2001-2016 with statistically significant increases in deaths among men and women aged 50 years and older (Deshmukh et al., 2019). Interestingly, 10-year anal cancer survival rates from 2001-2011 were lowest among individuals aged 60 years and older (64.5%, 95% CI 63.2-65.7) and those less than 40-years-old (66.1%, 95% CI 62.8-69.1) (Razzaghi et al., 2018). This trend was also seen at every cancer stage among individuals less than 40-years-old and those aged 60 years and older (localized: 76.4% and 77.1%; regional: 58.3% and 56.7%; and distant: 30.4% and 29.6%).

HPV-Associated Cancer Incidence and Mortality by Sex

HPV-Associated Cancer in Women

Cervical Cancer

Women experience higher HPV-associated cancer incidence when compared with rates among men (CDC, USCS, 2020). In 2017, the incidence rate for HPV-associated cancer among women was 13.7/100,000, with cervical cancer comprising the highest overall incidence (7.1/100,000). A study using national cancer registry data examined HPV-associated cancer incidence trends from 1999-2015 and found that cervical cancer decreased by 1.6% per year among women (Van Dyne et al., 2018). This decline in cervical cancer incidence may be attributed to improvements in access to cervical cancer screening in some populations and adolescent HPV vaccine uptake as cancer prevention (Benard et al., 2014; Lei et al., 2020; Moyer et al., 2012, USPSTF, 2018).

However, based on U.S. cancer registry data from 2013-2017, 20,902 women died from cervical cancer over the cumulative 5-year timeframe (2/100,000) (CDC USCS, 2020). A study of 833 women diagnosed with cervical cancer from 1995-2000 that used medical record data from three years prior to diagnosis found that at least half of the diagnosed cervical cancers were

among women who were rarely or never screened for cancer by a Pap test (Leyden et al., 2005). Razzaghi and colleagues (2018) analyzed NPCR/SEER cancer registry data and reported that out of 79,425 cervical cancers diagnosed from 2001-2011, women diagnosed at local stage experienced an 86% survival rate (95% CI, 85.3-86.7) while women diagnosed at regional stage had a 55.3% survival rate (95% CI, 54.5-56.1). While they noted that 9,049 cervical cancers were diagnosed at distant stage during the same timeframe, survival rate statistics were unavailable from the study.

Anal Cancer

According to Van Dyne and colleagues (2018), from 1999-2015, anal squamous cell carcinoma (SCC) incidence increased by 2.9% per year among women. HPV infection causes 90% of anal cancers and women experience a disproportionate burden and poorer health outcomes from this disease (Clifford et al., 2021; Saraiya et al., 2015). This may be due to the likelihood of HPV cross-site transmission from the cervix to the anus and later stage at anal cancer diagnosis and treatment (Clifford et al., 2021; Lin et al., 2019). Celie et al. (2017) linked cancer registry and Area Health Resources File (AHRF) data from 1973-2011 and found that women with anal cancer were 1.25 times more likely to die from the disease than their male counterparts (H.R. 1.25; CI 1.17-1.32, $p < 0.001$).

HPV 16 is the most pervasive high-risk DNA type detected within anal pre-cancer and cancer lesions, which is also predominantly found in cervical pre-cancers and lesions (Lin et al., 2019, Mix et al., 2019). From 2013-2017, NPCR/SEER registry data demonstrated that anal SCC incidence among women was 2.4/100,000, which is the second most common HPV-associated cancer diagnosed among women (CDC USCS, 2020).

In 2021, American Cancer Society estimates that almost 6,100 women will be diagnosed with anal cancer and 870 females will die from this disease (ACS, 2021). A study that looked at 5-year survival rates for HPV-associated cancers among women using NPCR/SEER cancer registry data reported that out of 16,541 anal cancers diagnosed from 2001-2011, women diagnosed at local stage experienced an 80.2% survival rate (95% CI, 78.5-81.7) while women diagnosed at regional and distant stage had a 63.4% (95% CI, 61.2-65.5) and 36.8% survival rate (95% CI, 33.5-40.0), respectively (Razzaghi et al., 2018).

Vulvar Cancer

Van Dyne and colleagues (2018) examined HPV-associated cancer trends using NPCR/SEER registry data from 1999-2015 and concluded that vulvar squamous cell carcinoma (SCC) incidence increased by 1.3% each year. Based on 2018 U.S. Cancer Statistics (USCS) data, CDC notes that about 5,496 females or 2.6/100,000 females were diagnosed with vulvar cancer and 1,316 women (0.6/100,000) died from the disease (2021). In 2021, based on NPCR/SEER registry data from prior years, an estimated 6,120 new cases of vulvar SCC will be diagnosed among women and about 1,550 deaths will occur from the disease (2021). Razzaghi and colleagues (2018) analyzed NPCR/SEER cancer registry data and reported that out of 19,345 vulvar cancers diagnosed from 2001-2011, women diagnosed at local stage experienced a 79% survival rate (95% CI, 77.7-80.3) while women diagnosed at regional and distant stages had a 52.5% (95% CI, 50.9-54.1) and 16.5 survival rate (95% CI, 13.2-20.2), correspondingly.

Oropharyngeal Cancer

Oropharyngeal cancer incidence rates among women increased by 0.8% per year from 1999-2015, based on an HPV-associated cancer incidence trend analysis using national cancer registry data conducted by Van Dyne et al. (2018). From 2013-2017, about 13.9% of

HPV-associated cancers among women were diagnosed in the oral cavity and pharynx (CDC USCS, 2020). In the same cumulative timeframe, the oral cavity and pharynx incidence rate among women was 1.7/100,000 and 14,042 women died from both types of cancers (1/100,000). Five-year oropharyngeal survival rates among women based on NPCR/SEER cancer registry data were 60%, 51.1%, and 29.9%, respectively, for cancer diagnosed at localized, regional, and distant stages (Razzaghi et al., 2018).

HPV-Associated Cancer in Men

Oropharyngeal Cancer

Oropharyngeal and anal cancers represent the most frequently diagnosed HPV-associated cancers among men. In 2017, NPCR/SEER cancer registry data showed that the rate of new HPV-associated cancers among men was 11/100,000, with oropharyngeal cancer accounting for most of these cancers (8.9/100,000) followed by anorectal cancer (1.3/100,000) (USCS, 2020). Men in the U.S. have poorer health outcomes associated with oropharyngeal cancers than their female counterparts. Nationally representative cancer registry data revealed that the number of men who died from cancers of the oral cavity and pharynx between 2013-2017 was 4-times higher than cases among women (men: 34,262 cases; 4/100,000 vs. women: 14,042 cases; 1/100,000) (USCS, 2020; NCI SEER, 2021c).

Based on 2001-2011 NPCR/SEER cancer registry data, 5-year oropharyngeal survival rates among men were 59.1%, 55.6%, and 30.9%, respectively, for cancer diagnosed at localized, regional, and distant stages (Razzaghi et al., 2018). During the same timeframe, men experienced better oropharyngeal cancer survival rates at regional and distant stages of diagnosis than women. Van Dyne et al. (2018) examined 1999-2015 national cancer registry data and found that oropharyngeal cancer incidence increased by 2.7% each year.

Anal Cancer

The same cancer trend analysis study found that anal cancer increased by 2.1% each year among males. A subsequent anal cancer incidence and mortality study using 2001-2015 national cancer registry incidence and 2001-2016 incidence-based mortality data, correspondingly, unveiled that anal SCC increased among men by 2.2% each year while incidence-based mortality increased by 3.4% each year among males (Deshmukh et al., 2020). Moreover, Razzaghi and colleagues used 2001-2011 national cancer registry data to conduct cancer survival analysis and discovered that 5-year anal SCC survival rates among men were 73.1%, 49.1%, and 18.6% for local, regional, and distant stages, respectively (2018). Anal cancer 5-year survival rates were lower among men when compared to rates among women. In 2021, about 3,020 men will be diagnosed with anal cancer and 560 men will die of the disease (ACS, 2021).

HPV-Associated Cancer Incidence and Mortality by Race and Ethnicity

In the U.S., some HPV-associated cancers disproportionately impact persons who are Black, Indigenous, or People of Color (BIPOC) (Hirth, 2019; Jemal et al., 2013; Megwalu and Ma, 2017; Melkonian et al., 2020; Yoo et al., 2017). Based on NPCR/SEER cancer registry data, cervical cancer incidence and mortality (2013-2017) are highest among Hispanic, non-Hispanic Black (NHB), and American Indian/Alaska Native (AI/AN) women (incidence: 9.6, 9.1, and 8.7/100,000, respectively; mortality: 2.6, 3.6, and 2.5/100,000) (Siegel et al., 2020). Although major strides have been made concerning reductions in cervical cancer incidence and mortality, foreign and U.S. born Hispanic females have a 40% higher likelihood of being diagnosed with cervical cancer and a 20% higher risk of cervical cancer mortality than their non-Hispanic White counterparts (ACS, 2020; Ortiz et al., 2021).

From 2000-2015, Hispanic women experienced lower cervical cancer screening (78.6%) rates than non-Hispanic females (83.7%) (White et al., 2017). In 2018, Hispanic women aged 18-44 years had a lower percentage of Pap testing within the past 3 years (74.4%) than non-Hispanic White (76.7%) and non-Hispanic Black women (84.8%) in the same age group (CDC HUS, 2019). Furthermore, based on health insurance coverage estimates among 18-64-year-old adults, 27.5% of Hispanics were uninsured, 18.9% were covered through Medicaid, and only 50.5% had private medical insurance in 2017. However, despite cancer screening and health care access disparities as well as other structural barriers, a study using 2011 to 2015 cancer registry data noted that Hispanic women experienced similar stage at diagnosis distribution for cervical cancer at localized, regional, and distant stages, and unstaged cancer when compared with their non-Hispanic White counterparts (42% vs. 44%; 37% vs. 35%, 13% vs. 15%, 8% vs. 6%) (Miller et al., 2018).

Although cervical cancer incidence rates steadily declined over the last 40 years among most racial and ethnic groups due to the development of the Pap test and availability of other cervical cancer screening modalities (e.g., HPV DNA test), NHB women experience lower 5-year relative cervical cancer survival rates at every stage when compared with NHW women (localized: 87% vs. 92%; regional: 49% vs. 57%; distant: 11% vs. 19%) (Collins et al., 2014; Siegel et al., 2020). Benard et al (2017) looked at cervical cancer survival among women by race and stage from 2001-2003 and during 2004-2009 and found that NHB women were more likely to be diagnosed with cervical cancer at regional and distant stages and experienced lower 1-year (3.5% lower) and 5-year survival (8% lower) than NHW females.

Furthermore, del Carmen and colleagues (1999) examined 1990-1995 NCI SEER data from 11 cancer registries and found that NHB women continued to experience sub-optimal cervical cancer health outcomes (19% higher mortality risk) even after adjusting for age, stage, initial treatment type, and histology when compared with NHW females.

Melkonian and colleagues (2020) analyzed 2013-2017 NCI SEER cancer registry data and revealed that HPV-associated cervical cancer incidence among AI/AN females was 10.3/100,000 and AI/AN females had a 58% higher cervical cancer incidence rate when compared with their NHW counterparts (10.3/100,000 vs. 6.5/100,000). Additionally, a study that examined AI/AN cervical cancer incidence and mortality from 1999-2009 by linking Indian Health Service data with cancer registry data noted that AI/AN women experienced higher rates of cervical cancer incidence at all stages and had elevated rates of later stage or unstaged cervical cancer diagnosis when compared with NHW women (Watson et al., 2014).

Anal cancer disparities in age and stage at diagnosis, treatment, and survival among non-Hispanic Black men and women are well documented in the literature (Arora et al., 2017; Cruz et al., 2018; Johnson et al, 2004; Ramey et al., 2018; Stenzel et al., 2020). Johnson and colleagues (2004) analyzed 1973-2000 NCI SEER registry data and found that NHB and NHW males had relative 5-year anal cancer survival rates of 38% and 61%, respectively, while NHB and NHW women experienced 57% and 65% 5-year survival rates during the same timeframe. Moreover, in a subsequent analysis of 1976-2016 NCI SEER cancer registry data that explored disparities in anal cancer survival by race and ethnicity, non-Hispanic Black women who were diagnosed before age 50 years experienced a 60% increased risk of mortality (Adjusted HR: 1.60; 95% CI 1.34-1.89) than non-Hispanic White women after adjusting for covariates and had a significantly

greater risk of dying within the first year of cancer diagnosis (Stenzel et al., 2020). Additionally, NHB women had higher incidence rates from anal cancer during 1973-1979, 1980-1986, and 1987-1993 than NHW women (Johnson et al., 2004).

After adjusting for age at diagnosis, stage, grade, tumor site, surgical status, radiation, chemotherapy, year of diagnosis, sub-type, and geographic region, non-Hispanic Black women had a 26% higher likelihood of dying from anal cancer than their non-Hispanic White counterparts (Stenzel et al., 2020). Oropharyngeal cancer among AI/AN males was 8.2/100,000 based on 2013-2017 cancer data from states grouped into six regions (Melkonian et al., 2020). However, non-Hispanic White (NHW) men have the highest incidence of HPV-associated oropharyngeal cancer (19/100,000), followed by non-Hispanic Black (NHB) (14/100,000) and Asian/Pacific Islander populations (API) (12/1000,000) based on NPCR SEER 2014-2018 cancer registry data (CDC USCS, 2021). While NHB males have lower incidence of oropharyngeal cancer, they are diagnosed at later stages of disease and suffer from lower cancer survival rates (Mahal et al., 2014; Ragin et al, 2011; Sheth et al., 2021).

A study of 348 (Black = 87; white = 261) head and neck cancer patients in Pittsburgh, PA found that when compared with Whites, Blacks diagnosed with oral cavity cancer were 3.6 times more likely to be diagnosed at an advanced stage of cancer after adjusting for gender, family history, tobacco use, alcohol use, socioeconomic status, insurance status, age, and tumor site (Ragin et al., 2011). While this study did not adjust for HPV status, over half of Black head and neck cancer patients were diagnosed at distant stage of disease. Interestingly, Lenze and colleagues (2019) conducted a systematic review of racial disparities and HPV status in oropharyngeal cancer and concluded that the cancer survival disparity among NHB and NHW

patients was not statistically significant after adjusting for HPV status. However, inclusion of additional population-based studies in future meta-analyses and systematic reviews may validate their study findings, as the study team's meta-analysis only included five studies.

Rural-Urban Differences in HPV-Associated Cancer

HPV-Associated Cancer Incidence

Approximately 46.1 million people or 14% of the U.S. population reside in rural (non-metropolitan) counties (USDA ERS, 2020). The U.S. Census Bureau (2016) defines urban areas as combinations of census tracts or blocks that comprise 50,000 or more residents, urban clusters as groups of census tracts or blocks that contain 2,500-50,000 residents, and rural areas as any tract or block outside of these two designations. Multiple and inter-related socioeconomic, behavioral, and cultural factors are associated with increased cancer incidence, mortality, and other health inequities in rural communities (Jemal et al., 2013; Rodriguez et al., 2018). Several studies have reported geographic differences in HPV-associated cancer incidence, mainly demonstrating that women and men living in rural areas experience higher cervical, vulvar, oropharyngeal, anal, and penile cancer incidence rates than those living in urban settings (Henley et al., 2017; Jemal et al., 2013; Rodriguez et al., 2018; Zahnd et al., 2018b; Zahnd et al., 2019).

Henley et al. (2017) utilized NPCR SEER registry data to study 2009-2013 cancer incidence and 2011-2015 mortality differences in U.S. nonmetropolitan and metropolitan counties and concluded that nonmetropolitan rural counties experienced significantly higher incidence and mortality rates for screening-amenable cancers such as cervical cancer (8.3/100,000 vs. 7.6/100,000 and 2.7/100,000 vs. 2.2/100,000) and later stage at diagnosis.

A study using 2009-2013 national cancer registry data examined rural and urban differences in HPV-associated cancer and noted that rural females had higher incidence rates of HPV-associated cancers (15.2/100,000 vs. 13.4/100,000) and rural males had higher incidence rates of oral cavity and pharynx cancer (18.3/100,000 vs. 16.9/100,000) when compared with females and males residing in urban areas (Zahnd et al., 2018a). While these studies stratified the cancer data using multiple variables to examine associations among variables such as age, race, ethnicity, and rural/urban residence, none adjusted for confounding using multivariate regression analysis.

Lastly, a study that used 1998-2001 NPCR/SEER registry data (39,946 cases) to examine rural and urban differences in cervical cancer found that significantly higher cervical cancer incidence rates occurred among rural women aged 45 years and younger (Benard et al., 2007). However, they found no significant differences in cervical cancer incidence by geographic location (rural vs. urban) among older women, after adjusting for race and poverty.

HPV-Associated Cancer Stage at Diagnosis

Very few studies exist that explore rural-urban differences, cancer stage at diagnosis, and incidence of HPV-associated cancers among women and men (Yu et al., 2019; Zahnd et al., 2018b). An incidence and stage at diagnosis study using 2009-2013 national cancer registry data identified that rural residents had significantly higher HPV-associated cancer incidence at local (2.6/100,000 vs. 2.4/100,000) and distant (1.2/100,000 vs. 1.1/100,000) stages when compared with their urban counterparts (Zahnd et al., 2018b). Another national study utilizing NPCR/SEER cancer registry data reported that rural counties suffered higher age-adjusted cervical cancer incidence at localized (5.2/100,000 vs. 4.7/100,000), regional (4.1/100,000 vs.

3.6/100,000), and distant (1.6/100,000 vs. 1.4/100,000) stages than urban counties as well as higher rates of unstaged cancer, which results in poorer health outcomes. However, both studies did not adjust for confounding factors such as education or income.

HPV-Associated Cancer Mortality

Over the last three decades, significant HPV-associated oropharyngeal cancer disparities continue to occur among NHW males residing in Appalachian states, including HPV-associated cancer diagnosis at much later stages of disease, which results in unfavorable 5-year survival rates (Papenberg et al., 2020; Reiter et al., 2013; Wilson et al., 2016). Interestingly, Kim et al. (2018) conducted a population-based cohort analysis of 3,036 patients diagnosed from 2001-2011 at five British Columbia Cancer Agency centers to assess rural and urban differences in head and neck cancer and found no differences in survival outcomes based on rurality after adjusting for type of treatment, tumor size, and smoking status. However, they were unable to adjust for HPV status, which is a known risk factor for oropharyngeal cancer (Saraiya et al., 2015).

Behavior Related to HPV Exposure and Persistent Infection

Previous observational studies concluded that engaging in risky sexual behaviors (e.g., unprotected sex, multiple sex partners, early sexual debut), low HPV vaccine uptake, and lack of access to regular health care among rural females and males are associated with increased HPV-associated cancer incidence (Brisson et al., 2013; Paskett et al., 2020; Reiter et al., 2013; Zahnd et al., 2018a; Zahnd et al., 2019). According to Thomas and colleagues (2014), the convergence of culture, economic opportunity, and geographic location impacts rural health knowledge,

behaviors, decisions, and outcomes at individual, family, and community levels. Cancer risk perception and ongoing trust in hospital and clinic services to prevent and manage illness among rural residents is heavily influenced by the established culture within their community of residence. Increased HPV vaccine uptake, cervical and anal cancer screening, and engaging in safer sexual behavior represent prevention and early detection strategies, which have the potential to narrow rural-urban differences in HPV-associated cancer incidence among females and males (Brisson et al., 2013; Giuliano et al., 2011; Wewers et al., 2006; Zahnd et al., 2019). Reducing HPV-associated cancer incidence in rural areas is dependent on individual and community knowledge that HPV infection is sexually transmitted, vaccine is available that may prevent HPV-associated cancer, and screening can detect some HPV-associated cancers at an early stage when treatment is most effective among individuals and communities (Brisson et al., 2013; Mohammed et al., 2018; Rodriguez et al., 2018).

Sexual Behavior as a Risk Factor

Most research on HPV risk and sexual behavior focuses on consensual sex. However, sexual assault survivors are a critical population of focus to assess HPV-associated cancer risk. Coker et al. (2009) conducted a cross-sectional analysis of over 4,700 participants from the Kentucky Women's Health Registry and found a statistically significant association between sexual violence against women and prevalence of cervical cancer. Additionally, although HPV vaccine is not recommended in children younger than 9 years of age, child sexual assault survivors who test positive or negative for high-risk HPV types should be provided the opportunity to be vaccinated against HPV, if recommended by the healthcare professional providing care and case management (Cao et al., 2017).

HPV vaccination is critical to protect children and adolescents, including sexual abuse survivors, from acquiring HPV-associated pre-cancer or cancer later in life. Vaginal, anal, and oral sex are established risk factors for HPV-associated cancer (CDC, 2019; D'Souza et al., 2014; Meites et al., 2020; NCI, 2021). Shigeishi and Sugiyama (2016) conducted a meta-analysis to examine significant risk factors for oropharyngeal cancer and found a statistically significant association between oral sex, oral HPV infection, smoking, and HPV-associated oropharyngeal cancer, whereas a hospital-based case-control study among cancer patients concluded that HPV-16 positive oropharyngeal cancer was independently associated with oral sex, increased number of partners, and marijuana use, but not associated with tobacco use (Gillison et al., 2008). This could be due to the different etiology of oropharyngeal cancer not caused by HPV infection versus HPV-associated cancer. Moreover, Applebaum et al. (2007) studied 485 head and neck squamous cell carcinoma (HNSCC) patients and 549 control cases in Boston, MA and concluded that chronic tobacco and alcohol use did not contribute to increased risk for HPV-16-associated pharyngeal cancer, and the risk associated with alcohol consumption, tobacco use, and high-risk HPV (e.g., HPV 16, 18) differed based on the anatomical site of the oropharyngeal tumor after adjusting for age, sex, race, education, and HPV-16 status.

They concluded that there was no dose-response relationship between alcohol use or smoking and HNSCC risk among patients who were HPV-16 positive. Studies have shown that an increased number of sex partners and early age at sexual debut are associated with an increased risk for cervical cancer diagnosis (Itarat et al., 2019; Peters et al., 1986; Ursin et al., 1996). A case-control study of 400 Latinx and non-Latinx women (ages 75 years and younger) in Los Angeles County found that Latinx females had a 3.5 times greater risk of acquiring cervical cancer than their non-Latinx counterparts when the following eight risk factors were analyzed

together to adjust for confounding: Number of sexual partners before age 20, douching, lower years of education, years since last Pap smear, years between menarche and sexual debut, smoking, use of barrier contraceptives, and episodes of genital warts (Peters et al., 1986). Furthermore, years of education (RR, 4.9) and number of years since last Pap smear (RR, 1.7) had the highest magnitude of risk for cancer among Latinx women when compared with their White counterparts while the number of sex partners before age 20 was not significantly associated.

Conversely, Ursin et al. (1996) examined the role of sexual and other factors in the etiology of cervical cancer in Los Angeles using a case-control study and concluded that the total number of sex partners and total number of partners before age 20 remained statistically significant with increasing number of partners after adjusting for education, household income, oral contraceptive use, and weight gain after age 18 to time of cancer diagnosis. This cervical cancer study examined only two of the same covariates (education and number of sex partners before age 20) used in the study by Peters and colleagues (1986); the discrepancies could be due to not adjusting for key confounders. Similarly, a retrospective study of 349 women in Thailand found that women who started having sexual intercourse at 19 years of age or younger had a 74% higher risk of being infected with HPV 16 and women who had greater than three sex partners had a 4.5 times greater risk of HPV 18 infection after adjusting for age, tobacco use, and parity (Itarat et al., 2019). HPV16 and 18 are considered high risk HPV types that cause cervical cancer (NCI, 2021a; Saraiya et al., 2015).

Lifetime number of sex partners plays a key role in the transmission of several sexually transmitted infections (STIs), including HPV, and increases anal cancer risk among men and women (CDC, 2021; Frisch et al., 1997; Nyitray et al., 2008). A population-based case-control

study of 417 anal and rectal cancer patients in Denmark and Sweden investigated the role of sexual practices and HPV in the development of anal cancer and found an increased risk of anal cancer with increased number of lifetime sexual partners among men (4-9 partners: OR = 1.4, 95% CI 0.6-3.2; 10 or more: OR = 2.5, 95% CI 1.1-5.5) and women (4-9 partners: OR = 2.6, 95% CI 1.7-4.0; 10 or more: OR = 4.5, 95% CI 2.7-7.4) after adjusting for education and smoking status (Frisch et al., 1997). Goodman et al. (2008) conducted a longitudinal study of 431 women in Hawaii to examine risk factors for acquiring anal HPV infection and natural history of infection and discovered a positive association between increased number of sex partners and high-risk anal HPV infection (≥ 6 partners: OR, 3.6, 95% CI 1.25-10.66). Additionally, in a cross-sectional study of 198 males residing in Tucson, Arizona and Tampa, Florida, Nyitray and colleagues (2008) conducted a multivariate analysis, which demonstrated that having 11-20 lifetime female sex partners (OR, 3.66, 95% CI 1.06-12.62) and 2-4 sexual encounters with females in the past month (OR, 3.89, 95% CI 1.03-14.63) were positively associated with increases in anal HPV infection.

Oropharyngeal cancer incidence has steadily increased over the last 30 years in the U.S. and compared to women, men experience higher rates that are driven by high-risk HPV infection (Chaturvedi et al., 2011; Ellington et al., 2020; Jemal et al., 2013; Van Dyne et al., 2018). Several studies examined the association between lifetime number of sex partners, risk for HPV infection, and subsequent HPV-associated oropharyngeal cancer (Chaturvedi et al., 2015; Chaturvedi et al., 2011; Drake et al., 2021; D'Souza et al., 2007). A hospital-based, nested case-control study of 300 patients in Maryland evaluated associations between HPV infection and oropharyngeal cancer (OPC) and found that having six or more lifetime vaginal and oral sex partners (6-25 vaginal partners: OR, 2.7 ($p = .001$, 1.4-5.5); 26 or more vaginal partners: OR,

4.2 (p = .001, 1.8-9.4); Six or more oral sex partners: OR, 8.6 (p = .001, 2.2-34.0) was strongly associated with OPC among HPV-16 positive patients after adjusting for poor oral hygiene, family history of cancer, alcohol use, tobacco use, sex, and age (D'Souza et al., 2007). Furthermore, Drake et al. (2021) explored differences in serologic response to HPV, sexual behavior, and relationship dynamics among 508 patients and controls to understand the role of behavioral factors in HPV-associated OPC and found that increased number of sexual partners (OR, 3.0, 95% CI, 1.8-5.1) was positively associated with increased odds of OPC after adjusting for confounding variables.

Additionally, A study that analyzed 2009-2010 and 2011-2012 U.S. National Health and Nutrition Examination Surveys (NHANES) data found that men reported engaging in riskier sexual behavior, as they noted a higher number of sex partners than women (18 vs. 7 total partners, respectively; oral sex: 9 vs. 4 partners, vaginal sex: 16 vs. 7 partners) (Chaturvedi et al., 2015). Lastly, Farsi et al. (2015) conducted a systematic review and meta-analysis of the relationship between head and neck cancer and sexual behaviors and concluded that increased numbers of vaginal and oral sex partners were associated with increased head and neck cancer risk. However, when the study team adjusted for HPV infection, the statistically significant association between number of sex partners and head and neck cancer was eliminated. Several studies examined condom use and HPV-associated cancer to understand whether unprotected sex increased HPV infection and associated cancer risk among men and women (D'Souza et al., 2007; Fontenot et al., 2014; Manhart and Koutsky, 2002; Winer et al., 2006).

D'Souza and colleagues (2007) noted that lack of or irregular condom use was associated with HPV-16 positivity and oropharyngeal cancer (OPC). Moreover, consecutive years of condom use also had a protective effect against cervical cancer (2-9 partners: matched RR, 0.5,

95% CI 0.3-0.9;10 or more: matched RR, 0.4, 95% CI 0.2-0.9) after adjustment for confounding in a cohort study among Latinx women and non-Latinx women in Los Angeles County (Peters et al., 1986). Studies examining HPV-associated anal cancer risk and condom use have produced inconsistent findings about condom use having a protective effect against high-risk anal HPV infection (NCI, 2020).

Lack of HPV Vaccine Coverage as a Risk Factor

According to National Immunization Survey-Teen (NIS-Teen) data, about 75% of adolescents (13-17 years) acquired ≥ 1 HPV vaccine dose, and close to 59% received all recommended HPV vaccine doses (2-3 doses based on age of vaccine initiation) in 2020 (Pingali et al., 2021). Several factors influence vaccine uptake among adolescents including geographic residence (Swiecki-Sikora et al., 2019; Pingali et al., 2021; Walker et al., 2020). Studies consistently demonstrate that rural adolescents have lower HPV vaccine coverage rates and rural adults experience higher HPV-associated cancer incidence rates and later stages at diagnosis than their urban counterparts (Swiecki-Sikora, 2019; Van Dyne et al., 2018; Viens et al., 2016; Walker et al., 2019; Walker et al., 2020; Yu et al., 2019; Zahnd et al., 2018a; Zahnd et al., 2018b; Zahnd et al., 2019, Zahnd et al., 2021). Lack of knowledge about HPV, HPV-associated cancers, and the importance of being immunized against HPV has an inverse effect on vaccine coverage in rural areas (Boakye et al., 2017; Mohammed et al., 2018; Walling et al., 2016).

A study by Mohammed and colleagues (2018) assessed knowledge and awareness about HPV, HPV-associated cancer, and HPV vaccine among urban (8,678) and rural (1,469) residents using multi-year (2013-2017) Health Information National Trends Survey (HINTS) data and reported that awareness of HPV (67.2%; 95% CI 72.5-77.3 vs. 55.8%; 95% CI 53.1-59.2), and HPV vaccine (65.8%; 95% CI 64.2-67.1 vs. 58.6%; 95% CI 56.3-61.5) was higher among urban

respondents when compared with rural study participants (Mohammed et al., 2018). The study adjusted for sex, age, race and ethnicity, education, household income, census region, health insurance (yes/no), regular healthcare professional (yes/no), and cancer status. Additionally, the study team found that rural respondents were less likely to be aware that HPV causes oral (27.1%; 95% CI 23.6-33.2 vs. 30.9%; 95% CI 28.4-32.1) and cervical cancer (64.4%; 95% CI 59.8-67.7 vs. 75.4%; 95% CI 72.5-77.3) and individuals acquire HPV through sexual activity (55.4%; 95% CI 50.3-58.7 vs. 65.9%; 95% CI 63.6-67.2) when compared with their urban counterparts. At the state level, higher poverty status is associated with lower HPV vaccination coverage, which impacts rural areas disproportionately when compared with coverage in suburban and mostly urban areas (Brisson et al., 2013; Walker et al., 2020; Williams et al., 2019).

Furthermore, Swiecki-Sikora et al. (2019) used 2012-2013 NIS-Teen data and zip codes to examine poverty and rural-urban differences in HPV vaccine uptake and concluded that low population density and poverty reduce the likelihood of vaccine initiation and completion among boys and girls residing in rural areas. Factors potentially contributing to HPV-associated cancer burden and low HPV vaccination rates in rural areas include lack of healthcare provider recommendation for vaccine initiation and completion, inadequate number of primary care physicians, lack of access to care, and transportation and health care-related costs (Curtis et al., 2014; Henry et al., 2016; Henry et al., 2018). Low vaccine completion rates deter progress towards community herd immunity and protection against HPV infection and associated cancers among U.S. women and men (Brisson et al., 2013; Drolet et al., 2015; Spinner et al., 2019).

The Advisory Committee on Immunization Practices (ACIP) recommends that 11-12-year-old males and females receive HPV (2 doses), meningococcal disease (1 dose), Tdap (1 dose), and influenza vaccine (1 dose every year) (CDC ACIP, 2021).

HPV vaccination coverage among 13-17-year-olds (the age group for which vaccination data are available through the NIS-Teen) is lower when compared with other recommended adolescent vaccines (Pingali et al., 2021; Walker et al., 2020; Walker et al., 2019). Table 2.1 shows U.S. vaccination coverage among 13-17-year-olds for HPV, meningococcal disease (MenACWY), tetanus, diptheria, and pertussis (Tdap), and influenza in 2019 and 2020 (CDC FluVaxView, 2019; Elam-Evans, 2020; Pingali et al., 2021). Adolescent coverage was greater for one or more doses of Tdap followed by one or more doses of meningococcal disease vaccine. Annual influenza, HPV, and meningococcal vaccine completion ranged from 52.2-58.6% over the same 2-year period (Elam-Evans, 2020; Pingali et al., 2021).

Lower Rates of Cancer Screening as a Risk Factor

Cervical cancer mortality among women has substantially declined over the last 30 years in the U.S. due to widespread use and implementation of the Pap test (Moyer et al., 2012; Scarcini et al., 2010). While some physicians offer and provide anal cancer screening to populations at increased risk for HPV infection (e.g., anal Pap test, digital rectal exam (DRE), high-resolution anoscopy (HRA)) to help diagnose anal pre-cancer, cervical cancer screening (Pap test or HPV DNA test) is the only widely available and universally recommended screening for HPV-associated cancer (Clarke and Wentzensen, 2018; Clifford et al., 2020). The U.S. Preventive Services Task Force (USPSTF) (2018) recommends that 21-29-year-old females receive only cytology-based screening (Pap test) every 3 years, and 30-65-year-old women

receive cytology-based screening every 3 years or an HPV test every 5 years, or both modes of screening (co-testing) every 5 years. The USPSTF does not recommend that women 65 years and older and women without a cervix be screened for cervical cancer unless there is a known risk for disease, and that women over 65 years who have been adequately screened during the previous decade do not require screening for cervical cancer.

Despite availability and access to screening through the Congressionally mandated CDC National Breast and Cervical Cancer Early Detection Program (NBCCEDP) for low-income, un-, and underinsured women, cervical cancer screening test use disparities persist by geography, socioeconomic status, access to healthcare, and race and ethnicity (CDC PSB, 2020; Doescher and Jackson, 2009; White et al., 2017). While 83% of women reported being up to date with cervical cancer screening from 2000 to 2015, this was below the Healthy People 2020 target of 93 percent (ODPHP, 2017). A study that examined cervical cancer screening and health care access using National Health Interview Survey results found that cervical cancer screening test use was less than 64% among uninsured women, 71-75% among Asian women, around 79% among Hispanics, and 65% among women who did not have a usual source of health care (White et al., 2017). Furthermore, Benard et al. (2014) analyzed 2012 Behavioral Risk Factor Surveillance System (BRFSS) data and found cervical cancer screening inequities by age, race, ethnicity, and geography.

However, Doescher and Jackson (2009) used BRFSS data to examine trends in cervical cancer screening use among rural (83.2%; 95% CI 81.7-84.8) women who received a Pap test and urban (86.1%; 95% CI 85.7-86.6) women who acquired the same cancer screening test and found no significant geographic differences after adjusting for covariates (age, race and ethnicity,

education, income, employment status, census region, self-reported health, and insurance plan). Conversely, Orwat and colleagues (2017) analyzed 2011 UnitedHealthcare commercial health claims data for cervical cancer screening in 248 Hospital Referral Regions (HRRs) nationwide and indicated that privately insured women residing in rural areas had lower rates of screening (75%) than their urban (84%; $p < .05$) counterparts and that screening rates were lower for female patients of rural physicians in more than half of the HRRs. These studies had conflicting findings because they used different data sources and approaches to measure cervical cancer screening uptake.

BRFSS uses nationally representative, self-reported telephone survey data, which may be subject to respondent bias (BRFSS, 2021). The questions asked participants about whether they were screened for cervical cancer over the last three years, which may overestimate the percent of women screened for cervical cancer (Powell-Greiner, 1998; Rauscher et al., 2008). Orwat's study depended on health insurance claims data from one health insurance organization and did not include screening provided at low-cost or no-cost mobile and community clinic screening sites, which means under- and uninsured women were not included in the sample (2017). Furthermore, Watson and colleagues found that healthcare claims data underreported cervical cancer screening procedures, which yielded lower screening rates when compared with rates acquired from national surveys (2018).

Cervical cancer elimination is possible in our lifetime and depends on providing access to care for all females recommended for screening to catch cervical pre-cancer and cancer at their earliest stages.

Community-level Characteristics

Poverty and Education

Indicators of socioeconomic status (SES), including poverty and education, have been consistently associated with health knowledge and preventive health activities including immunization and health care access (e.g., cancer screening) (Damiani et al., 2015; Freeman, 2004; Loehrer et al., 1991; Oldach and Katz, 2014). Several studies found an association between increased cervical cancer incidence, lower level of educational attainment, and poverty (Benard et al., 2007; Froment, 2014; Singh et al., 2004; Singh, 2012; Singh and Jemal, 2017); yet few studies specifically explored how SES impacts HPV-associated cancer incidence and stage at diagnosis (Boscoe et al., 2016; Chakravarthy et al., 2021; Saghari et al., 2015). Furthermore, there is a paucity of research available that examined the associations between SES, rurality, and HPV-associated cancer incidence (Benard et al., 2008; Peterson et al., 2017; Zahnd et al., 2018a). Benard et al. (2008) analyzed NPCR/SEER cancer registry data and SES county level variables from 1998-2003 and found that lower education, lower income, and a greater percentage of poverty were associated with elevated cervical cancer incidence, especially among Hispanic females.

Increased poverty status was associated with elevated female anal, vaginal, and cervical cancer incidence. Additionally, Benard's study found a statistically significant association between lower educational attainment and increased incidence of vaginal, penile, and female oropharyngeal and oral cavity cancers (2008). However, a higher level of education was also associated with increased anal, oropharyngeal, and oral cavity cancer incidence among men and women, which demonstrates that higher educational attainment did not have a protective effect in

reducing HPV-associated cancer risk. Similarly, Boscoe and colleagues (2014; 2016) analyzed 2005-2009 national cancer registry data from 16 states (about 42% of the U.S. population) as well as data on poverty status, age, and race and ethnicity, and concluded that cervical and penile cancer represented the HPV-associated cancer sites most strongly associated with increased poverty.

Furthermore, residents in higher poverty areas were more likely to experience later stage cancer diagnosis than residents from lower poverty areas. A cross-sectional study of 11,464 matched patients using NCI SEER and National Longitudinal Mortality Study (NLMS) linked data included 110 women diagnosed with cervical cancer in the U.S. and concluded that women who did not complete high school experienced a 3 times higher risk of cervical cancer than women who graduated from college (Clegg et al., 2009). Additionally, Singh and Jemal (2017) examined national disparities in cancer incidence, mortality, and survival using the 1979-2011 NLMS Study data combined with NCI SEER registry data and found that from 2003-2011, women who did not complete high school had a 6.3 times greater likelihood of dying from cervical cancer than women with higher educational attainment. Conversely, using National Cancer Database data, Peterson and colleagues (2017) examined individual and area-level variables associated with HPV-16 or 16/18-positive head and neck squamous cell carcinomas (HNSCCs) among 21,524 non-Hispanic Black and White males diagnosed from 2009 to 2013 and concluded that new HPV-positive HNSCCs were diagnosed most frequently among 45-49-year-old males ($RR_{Adjusted}$ = 1.57, 95% CI 1.42-1.73) residing in zip code areas with higher educational attainment and median household income.

Additionally, their multivariate analysis revealed a significant interaction between area-level SES and race, as the risk of HPV-positive HNSCC increased with increased SES for both racial groups, but the effect was stronger among non-Hispanic Black males ($RR_{Adjusted}$ = 1.76, 95% CI 1.49-2.09) when compared with their white counterparts ($RR_{Adjusted}$ = 1.12, 95% CI 1.08-1.16). The inverse relationship between income, education level, and incidence of HPV-associated oropharyngeal cancer in Peterson's study demonstrates the evolving role of sociodemographic factors and HPV-associated cancer risk over the last decade among men. Sexual behavior (e.g., unprotected oral sex) and number of sexual partners represent the two biggest drivers of increasing HPV-associated oropharyngeal cancer incidence among males, and when compared with lifetime sex partners in women, men report significantly higher numbers of lifetime partners for any sexual activity (e.g., oral sex, (9 partners for men vs. 4 for women) (Chaturvedi et al., 2015). While Chaturvedi's study found an independent association between high-risk oral HPV prevalence and age, sex, smoking, and number of lifetime sex partners for both genders, the associations were significantly stronger among males.

Having oral sex with unvaccinated partners increases risk of exposure to oncogenic HPV types, including HPV 16, which may increase HPV-associated oropharyngeal cancer in men (Chaturvedi et al., 2015; Drake et al., 2021; Peterson et al., 2017). Finally, Zahnd et al. (2018a) analyzed 2009-2013 national cancer registry data that included county-level poverty status and noted that in rural areas where at least 10% to 19.99% and 20 or more percent of residents lived below poverty, HPV-associated cancer incidence rates were significantly higher than rates found among urban area residents (12.3/100,000 vs. 11.9/100,000; 13.5/100,000 vs. 12.7/100,000). However, this study was unable to adjust for educational attainment.

Primary Care Physician Density

Primary care physician density (PCPD) is estimated by calculating the number of primary care physicians (e.g., allopathic and osteopathic family medicine, general practice, general internal medicine, and general pediatric physicians) per 10,000 people at the county level (Aboagye et al., 2014; Macinko et al., 2007; UWPHI, 2021). Primary care physician density has often been used as a proxy for health care access, wherein communities with lower PCPD have less engagement with health care, higher emergency room visits, and poorer cancer health outcomes, including later stage at cancer diagnosis and sub-optimal survival rates than communities with more physicians per capita (Campbell et al., 2003; Ferrante et al., 2000; Fleisher et al., 2008; Roetzheim et al., 2000). Unequal or lack of access to care impedes early detection of cervical, colorectal, breast, and prostate cancer, which results in cancer diagnosis at a later stage (Benard et al., 2007; Daley et al., 2011; Moss et al., 2017; Nguyen et al., 2018; Shipp et al., 2005). Higher physician (primary and specialized care) density has been associated with earlier detection and lower incidence of screening amenable cancers (Adams et al., 2015; Ananthakrishnan et al., 2010; Campbell et al., 2003; Daley et al, 2011; Ferrante et al, 2000; Gorey et al., 2009; Nguyen et al., 2018).

HPV Immunization Policy

Mass vaccination as disease prevention is considered one of the greatest public health achievements of the 20th century and vaccine mandates enable states to reduce morbidity and mortality from communicable diseases by increasing vaccine access, utilization, and coverage among children and adolescents and decreasing disparities rooted in interwoven social determinants of health (CDC, 1999; Morita et al., 2008; Orenstein and Hinman, 1999).

Scientific advances, including the discovery of new vaccines (e.g., HPV, COVID-19), impact every sector of society: individuals, families, communities, public health, policymakers, schools, health care facilities/practices, and workplaces. CDC notes that among children who were born during 1994 through 2018, immunizations prevented approximately 26.8 million hospitalizations, 419 million illnesses, and 936,000 early deaths, which saved the U.S. $406 billion in direct costs and $1.9 trillion in total societal costs (2011; 2019; Zhou et al., 2014). Quadrivalent, bivalent, and nonavalent HPV vaccines were approved by the U.S. Food and Drug Administration (FDA) in 2006, 2009, and 2015, respectively (Markowitz et al., 2007; Markowitz et al., 2014; Petrosky et al., 2015).

All 50 states, the District of Columbia, and Puerto Rico have enacted laws that require specific childhood immunizations and vaccination documentation before school entry as part of infectious disease prevention and control measures (Hodge and Gostin, 2001; National Conference of State Legislatures (NCSL), 2021). Immunization law was formally established at city and state levels to eradicate smallpox in the 1820s and was expanded as disease threats such as polio, measles, hepatitis, diptheria, and meningitis rapidly spread across communities through person-to-person transmission and vaccines were developed (Cole and Swendiman, 2014; Hodge and Gostin, 2001; Javitt et al., 2008). In 1827, Boston was the first U.S. city to mandate that all children attending public schools show proof of vaccination to smallpox to attend school (Hodge and Gostin, 2001). Policymakers review and update state immunization laws as warranted (e.g., in response to measles outbreaks; HPV vaccination as cancer prevention), which include sub-components such as health promotion and education, vaccine programs, immunization surveillance, school-entry requirements, vaccine recommendations, access to vaccine (e.g., availability of free or low-cost vaccination), and vaccine finance (Hoss et al., 2019).

In 2007, policymakers in at least 40 states proposed revising vaccine legislation to include HPV vaccine language that encompassed insurance coverage, educational campaigns, community-based initiatives, and other strategies to bolster adolescent HPV vaccine uptake (NCSL, 2020). Additionally, 24 states introduced bills to make immunization against HPV a requirement for school attendance. A plethora of these bills failed to gain approval, partly because some argued that HPV vaccine was too novel and not studied extensively, that the virus was a sexually transmitted communicable disease and legislators feared backlash from parents and anti-vaccine advocacy groups (Abiola et al., 2013; Colgrove et al., 2010; Javitt et al, 2008). Furthermore, many states were not financially or administratively prepared to implement school mandates or pay for HPV vaccine supply due to competing health policy priorities.

The Story of School Entrance Mandate Attempts for HPV Vaccination

Although state HPV vaccination policy adoption helps increase knowledge and awareness about HPV and the availability of HPV vaccine as cancer prevention, makes vaccine available through pharmacies, and provides funding for free vaccine for populations of focus, immunization policy is only one piece of a critical, multi-component strategy to improve adolescent vaccine coverage in the U.S. (Abiola et al., 2013; Colgrove et al., 2010; Keim-Malpass et al., 2017). This multi-component strategy consists of a strong physician recommendation, parental awareness and acceptance of HPV vaccine safety, efficacy, and necessity, vaccine access, and strong political will to promote vaccine uptake in rural and urban communities across the country (S. Stokley, personal communication, July 27, 2021). There is variability within the contents of state and territorial legislation and inconsistency in implementation and enforcement of vaccine policy, especially related to acceptable reasons for

adolescent vaccine exemption (Colgrove et al., 2010; Hoss et al., 2019; Roberts et al., 2018). This hampers widespread vaccine initiation and completion necessary to achieve herd immunity and substantially reduce HPV-associated cancer incidence and mortality.

From 2006-2015, 24 states introduced legislation to mandate HPV vaccine in school-aged females while five introduced policies aimed at creating HPV immunization school mandates for males (Keim-Malpass et al., 2017). Originally, Virginia's HB 2035 and DC's Human Papillomavirus Vaccination Act of 2007 (Law 17-10) only mandated vaccine for school-aged girls, which resulted in missed opportunities to require vaccination among school-aged boys for several years (NCLS, 2021). Compared with meningococcal and Tdap vaccine uptake among adolescents over the last decade, HPV vaccine uptake lags far behind (Elam-Evans et al., 2020; Walker et al., 2019; Walker et al, 2020). Only one state, Rhode Island (RI), enacted legislation through the Department of Health (RIDOH), which allowed RIDOH the authority to enforce this school vaccine mandate without legislative action.

In early 2007, Texas Governor Rick Perry imposed an executive order requiring HPV vaccine for girls entering middle school, which was quickly repealed through Texas HB 1098 and replaced with immunization policy content focused on making HPV educational material available to parents and guardians by schools (Haber et al., 2007; Keim-Malpass et al., 2017). Indiana's proposed HPV legislation requiring HPV vaccination for school entry was also rejected and turned into a policy that prohibited HPV vaccination school-entry requirements and promoted HPV vaccine education for parents and community members (Abiola et al., 2013). Early attempts at passing immunization legislation that mandated HPV vaccine for adolescents failed in most states because stakeholders didn't have ample time to meet with community

members and advocacy groups to gather feedback on proposed language; some states (e.g., Indiana) also experienced opposition from religious and conservative political groups (Abiola et al., 2013; Colgrove et al., 2010; Haber et al., 2007). Legislative bills were introduced too abruptly after HPV vaccine was approved by FDA without enough vaccine safety and efficacy information gathered from implementation efforts, which left little time to weigh the benefits and drawbacks of implementing vaccine policy among parents, advocacy groups, and community members (Abiola et al., 2013; Colgrove et al., 2010; Haber et al., 2007).

Additionally, meningococcal and Tdap adolescent immunizations, which are mandated for school entry, had well-established requirements for decades and were accepted by parents and guardians since the vaccines protected adolescents from infections that could be transmitted through close contact in a school setting (except for tetanus) and not through intimate sexual contact. These vaccines have high coverage rates when compared with HPV vaccine (Table 2.1) because they have been endorsed by health care professionals and administered to boys and girls for years (Elam-Evans et al., 2020; Haber et al., 2007; Laugesen et al., 2014; Walker et al., 2019). These factors resulted in substantial improvements in meningococcal and Tdap vaccine acceptance, uptake, and infectious disease prevention. Colgrove et al. (2010) conducted 73 in-depth interviews with stakeholders from CA, IN, NY, NH, TX, and VA and found resistance to mandating HPV vaccine for school entry in states was due to the sexually transmitted nature of the virus and parent's lack of acceptance that their children may be sexually active.

Olshen et al. conducted focus groups and in-depth interviews with 25 parents in New York to explore parental views on HPV vaccine and noted that some parents were vaccine hesitant because they feared it would encourage early onset of sexual activity among their

adolescents and parents felt uncomfortable discussing HPV infection with their children since it entailed having a conversation about sex (2005). Moreover, additional reasons for HPV vaccine policy opposition based on study findings included the novelty of the vaccine; Merck's aggressive lobbying and marketing efforts; high vaccine cost per dose; the lengthy and resource intensive policymaking process; and the potential infringement on parental autonomy and a parent's right to opt out of vaccinating their child (e.g., for philosophical, religious, or medical reasons) (Abiola et al., 2013; Colgrove et al., 2010). Moreover, in a study that analyzed 2009-2013 National Immunization Survey-Teen data to examine effectiveness of HPV vaccine mandates and differences between states with and without HPV vaccine mandates for school entry, Perkins and colleagues (2016) discovered no significant difference in HPV vaccine coverage among girls in states and territories with school-entry or education requirements versus coverage among girls residing in states and territories without these mandates.

Another study assessed different combinations of HPV vaccine policy sub-components to discover which combinations resulted in increased rates of HPV vaccine uptake (Roberts et al., 2018). The study team conducted a qualitative comparative analysis of HPV immunization policies and noted that RI and DC adopted a combination of immunization policies that proved to be the most effective in improving vaccination rates. Both policies permitted HPV vaccination in pharmacies, included Medicaid expansion through the Affordable Care Act, adolescent school entry requirements, classroom sex education mandates, and an absence of parental education mandates, which was the grouping of policies yielding the highest rates of HPV vaccine uptake among adolescents. In the U.S., nonavalent HPV vaccine is the only vaccine currently administered to adolescents and adults to prevent HPV-associated cancers (Senkomago et al., 2019).

Currently, three states and two territories require HPV vaccination for school entry: Rhode Island, Virginia, Washington, DC, Puerto Rico, and Hawaii (NCSL, 2020) . However, most states do not include specific language about HPV vaccine policy, which demonstrates geographic and regional differences in immunization policy implementation and priorities. Furthermore, the HPV policy landscape has evolved over the last 5-7 years and is worth additional investigation and analysis to address gaps in knowledge related to understanding the major components of an effective and comprehensive vaccine policy, state-specific successes and barriers to HPV vaccine policy implementation, and current perspectives on HPV vaccine legislation from stakeholders. This is especially critical in rural areas where vaccine uptake and access are low compared to urban areas, and HPV-associated pre-cancer and cancer incidence continues to escalate (Swiecki-Sikora et al., 2019).

Since some states and territories approved HPV vaccine legislation that included a school mandate and several states continue to exhibit sub-optimal vaccine coverage and higher incidence of HPV-associated cancer, performing a content analysis of policies to examine similarities and differences in five states provides an opportunity to better understand the most current HPV policy landscape. Additionally, conducting stakeholder interviews with state program, policy, and advocacy experts adds to and strengthens the existing body of literature available on HPV vaccine legislation. This policy analysis provides additional insight into what role, if any, vaccine legislation plays in influencing adolescent HPV vaccine uptake.

Table 2.1.

U.S. Vaccination Coverage Among 13-17-Year-Olds, 2019-2020

Vaccine	Year	Year
	2019 (n = 18,788) % (95% CI)	2020 (n = 20,163) % (95% CI)
HPV vaccine ≥ 1 dose[a,b]	71.5 (70.1-72.8)	75.1 (73.9-76.2)
HPV vaccine up to date[a,b]	54.2 (52.7-55.8)	58.6 (57.3-60.0)
Meningococcal (MenACWY) ≥ 1 dose[a,b]	88.9 (88.0-89.8)	89.3 (88.4-90.2)
Meningococcal MenACWY) ≥ 2 doses[a,b]	53.7 (49.9-57.4)	54.4 (51.2-57.5)
Tdap ≥ 1 dose[a,b]	90.2 (89.2-91.1)	90.1 (89.2-90.9)

[a]National Immunization Survey Teen 2020 (Pingali et al., 2021)

[b]National Immunization Survey Teen 2019 (Elam-Evans et al., 2020)

[c]CDC FluVaxView estimates cover the 2018-2019[d] and 2019-2020[e] flu seasons (CDC FluVaxView, 2019)

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CHAPTER 3

EXAMINING THE ROLES OF POLICY, PARENT, HEALTHCARE PROFESSIONAL, AND STATE IN IMPROVING ADOLESCENT HPV VACCINE UPTAKE: STAKEHOLDER PERSPECTIVES FROM FIVE STATES[1]

[1] Pordell, P., Podewils, L., O'Connor, J., Young, M., & Ebell, M. 2022. To be submitted to *Journal of Adolescent Health or Preventing Chronic Disease*.

Abstract

Introduction: Adolescent HPV vaccine coverage remains below 60 percent in the U.S. While numerous studies have examined facilitators and barriers to HPV vaccine uptake, little is known about HPV vaccine policy introduction and its role in improving vaccine initiation and completion. In this qualitative study, we explored the policy environment and process in states that passed HPV vaccine school mandate legislation and assessed HPV and cancer risk knowledge, attitudes, beliefs, and perceptions among state stakeholders.

Methods: During November-December 2021, we interviewed HPV vaccine policy stakeholders in five states to explore facilitators and barriers to HPV vaccine policy introduction and vaccine uptake. We used criterion, snowball sampling to recruit participants from state health departments, cancer advocacy organizations, and academic institutions. Interview transcripts were analyzed using thematic content analysis methods. We identified and categorized a priori and emergent themes using an iterative process.

Results: In interviews (N = 13), stakeholders described parent, healthcare professional, and state as intersecting at three roles essential to adolescent vaccine uptake: as educator, public health advocate, and vaccine champion. Stakeholders cited Department of Health (DOH) leadership, changing existing DOH rules or regulations instead of creating a new policy, and strong community involvement as major facilitators to HPV vaccine policy introduction. Participants identified opposition from anti-vaccine groups and a lengthy regulatory review, revision, and approval process as barriers to vaccine policy introduction.

Conclusion: Parents, healthcare professionals, and the state can collectively use their influence and shared responsibilities as vaccine advocate, educator, and champion to improve state

vaccination rates post-COVID-19. Stakeholders we interviewed provided testimony, drafted policy revisions, or engaged in early policy discussions and advocacy efforts to propose vaccine policy changes. States considering HPV vaccine policy introduction may benefit from speaking with states implementing regulations, as this provides an invaluable opportunity to learn about feasible policy models.

Index words: HPV, Human papillomavirus, Adolescent vaccine uptake, Immunization policy, School mandate, HPV vaccine.

Introduction

Human papillomavirus (HPV) is the most common sexually transmitted infection (STI) in the United States and causes approximately 14 million new infections among males and females annually (CDC, 2017). Two doses of 9-valent HPV (9vHPV) vaccine administered before the onset of sexual activity in adolescents (age 11-12 years) can reduce the risk of acquiring HPV-associated cancers caused by seven high-risk HPV types (HPV type 16, 18, 31, 33, 45, 52, and 58) later in life (CDC, 2017; Huh et al., 2017, Jemal et al., 2013; Kjaer et al., 2020). According to National Immunization Survey-Teen (NIS-Teen) data, about 75% of adolescents (13-17 years) acquired ≥ 1 HPV vaccine dose, and close to 59% received all recommended HPV vaccine doses (2-3 doses based on age of vaccine initiation) in 2020 (Pingali et al., 2021). Despite availability of HPV vaccine through the federally funded Vaccines for Children program, as part of adolescent healthcare visits, in pharmacy settings, and some school-based clinics, the HPV vaccine completion rate in most states remains below the Healthy People 2030 Goal of 80% coverage among adolescents (DHHS, ODPHP, n.d.; Pingali et al., 2021).

The social ecological perspective on health promotion by McLeroy et al. (1988) recognizes that behavior is shaped by 1) individual factors; 2) interpersonal processes and primary groups; 3) community factors; and 4) societal or structural level factors. The Social Ecological Model (SEM) serves as the theoretical framework for this qualitative study because empowered and sustainable change is necessary at individual, interpersonal, community, and structural levels to promote cancer prevention and a reduction in HPV-associated cancer disparities among women and men (Frieden, 2010). The interconnected nature of components such as individual knowledge and behavior, social networks and family, school, church, and

access to health care as well as geographic location, culture, employment, economic development, and state immunization policy exemplifies the multifaceted relationships between behavior, spheres of influence, and environment (Glanz, 2016; McLeroy et al., 1988).

Policymakers review and update state immunization laws as warranted (e.g., in response to disease outbreaks (e.g., measles, COVID-19), to improve adolescent HPV vaccine uptake), which includes health promotion and education, vaccine programs, immunization surveillance, school-entry requirements, vaccine recommendations, access to vaccine (e.g., availability of free or low-cost vaccination, vaccines provided in pharmacy settings, vaccination without parental consent), and vaccine finance (e.g., universal purchase, vaccine covered by insurance) (Hoss et al., 2019). Barriers to adolescent vaccine uptake such as lack of HPV vaccine knowledge and awareness, parental hesitancy, lack of strong provider recommendation, and lack of vaccine access are well established in the literature (Cartmell et al., 2018; Escoffery et al., 2019; Ferrer et al., 2014; Holman et al., 2014). Few studies to our knowledge have examined facilitators and barriers to introducing HPV vaccine policy while also exploring stakeholder knowledge, attitudes, beliefs, and perceptions about HPV, HPV vaccine, and cancer risk.

Additionally, few qualitative studies have explored stakeholder perspectives concerning barriers and facilitators to adolescent HPV vaccine uptake and policy introduction in states with and without vaccine mandates, as prior studies examining facilitators and barriers to adolescent vaccine uptake have been restricted to a single state (Carhart et al., 2018; Cartmell et al., 2018; Newcomer et al., 2020). The current study targeted several states with varied immunization practices, policies, populations, and geographies, with the aims to: (1) explore the policy environment, process, and stakeholder involvement in states that passed HPV vaccine school

mandate legislation as part of immunization policy; and (2) assess HPV and cancer risk knowledge, attitudes, beliefs, and perceptions among state stakeholders and how this may impact rejection or passage of HPV vaccine legislation.

Methods

The study aimed to include a diverse selection of five states in the U.S. based on geography, population sociodemographics, and HPV vaccination rates. We used U.S. Census QuickFacts 2021 (for sociodemographic data) and CDC National Immunization Survey-Teen 2019-2020 data (HPV, meningococcal, and Tdap vaccine doses) to identify states for inclusion. We selected eight states and contacted cancer and immunization program points of contact at state health departments in each state. Points of contact from five states responded to our initial recruitment phone call or email in a timely manner and agreed to assist with study recruitment efforts.

Researchers initiated a qualitative study consisting of in-depth interviews (IDIs) using criterion, snowball sampling to identify state HPV vaccine policy stakeholders from health departments, academic institutions, and cancer advocacy organizations. The PI sent a recruitment letter to colleagues and recipients from CDC-funded state cancer and immunization programs, within academic institutions, and from state advocacy groups to help generate a list of potential participants from each state. The PI followed up with stakeholders who met the following inclusion criteria: (1) a state resident for at least two years; (2) employed in their current professional position for at least two years or had prior HPV-related public health, policy work, or volunteer experience within the last 5 years; and (3) available for a 60-minute virtual interview. Participants signed informed consent forms prior to interviews.

The study team recorded interviews only if verbal and written consent was provided by the participant. The consent form and study participant recruitment letter included information about the study purpose and aims, study duration, confidentiality, risks and benefits, and study team contact information. The University of Georgia Institutional Review Board (IRB) reviewed the study protocol and designated it as not human subjects research. The HPV immunization policy and vaccine uptake stakeholder IDI guide included nine questions about knowledge, attitudes, beliefs, and perceptions about HPV, cancer risk, and immunization; vaccine policy issues, discussions and decisions; key components of a comprehensive HPV immunization policy; and lessons learned from the vaccine policy proposal and approval process.

The stakeholder IDI guide was based on a state legislator and public health official qualitative interview instrument created by Abiola and colleagues (2013) that was used to collect data from key informants on the politics of HPV vaccine policy formation in the first decade of vaccine availability and implementation. Interviews were transcribed using Otter.ai software (Los Altos, CA) and reviewed by the PI to identify and reconcile any errors in transcription and to ensure question responses were identified by participant ID number. As part of member checking and participant validation, the PI shared interview transcripts with each study participant to ensure that their responses were captured accurately. Based on the survey responses, stakeholder HPV knowledge was considered good if at least two of the following five HPV descriptors were mentioned: modes of transmission; sexually transmitted infection; causes cancer; caused by a virus; several sub-types.

The policy review also identified health policy sub-components for each state. Stakeholders were provided a comprehensive list of policy sub-components and asked to rank each according to the level of importance for creating a model policy: from 0 to 5 (0 = not

recommended, 1 = not a priority, 2 = low, 3 = medium, 4 = high, 5 = essential). Qualitative analysis entailed identifying emerging and overarching themes and grouping similar themes together, as each theme was the primary unit of analysis (Abiola et al., 2013). The study team used an iterative process until theme saturation was reached.

The PI and a researcher served as coders and created a codebook that identified the emerging theme, overarching theme (a priori), and theme definition; they abstracted illustrative quote(s) from transcripts to exemplify what participants shared during interviews. Coders reviewed transcripts individually, identified themes independently, and met to discuss results and reach consensus on overarching themes and definitions to ensure intercoder reliability (O'Connor and Joffe, 2020). The researcher and PI finalized the codebook after completing transcript reviews and discussing themes. In-depth interview transcripts were analyzed using NVivo software (QSR International, Victoria, Australia).

Results

The following states were included: CA, GA, HI, MA, and RI, and Table 3.1 summarizes in-depth interview (IDI) participant characteristics by state, organization represented, number of years in role, and gender. Females comprised 76.9% of interview participants while 46.2% of stakeholders served at their respective organization for 16 or more years. Interview participants represented state health departments (30.8%), advocacy organizations (30.8%), and academic institutions (38.4%).

Stakeholder Knowledge, Attitudes, Beliefs, and Perceptions About HPV, Cancer Risk, and Immunization

HPV Knowledge

Stakeholders exhibited good knowledge about HPV infection and identified several critical areas of focus related to information about HPV: a male or female can be infected with HPV without knowing they are infected; HPV causes cancer and is the most common STI; high-risk and low-risk HPV sub-types; HPV infection can be transient or persistent depending on the HPV sub-type; HPV is transmitted through oral, vaginal, and anal sex; women are particularly vulnerable to HPV infection and associated cancers; and the importance of adolescents starting and completing the vaccine series prior to being sexually active. One participant shared that HPV virus "…cause[s] warts and cancers such as cervical and oropharyngeal…sometimes persistent infection can lead to pre-cancer or cancer…[HPV is] a fairly common sexually transmitted virus," while another stakeholder added that "…there are multiple [HPV] subtypes that fall into different oncogenic groups that can lead over time, if undetected, to six different types of cancers." Several participants discussed the impact of HPV infection on women as an unequal burden, especially when it leads to an HPV-associated cancer diagnosis.

A stakeholder described a cancer survivor's experience being diagnosed with cervical cancer as lifechanging, traumatic, overwhelming, and as "…sort of harrowing…so disruptive for her…she was newly married, she was young, in her later 20's…[the] impact on her marriage, her finances, her ability to have children." Another participant emphasized that "…men are the highest carriers, although they don't oftentimes know that they do have HPV…we see that undue [disease] burden on women when they do contract it." Additionally, a stakeholder mentioned that "…if you have HPV and you have a high-risk strain, then you're more likely to see abnormal pap

tests, things of that nature, which can lead to [cervical cancer] [and] necessitate treatment." Lastly, an interview participant noted that "…it's [HPV] mostly common in women, but also can be spread by men…it's important for everyone to get vaccinated against HPV."

Cervical, oropharyngeal, and anal cancers were the HPV-associated cancers most often described by participants. These cancer types represent the HPV-associated cancers diagnosed most often among men and women in the U.S. (CDC USCS, 2022). Several stakeholders identified oropharyngeal cancer as more common in men and cervical cancer as the most common HPV-associated cancer among women.

Ways to Prevent HPV Infection and HPV-associated Cancer

When the study team asked stakeholders about actions people can take to prevent HPV infection and HPV-associated cancers, all stakeholders discussed HPV vaccination as the most effective way to prevent HPV infections and subsequent associated cancers. Participants also mentioned practicing abstinence, limiting the number of sex partners, cervical and anal cancer screening, and they described condom use as ineffective in preventing HPV infection. A stakeholder summarized that "vaccination [is] probably the most powerful single intervention while barrier methods are not very good protection, and so other than, say abstinence, that vaccination would be the most important intervention."

Moreover, another participant stressed the importance of getting vaccinated before sexual debut when she stated "…definitely the [HPV] vaccine is the number one thing, [being] able to get the vaccine before any kind of sexual experience…"

An additional stakeholder noted that "condoms aren't as effective as they are for other STIs…the vaccine is definitely our number one priority and the number one way we can prevent this [HPV infection]." Many participants described the target age group to begin the HPV

vaccine series, as one participant noted that “the most important is HPV vaccination in adolescents prior to [HPV] exposure [at] the recommended ages of 9-12,” and another stakeholder stated that “…ideally, children at the age of 11 and 12 could get vaccinated, so they’re protected as they become sexually active…that’s number one.” Several respondents mentioned practicing abstinence and vaccinating adolescents against HPV as the only ways to prevent HPV infection. A stakeholder emphasized these two strategies when she said, “I mean it's either you get a[n] [HPV] vaccine, or you, you know, never have any sexual activity, like those are the ways you can prevent HPV because I don't think there are other ways you can really prevent it.”

A few stakeholders discussed cervical and anal cancer screening as effective strategies to detect HPV-associated pre-cancerous lesions, as one participant mentioned that “…there are new studies showing that screening for anal cancer in high-risk individuals may actually prevent the development of anal cancers, 90% of which are HPV-related,” and “…we'll be seeing more screening guidelines related to that [anal cancer] soon because the ANCHOR [clinical] trial was just stopped early because it was successful.” Another stakeholder added that “for women, we can get screened as early as we start going to see our OB/GYN or just our doctors for wellness checkups for [a] Pap test…” The same stakeholder talked about HPV-associated cancer screening and early detection being more difficult for men as she shared that “unfortunately, for men, it makes it a lot more difficult for screening…the one biggest problem with men is that they don’t go to the doctor to even get regular checkups, so how are you going to get that [anal swab test] done? But with men, obviously, to prevent it, vaccination would be key…”

While all stakeholders stressed completing all doses of HPV vaccination during adolescence as the opportune way to prevent HPV infection and cancer, some participants also mentioned cancer screening as an effective tool in detecting cervical and anal pre-cancers, which may prevent the progression to HPV-associated cancers.

HPV Vaccine Knowledge

The most prominent theme identified by all stakeholders was the use of HPV vaccination as a cancer prevention strategy. Stakeholders discussed the following additional themes during interviews: HPV vaccine has minimal side effects; it is safe and effective; the vaccine doesn't work if a person is already infected with HPV; vaccine hesitancy; and the number of doses needed is age dependent. One participant stated that she "…worked in cancer prevention and control for many years, and to see a vaccine come along to prevent it [cancer]…imagine how incredible- a way to reduce or eliminate cancer or suffering in a shot." Another stakeholder described HPV vaccine as "…the best thing to prevent cancers. It's better than a cure for cancer [because] it actually prevents cancer, and it's covered by insurance for children."

Concerning knowledge areas such as vaccine safety and efficacy and age to initiate vaccine, a respondent noted that "… the vaccine is very safe. It's very effective…should be given early …certainly giving it to kids at 11 years old, making sure that they're on track getting those vaccines as early as possible," while another participant said "…HPV vaccines are extremely effective against infection and sequela including pre-cancerous and cancerous changes." Lastly, a stakeholder talked about the safety and efficacy of HPV vaccine and how there are studies that prove it prevents cancer, as she stated that "HPV vaccination is safe and effective. We now have data that it prevents [HPV] vaccine type infections, pre-cancers, and…data from two different studies [concluded] that it prevents cervical cancer in women under [age] 30."

A stakeholder described minimal side effects as "…like any vaccination, whether it's flu [or] now COVID-19…sometimes people will have side effects… whether they're fatigue[d] afterwards [or] for some, [it] is just tenderness in the arm…overall, we know it's safe." Vaccine hesitancy came up several times during in-depth interviews with stakeholders. Most participants identified vaccine misinformation, mistrust, and parental hesitancy as the main reasons for vaccine hesitancy. An immunization subject matter expert shared that "…a significant portion of the population remains suspicious, concerned, or indifferent about immunization…due to concerns about adolescent sexuality, information on social media and the internet around potential safety risks around the vaccines, or misinformation." Additionally, another stakeholder mentioned that "…some parents feel this hesitancy toward it [HPV vaccine] because of its, you know, association with sexually transmitted infections."

Moreover, an interview participant mentioned that while some parents fear that their kids will start having sex, if vaccinated, some kids are participating in sexual activities that put them at risk for HPV, as he added that "…a lot of parents are very concerned that it [HPV vaccine] will give their children or their adolescent the kind of say so or the go ahead to have sex, even though these kids are already having sex anyway... they're having oral sex, which they don't see as having sex and therefore exposing themselves to [HPV, which can cause] oral cancer…" Lastly, a respondent talked about the myth around HPV vaccination being a pre-cursor for adolescent sexual promiscuity, as she stated "I know that some parents think it's [HPV vaccine] going to like, get their pre-teenager interested in sex and get them involved in sex [laughs], because now that they've got the vaccine, they're "protected,"…as a parent, myself, I never subscribed to that belief." Several stakeholders described the importance of taking their adolescents for HPV immunization even if their child's doctor didn't provide a strong

recommendation. The knowledge, attitude, belief, and perception that HPV vaccine is safe and effective, and it is the stakeholder's duty to protect their adolescent from cancer risk by having them initiate and complete the HPV vaccine series despite several interpersonal (lack of strong provider recommendation) and community (anti-vaccine groups) level obstacles demonstrated strong stakeholder commitment to improving HPV vaccine uptake at multiple SEM levels (interpersonal, community, and structural levels).

Barriers and Facilitators to HPV Vaccine Uptake

Interview participants identified several barriers (Table 3.2) and facilitators (Table 3.3) to adolescent HPV vaccine uptake. Figure 3.1 shows relevant themes mapped to SEM levels.

Barriers to HPV Vaccine Uptake

Stakeholders identified a lack of HPV knowledge (individual), lack of strong provider recommendation (interpersonal), parental hesitancy (interpersonal), vaccine misinformation and mistrust (interpersonal and community), anti-vaccine groups (community), lack of school requirement (structural), and less frequent healthcare visits for adolescents (interpersonal) as major barriers to HPV vaccine uptake (Table 3.2). Participants described that a lack of strong provider recommendation was due to a multitude of reasons including provider discomfort discussing HPV vaccine and sex with parents, lack of time to discuss HPV vaccine during a clinic visit, lack of HPV vaccine training, and inconsistent vaccine messaging among healthcare staff. Several study participants identified the impact of COVID-19 on routine vaccination (interpersonal, community, structural) as a significant barrier to HPV vaccine uptake, and a stakeholder shared that " …all of our work has been on COVID-19 for the past year, actually even longer…it's crazy how one disease can overrun everything that you do."

Another participant added "…we're very behind on vaccines in general and just making sure that adolescent vaccines and HPV vaccine are included in that sort of campaign to get people back into the office to vaccinate."

Facilitators to HPV Vaccine Uptake

Stakeholders designated a strong provider recommendation, healthcare professional training, community-based health education and promotion (e.g., targeted HPV vaccine campaigns), stakeholder support, and structural strategies such as vaccine mandates for school entry and adolescent vaccination in pharmacy settings as facilitators to HPV vaccine uptake. Participants from several states described improving access to vaccine as critical to improving adolescent coverage. A study participant shared "where it [state] has been successful is the universal purchase…..universal purchase to take away the access barrier…we also have Medicaid expansion and universal health insurance." Additionally, a stakeholder mentioned the public health synergy created between state HPV vaccine awareness, access, and immunization policy change as he mentioned that "…by making it a requirement for school entry, we equalize that requirement that everybody get access to this vaccine…we equalize the opportunity to access the vaccine." Framing HPV vaccine as cancer prevention instead of linking it to a sexually transmitted infection was also mentioned as an effective non-policy strategy to improve adolescent uptake.

Parent, Healthcare Professional, and State Roles and Responsibilities

Parents, health care professionals, and the state played critical roles in increasing adolescent vaccine access and uptake. Stakeholders described parents as decision makers,

educators, advocates, and gatekeepers responsible for vaccinating their children. Additionally, health care professionals were defined as vaccine advocates, champions, and educators who answered questions and helped parents make informed decisions about the vaccine. Interview participants felt that the state's role entailed promoting and offering HPV vaccine, creating and disseminating community and provider education, increasing vaccine access, and managing immunization information systems.

Figure 3.2 shows the interconnectedness and influence of parent (interpersonal), healthcare professional, (interpersonal) and state (structural) as change agents in increasing knowledge and awareness of and access to HPV vaccine. Participants perceived the parent, healthcare professional, and state as intersecting at three roles: as educator, public health advocate, and vaccine champion. When asked how the state supports adolescent HPV vaccine uptake, stakeholders mentioned that the state: 1) oversees the Vaccines for Children program; 2) incorporates a school vaccine mandate; 3) serves dual roles as educator and regulator; 4) implements universal purchase programs; 5) creates and disseminates health education campaigns; 6) allows for adolescent vaccination in pharmacy settings; 7) actively participates in comprehensive cancer control and immunization coalitions; 8) participates on the HPV Vaccine Roundtable; and 9) hosts special advocacy days and events to increase HPV vaccine and HPV-associated cancer awareness and vaccine uptake.

Table 3.4 summarizes the health policy sub-components adopted by each state. After review of immunization and health-related policies or regulations for CA, GA, HI, MA, and RI, all states adopted the following three policy sub-components: (1) policies permitting HPV vaccination in a pharmacy setting; (2) reporting of HPV vaccination data through immunization

information systems; and (3) medical exemption. MA and RI adopted universal purchase for adolescent vaccines while only CA passed legislation that allows adolescents to receive HPV vaccine without parental consent. All states except CA allow school immunization exemption based on religious beliefs.

States propose or include many of these sub-components as part of stand-alone (e.g., vaccination permitted in pharmacy settings, adolescents can receive HPV vaccine without parental consent) or multi-component immunization policies (e.g., immunization requirements for school entry, religious and/or medical exemption, etc.). Figure 3.3 illustrates median values for each policy sub-component. The highest ranked sub-components focused on including language about vaccine bundling as a strategy to increase adolescent HPV vaccine uptake and reporting of vaccine (# of doses) data through immunization information systems to effectively monitor vaccine coverage. School mandates and policy sub-components intended to increase HPV vaccine access were ranked as high priority by stakeholders.

Philosophical and religious exemptions received the lowest priority although most states or territories permit religious exemption (44/50 states and Washington, DC) and about 30% allow philosophical exemption (NCSL, 2021). Recommended policy sub-components categorized as “other” involved requiring translation of HPV health education materials into multiple languages, standardizing a required HPV training curriculum for physicians and medical students, and allowing dentists to provide HPV health education and immunization to adolescents.

Policy Environment, Process, and Stakeholder Involvement in Hawaii and Rhode Island

Facilitators to Introducing HPV Vaccine Policy

Rhode Island and Hawaii successfully passed HPV vaccine mandates for 7th grade school entry as part of Department of Health regulations in 2007 and 2019, respectively. A key component of their success with immunization policy change involved revising existing public health rules and regulations instead of creating a new policy and submitting it to the Legislature as an Act. Both states also included the HPV vaccine school mandate piece as one component in a larger package of regulations related to the health and safety of students. Major facilitators included Department of Health (DOH) leadership, making changes to existing DOH rules or regulations, and strong community involvement (e.g., vaccine and cancer coalitions, workgroups, and advisory committees).

A Rhode Island participant described the role of Department of Health as …"a strong voice in moving things forward…DOH drove regulatory efforts." A Hawaii stakeholder added that "…the Department of Health was 100% behind it…that helped…we have our University Cancer Center…when it comes to policy…we sort of realized that we relied on them to be the experts." Another Hawaii respondent shared that "without the Department of Health and the immunization program leading it, I don't think it [Hawaii Administrative Rule] would have gone anywhere…the key stakeholders that supported this effort from the medical community, to education, to various groups throughout…kept moving us forward, but it was the Department's lead on this that kept it alive throughout the process." Coalition, workgroup, and advisory committee involvement in the policy introduction process was vital, as one participant mentioned

that "…we have a vaccine advisory…they were key in all of this…it's a group of physicians around the state…they make recommendations to the Director of Health."

Additionally, another stakeholder added that "…what you need to do is have the community, your community champions, ready and primed for just being present and submitting testimony…putting forth as much evidence of support…" Lastly, a study participant emphasized the importance of community representation and stakeholder support, as she said "…we had the vaccine preventable workgroup, the [University] Cancer Center, Department of Health….and we integrated a lot of community voice." When asked about the state immunization policy process and steps to introducing changes, a stakeholder stated that "they looked at all of the vaccines across the board for children: childhood vaccines, adolescent vaccines, and they updated not just HPV, they updated several others…they presented [the regulations] as a package…" Moreover, another study participant emphasized that "…when we open the reg[ulation]s, what we do is we include other things…it might be influenza for childcare…anything we want to add to the regulations are added at that particular time…"

A stakeholder described the importance of having a reliable vaccine proponent within the State Legislature as a policy collaborator, as he recalled that "…we were fortunate enough to have a champion in our legislature, who's like a cervical cancer survivor, and this is like personal for her….she introduced an HPV-related bill… it never really moved or was able to get out of the legislature, but you know, she's always willing to introduce the bill."

Barriers to Introducing HPV Vaccine Policy

Stakeholders described opposition from anti-vaccine groups as the main community-level barrier to introducing HPV vaccine policy (Figure 3.4).

A Rhode Island stakeholder recalled, “when RIDOH was working on the regulation, you heard from the anti-vaccine community, not a large group at the time, but I recall they were very vocal at a public hearing I attended.” Furthermore, a participant from Hawaii added that “…it's just the anti-vaxxers, you just need a given few to be so loud, right… they were flying people in from the continent, to show up at our capitol, to provide testimonies.” A stakeholder actively engaged in the policy process shared that “…when we did our public hearings…the testimonies provided by the anti-vaccine [groups]… I can still recall the negativity, the just, the awful language people use[d]…...people were very mean…instead of having a dialogue [to] communicate… that was really traumatic for myself and my staff during that [public hearing] process.”

Another barrier (structural) to introducing policy was the long and laborious rules submission, revision, and approval process, as a stakeholder shared that “…it is a lengthy process…as you move along, then you have to make sure you complete one step to the next step to the next step…oftentimes [it] could be over a year or two, maybe two years, even longer. Lastly, stakeholders discussed specific policy reviewers as barriers, as a stakeholder shared that “the AG clearly was a barrier, because they were stuck on certain aspects of the Administrative Rules,” and another participant validated that “…the constant review of our Deputy AG to make sure we’re not in any violation of any other current statutes…going back and forth, checking to verify.”

How Vaccine Policy Introduced

When stakeholders were asked about how vaccine policy was introduced in Hawaii, a participant noted that “….when it failed in the legislature, [it] became the new rallying kind of motivating force…in trying to push the already existing vehicle to update the Administrative Rules... that just kind of pushed it along a little bit quicker.” Another stakeholder detailed the

process when he described that "…under law, the [Hawaii] Department of Health has the authority to create Administrative Rules. They have to go through this process, and they have to go through three public hearings…because the rulemaking authority is given to the Department [of Health], it sort of takes the politics out of it…the Administrative Rule process is a lot longer." Rhode Island described the Advisory Committee's important role in the policy process as "…the recommendations they [the VAC] make are written in a letter…they decide what, as a governing group, they want….[they] present it [their recommendations] to the Director of Health, and then she has a conversation with the immunization program manager."

Hawaii and Rhode Island vaccine policy processes shared similarities in that both states revised existing DOH rules or regulations and presented the changes to policymakers as a package. Learning more about the experiences and obstacles another state faced to introduce and pass HPV vaccine policy provided critical insight into the policy process, as Hawaii consulted with Rhode Island during the policy planning and revision phases to understand their timeline, process, policy landscape, and level of stakeholder engagement. Box 1 below highlights state stakeholder lessons learned that were shared during interviews.

Stakeholders named the state immunization and comprehensive cancer control coalitions, the Department of Health, health care providers, school nurses, and the Department of Education as organizations involved in policy advocacy and regulatory discussions. Study participants described their organizational role in the policy process as having no role, leading policy efforts, providing public testimony, or serving in a communication or education role, particularly if the organization was unable to take an official position on HPV vaccine policy.

Discussion

We identified barriers and facilitators to HPV vaccine uptake and policy introduction at individual, interpersonal, community, and structural social ecological levels in five, geographic and culturally diverse states. Our study team explored the policy environment, process, and RI and HI stakeholder involvement in passing HPV vaccine school mandate legislation as part of immunization policy. Additionally, we assessed HPV and cancer risk knowledge, attitudes, beliefs, and perceptions among state stakeholders and how this may impact rejection or passage of HPV vaccine legislation. This study provides valuable insight into the role of state vaccine policy in increasing adolescent HPV vaccine uptake from stakeholders embedded in different policy environments.

In-depth interview results underscore the critical roles of healthcare professional, parent, and state in adolescent HPV vaccine initiation and completion and how each of their shared responsibilities as vaccine advocate, educator, and champion can be utilized to improve vaccine coverage. By treating HPV vaccine like Tdap, meningococcal, or other routine adolescent vaccines, their collective agency, operating at interpersonal, community, and structural SEM levels, enables the normalization of HPV vaccine. Clear and consistent communication between the health care professional and parent about the risks and benefits of HPV vaccine and a strong provider recommendation reinforces the healthcare professional as vaccine advocate, educator and champion, and empowers the parent to make an informed decision about adolescent immunization against HPV (Gilkey et al., 2015; Gilkey and McRee, 2016; Malo et al., 2016).

Parent, healthcare professional, and state roles can be leveraged through community engagement, partnerships, and collaborations between stakeholder organizations to increase adolescent HPV vaccine uptake in rural and urban communities across the U.S.

Lessons Learned

Stakeholders identified the following lessons learned due to participation in the HPV immunization policymaking process:

- Include and identify diverse stakeholders
  - Identify and recruit vaccine champions to participate
  - Garner healthcare professional support and advocacy
- Never underestimate your opposition
- Clear and consistent HPV vaccine policy messaging
  - Be clear about policy goals and benefits
  - Share clear and consistent messages about why vaccine policy is important, what HPV vaccine is, and benefits of adolescent vaccination
- Explore policy options
  - Identify alternate ways of introducing vaccine policy in case the first attempt fails (as a law or as public health rules or regulations)
  - Be realistic- know your policy landscape and environment
- Collect and analyze data to make the case for policy
  - Evaluate your efforts (Ensure you can capture data to measure if what you are doing is working)
- Be proactive
  - Address fears about HPV vaccine in the community
  - Identify concerns about passing policy

Their inclusion on cancer and immunization coalitions, advisory groups, and during policy development is essential to implementing effective HPV vaccine policy and non-policy strategies. The state plays a critical role in adolescent HPV vaccine uptake as educator, advocate, and champion by managing immunization information systems, increasing access to HPV

vaccine through policies, and disseminating HPV vaccine education and awareness campaigns. While parents and healthcare professionals represent decision makers at the interpersonal level, the state serves as the decision maker at the community and structural levels, which yields the greatest public health impact. Stakeholders identified a strong provider recommendation, healthcare professional training, community-based health education and promotion, stakeholder support, and structural strategies such as vaccine mandates for school entry and adolescent vaccination in pharmacy settings as the main facilitators to HPV vaccine uptake.

These results mirror findings from previous studies that examined facilitators and barriers to HPV vaccine uptake from different stakeholder perspectives including nurses, physicians, health department staff, and advocacy groups. Moreover, stakeholders discussed a lack of HPV knowledge, lack of strong provider recommendation, parental hesitancy, vaccine misinformation and mistrust, anti-vaccine groups, lack of school requirement, and less frequent adolescent healthcare visits as major barriers to HPV vaccine uptake, which validate prior study findings (Cartmell et al., 2018; Carhart et al., 2018; Holman et al., 2014; Mansfield et al., 2021; Newcomer et al., 2020). Study participants described the COVID-19 pandemic as a deterrent to routine adolescent immunization (individual, interpersonal, community, and structural levels), as COVID-19 overwhelmed most health systems and Departments of Health, which focused on testing, treatment, or vaccination rollout to diagnose, manage, or prevent COVID-19 infection for over two years. Delays in vaccination may leave some adolescents unvaccinated or partially vaccinated due to a missed opportunity to acquire their subsequent vaccine dose(s) on time. This decline in state HPV vaccine coverage has long-term consequences for cancer and STI prevention and incidence (Gilkey et al., 2020).

A recent study of clinics implementing the Vaccines for Children program found that increases in telehealth visits, patient fear of acquiring COVID-19, and understaffed and overburdened healthcare staff negatively impacted HPV vaccination rates in a rural state (Ryan et al., 2022). Stakeholders told us that HPV vaccine was not a priority for healthcare professionals or parents because of the focus on staying home, COVID-19 testing and vaccination, and staff reassignments to COVID-19 response. States, healthcare professionals, and parents have an obligation to reinvest in promoting adolescent HPV vaccination to prevent future HPV-associated pre-cancers and cancers. To increase vaccination rates, a potential solution is to begin the HPV vaccination series at age 9, which is the recommended age based on the American Cancer Society HPV Vaccination Guidelines (Saslow et al., 2020).

A 2016 population-based cohort study concluded that on-time completion of the HPV vaccine series (2-3 doses) between the ages of 13 to 15 years was significantly associated with an adolescent receiving the first dose by age 9 or 10 as opposed to initiating HPV vaccine at age 11 or 12. Researchers adjusted for insurance status, sex, race, year the first dose was received, and frequent health care visits (St. Sauver et al., 2016). Immunizing adolescents earlier may result in less missed opportunities, less need for multiple vaccines in one visit, and allows for adolescents to receive their vaccine doses prior to the onset of puberty. While prior studies examined facilitators and barriers to HPV vaccine uptake from a stakeholder standpoint, very few have explored stakeholder perspectives in multiple states and included HPV vaccine policy.

A multi-state qualitative study explored stakeholder perspectives about the politics behind HPV vaccine policy formation and found that policy entrepreneurs played a significant role in influencing which public health policies were prioritized for consideration and approval

(Abiola et al., 2013). Our study found that focusing on cancer prevention when explaining or introducing HPV vaccine policy (community and structural levels), incorporating vaccine champions in the policy creation, introduction, and approval process (community and structural levels), and revising an existing policy or regulation (structural) represented facilitators to HPV vaccine policy introduction at the state level. Stakeholders discussed the importance of strong community involvement such as engagement of cancer or immunization coalitions, advocacy groups, or advisory committees as an additional community level facilitator. Stakeholders cited a lengthy review and approval process and a lack of policy opportunity (structural level) and opposition from anti-vaccine groups (community level) as barriers to policy introduction.

Nonetheless, Rhode Island and Hawaii successfully passed rules and regulations mandating HPV vaccine for 7th grade school entry through the Department of Health and both revised existing rules and regulations instead of creating a new policy and submitting it to the Legislature. Both states had strong community involvement and backing from vaccine workgroups, advisory committees, and cancer and immunization coalitions. Members of these community groups served as advocates and subject matter experts who provided testimony, reviewed policy language, researched immunization policy in other states, or took the lead in introducing regulatory changes to existing immunization policy. RI and HI Department of Health spearheaded and managed policy change efforts until regulation approval and played a significant role in rollout and enforcement of new school immunization policies.

States who are considering passing HPV vaccine policy may benefit from speaking with states implementing regulations, as this provides an invaluable opportunity to learn about feasible policy models. Stakeholders ranked reporting of vaccine doses into immunization

information systems and vaccine bundling (providing more than 1 age-recommended vaccine in one clinic visit) as required policy components while they identified school mandates and policies that improve vaccine access as high priority.

Strengths

Our study has several strengths. The study team included perspectives from five states (CA, GA, HI, MA, RI), which share similarities and differences related to population, geography, political environment, and implemented HPV vaccine or related policy sub-components (e.g., states with and without school mandate, states implementing universal purchase). We piloted the IDI guide with local stakeholders, which gave us an opportunity to receive valuable input on the questions and a chance to make revisions before study implementation with states. The study relied on qualitative methods using a constructivist paradigm rooted in phenomenology, which allowed us to define the stakeholder as expert and collect rich, detailed information about their individual experiences with and perceptions about the policy process, the political environment, and facilitators and barriers to adolescent HPV vaccine uptake and policy introduction (Dowling 2005; Racher and Robinson, 2003). Additionally, the principal investigator shared transcripts with study participants to ensure that discussions during interviews were captured accurately.

Limitations

This study has several limitations. Each state did not have the same number of study participants (range: 2-4) interviewed, so our findings may not reflect all participating states equally. Additionally, stakeholder in-depth interview results represented viewpoints from five

states, so results are not transferable to other settings in the U.S. Furthermore, all stakeholders interviewed were vaccine proponents, so we were unable to capture viewpoints from HPV vaccine opponents.

Lastly, study results may not represent stakeholder perspectives from health insurance companies, schools, federally qualified health centers, or anti-vaccine groups, as recruitment targeted public health professionals and clinicians representing Departments of Health, academic institutions, and a national cancer advocacy organization.

Conclusion

Our results offer critical insight into the role of HPV vaccine policy in improving adolescent vaccine uptake from several stakeholder points of view. Moreover, some of the stakeholders we interviewed actively participated in the immunization policy change process by providing testimony, drafting policy revisions, or engaging in early policy discussions and advocacy efforts to propose changes. Future research could entail the use of focus group discussions and inclusion of state policymakers from the Legislature because they may have interesting and potentially opposing viewpoints about introducing and approving HPV vaccine policy within their respective state. Additionally, utilizing a focus group discussion method may glean more detailed information and provide a greater level of understanding about the state policy process since responses build upon one another and gaps in details are filled in as the discussion unfolds.

Future studies could also examine stakeholder perspectives from other geographic areas within the U.S. and focus on a combination of states with high (75% and higher), medium (60-74%), and low (59% or less) HPV vaccine coverage rates using 80% HPV vaccine coverage as the reference point for success. Imminent research should also examine policy and non-policy

strategies that increase adolescent HPV vaccine uptake such as adolescent vaccine bundling, community engagement, temporary school-based vaccine clinics, facility reminder/recall systems, or the use of community health workers and physicians as HPV vaccine advocates and communicators of accurate vaccine information to parents. This is especially important due to significant declines in routine adolescent vaccinations over the last two years because of the COVID-19 pandemic (Pingali et al., 2021). Some of the prior or existing COVID-19 immunization infrastructure in communities may help inform novel approaches to augmenting adolescent HPV vaccine coverage, so that adolescents can catch up on missed vaccine doses that may prevent them from acquiring HPV-associated cancer later in life.

Table 3.1.

Stakeholder Interview Participant Characteristics

	***n* (%)**
State	
California	2 (15.4%)
Georgia	2 (15.4%)
Hawaii	4 (30.8%)
Massachusetts	3 (23%)
Rhode Island	2 (15.4%)
Stakeholder Current/Former Organization Represented	
State Health Department	4 (30.8%)
Advocacy Organization	4 (30.8%)
Academic Institution	5 (38.4%)
Number of Years in Current/Former Position	
≤ 5 years	5 (38.4%)
6-10 years	1 (7.7%)
11-15 years	1 (7.7%)
16-20 years	3 (23.1%)
> 20 years	3 (23.1%)
Gender	
Female	10 (76.9%)
Male	3 (23.1%)

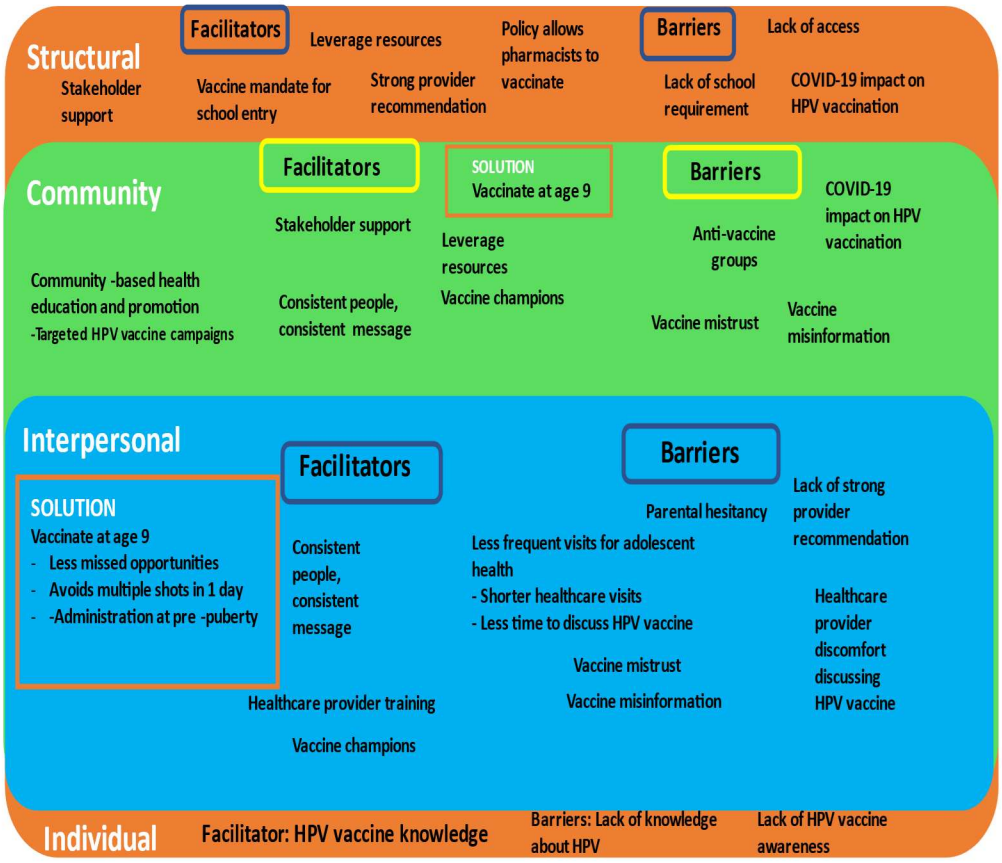

Figure 3.1. *Barriers and Facilitators to Adolescent HPV Vaccine Uptake Social Ecological Model* (McLeroy et al., 1988)

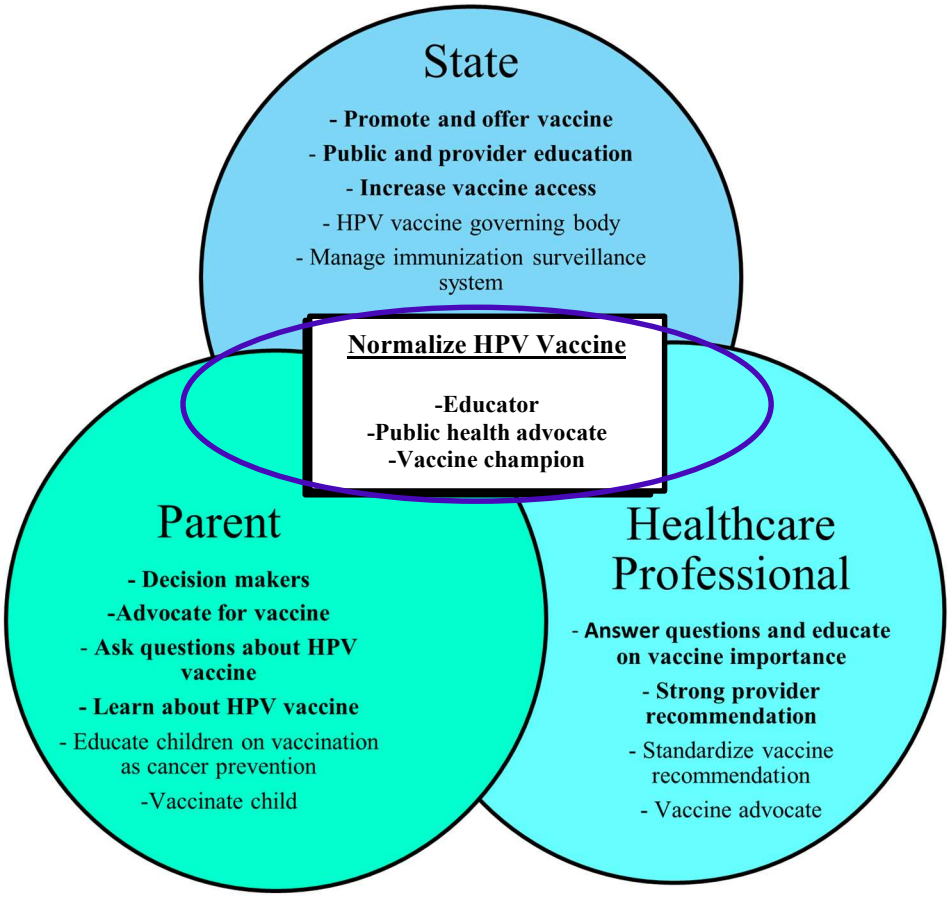

Figure 3.2. *State, Parent, and Healthcare Professional HPV Vaccine Roles and Responsibilities*

Table 3.2.

Barriers to HPV Vaccine Uptake Organized by SEM Level

Theme	Theme definition	Illustrative quote [participant number]
Barriers to HPV Vaccine Uptake	Factors or things that impede high adolescent HPV vaccine uptake	
Individual level		
Lack of knowledge about HPV		"The second barrier is just not knowing, and just the lack of education." [202105]
Interpersonal level		"The other thing is lack of information. So, in Hawaii, Native Hawaiians and Filipinos weren't getting the vaccine because they didn't know a lot about it." [202104]
Lack of strong provider recommendation		"So, the barriers were…a lack of a strong physician recommendation that, by far was number one across all ethnicities…when we say strong, we want the doctor to say I highly recommend your child to get this [vaccine] at this point, at 11 and 12 years old, this is the best time to get it…. instead of saying, you know, maybe this is a good time, maybe not, it's up to you." [202104]
		"…it's still to some degree in terms of the strength of the [provider] recommendation and primary care providers being an especially important voice..." [202102]
Parental hesitancy		"…some of it is the framing around HPV being a sexually transmitted infection, and, you know, parental hesitancy… [202108]
		"…a lot of parents are more hesitant or put it [HPV vaccine] off for their child, especially when they go in for vaccinations. [202109]
Less frequent visits for adolescent health		"Many factors associated with the delivery of adolescent health care- less frequent visits than earlier in

		childhood, for both well visits and sick visits." [202102]
		"Teens are just coming in for preventive therapeutic care less often, so fewer opportunities to immunize on time." [202102]
Community level		
Anti-vaccine groups		"…just attitudes some folks have towards vaccines in general… in any type of legislation around [vaccination] issues, [it's] always strenuously fought with this one group of people who just don't believe in vaccinations." [202109]
		"When DOH was working on the regulation, you heard from the anti-vaccine community and individuals who didn't support vaccine regulation or vaccines." [202103]
Vaccine misinformation (Individual, interpersonal, community levels)		"…misinformation about the safety of the vaccine that's been propagated" [202102]
Vaccine mistrust (Individual, interpersonal, community levels)		"People don't trust vaccines. Minorities don't trust vaccines. Minorities don't trust healthcare providers, and they do not trust healthcare systems….they definitely don't trust the US government…so that in itself is still something that we're seeing with COVID-19 that presents itself even with HPV vaccination." [202112]
Structural level		
Lack of school requirement		"…there [was] a lot less urgency among parents to get the HPV vaccination prior to when it was required." [202109]
		"I tend to work more closely with vulnerable populations. And what I see within these populations that if they are going in for well child visits, or for vaccines, it's usually not this one [HPV] and it's usually something that's required by their school." [202106]
All SEM levels		
		"…I don't even think HPV-associated cancer is like at the

COVID-19 impact		top of anyone's list right now….because of the COVID-19 life we're all living…" [202106]
		" …all of our work has been on COVID-19 for the past year-ish, actually even longer…it's crazy how one disease can overrun everything that you do." [202111]
		"...COVID-19 has really prevented us from doing some ongoing work because we've been totally consumed by rolling out the [COVID-19] vaccine…" [202101]

Table 3.3.

Facilitators to HPV Vaccine Uptake Organized by SEM Level

Theme	Theme definition	Illustrative quote [participant number]
Facilitators to HPV Vaccine Uptake	Things or factors that help improve or increase adolescent HPV vaccine uptake.	
Sub-themes		
Interpersonal level		
Strong provider recommendation		"Advocating from the physicians…making sure you bundle it…your child is due for XYZ vaccinations today, and I always put HPV in the middle…it's all about the delivery." [202105]
		"…they [health care professionals] might say something like, oh, you're here for x, y, and z. And if you want, we can also do HPV….it's better to say, hey, you're here, you're due for XYZ and HPV, right? That is a much stronger recommendation than just if you want, which is what we're also hearing." [202106]
Healthcare provider training		Certainly, provider education and having providers knowledgeable and comfortable about [and] informed about the vaccine and being able to have discussions with willing or hesitant parents…" [202102]
Community level		
Community-based health education and promotion		"And I will say, for the education component, because we did a Marta bus campaign." [202105]
		More awareness…I would say more targeted [HPV vaccine] campaigns to our vulnerable populations." [202106]
		"…we've been able to gather HPV vaccination data by county and you know, no surprise, our rural communities tend to have lower HPV vaccine rates, and so having more targeted information going in that direction…" [202106]
Community and structural levels		"I think timing is everything, like having the right people in power… our legislators, our governor, policymakers, and then having coalition members that I think helped us because we were part of the vaccine preventable cancers workgroup. And we were part of the [comprehensive cancer control] coalition." [202104]
Stakeholder Support		"But it was great to have the same consistent people and the same consistent message." [202104]

		"And we moved collectively, I think, because we were so cohesive as a workgroup, and we knew each other personally and professionally, that we kept each other accountable." [202104]
		"… so there's the champions for this particular issue…there's a pretty strong vaccine or immunization infrastructure in the state…leaders in the field, champions within the State Department of Public Health…all the research universities, you know, that have contributed to vaccine knowledge and development over the years…. there's sort of a strong tradition of vaccination or immunization, pro-immunization advocacy within the state." [202110]
Structural level		
Vaccine mandate for school entry		"Well, because we are a state with a mandate, it changes things for us. It helps improve uptake." [202103]
		So, it's really helped increase the vaccination rate in Rhode Island by mandating it [HPV vaccine]." [202101]
		And it was a change, but it was 10 years in the making, like we were fighting, and talking with Department of Health to really make that admin. change." [202104]
		"…why are some vaccines like routine and mandatory but then we give HPV like this, oh, it's up to you… throw it in with the schedule and call it a day. …build it into the vaccines that they [adolescents] need for school." [202112]
		…the first thing was the work of the workgroup led by the Department of Health to pass and move forward with having HPV as a requirement for school entry." [202111]
Policy allows pharmacists to vaccinate		"… with the shift of COVID-19… there were some changes in legislation that allowed for pharmacists to be able to provide HPV vaccination…" [201212]

Table 3.4.

HPV Vaccine-Related Policy Sub-Components Implemented by States and HPV Vaccine Coverage Among 13-17-Year-Olds

State	Policies Permitting HPV Vaccination in Pharmacy Settings	Medicaid Expansion Through the Affordable Care Act	Universal Purchase	Vaccine Mandate for School Entry	Sex Education Requirement in Schools	Reporting of HPV Vaccination Data through Immunization Information Systems	Religious Exemption	Medical Exemption	Philosophical Exemption	Adolescents can Receive Vaccine without Parental Consent	*≥ 1 HPV Vaccine Dose among Adolescents (2020) %	*HPV Vaccine Coverage among Adolescents (Up-to-Date, 2020) %
California	X	X			X	X		X		X	78.2	62.3
Georgia	X				X	X	X	X			73.1	54.9
Hawaii	X	X		X		X	X	X			84.9	73.9
Massachusetts	X	X	X			X	X	X			87.4	73.4
Rhode Island	X	X	X	X	X	X	X	X			93	83

*CDC National Immunization Survey-Teen, 2021

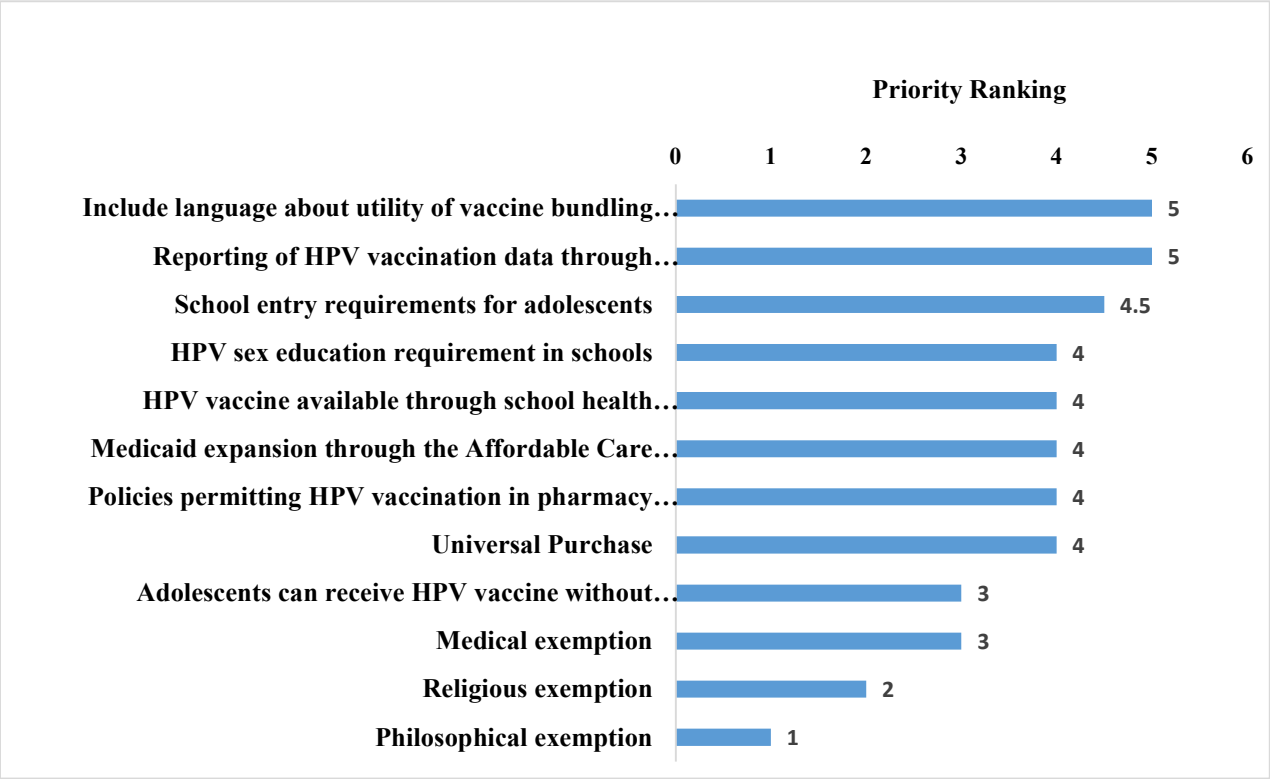

Figure 3.3. *HPV Vaccine Policy Stakeholder Ranking of Policy Sub-Components-Median Values*

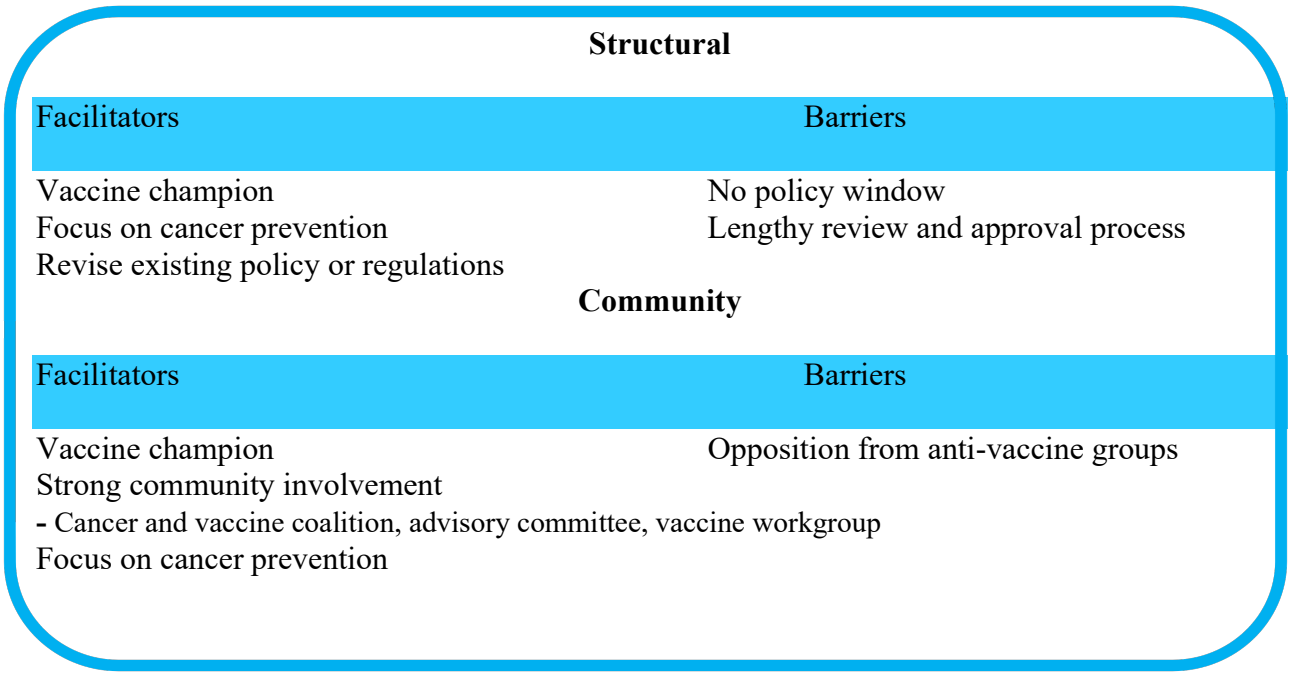

Figure 3.4. *Barriers and Facilitators to HPV Vaccine Policy Introduction SEM*

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CHAPTER 4

DOES RURALITY MATTER? EXAMINING GEOGRAPHIC DIFFERENCES IN HPV-ASSOCIATED CANCER INCIDENCE AMONG WOMEN AND MEN IN THE US, 2008-2018[2]

[2]Pordell, P., Podewils, L., Senkomago, V., Thomas, C.C., Benard, V., & Ebell, M. (additional CDC authors to be decided). 2022. To be submitted to *Cancer Epidemiology, Biomarkers, and Prevention*.

Abstract

Purpose: Human papillomavirus (HPV) is the most common sexually transmitted infection (STI) in the United States and most people acquire the virus in their twenties or thirties. Prior research explored rural-urban differences in HPV-associated cancer by age, sex, race/ethnicity, high school education, and poverty status. Few studies have examined primary care physicians (PCP) rate and lack of health insurance to understand differences in HPV-associated cancer incidence by geography. The study's overall purpose is to better understand the impact of rurality on HPV-associated cancers among women and men from 2008 through 2018.

Methods: CDC National Program of Cancer Registries (NPCR) and NCI Surveillance, Epidemiology, and End Results (SEER) 2008-2018 program data representing 98% of the U.S. population was used along with healthcare access (percent uninsured, PCP rate) and socioeconomic status data (percent some college, economic status) to calculate mean age-adjusted incidence rates and incidence rate ratios for cervical, vaginal, vulvar, penile, oropharyngeal, anal, and all HPV-associated cancers. Negative binomial bivariate and multivariate regression analyses were performed in Stata 17 SE.

Results: Rurality was associated with elevated penile and vulvar cancer incidence after adjustment for confounders. Economic status was independently associated with increased all HPV-associated, cervical, vulvar, oropharyngeal, and anal cancer after adjusting for age, sex, race/ethnicity, and geographic residence. A lower PCP rate at county level was associated with increased cervical cancer incidence after adjustment for confounders. Every 1% increase in percent females was associated with higher all HPV, vulvar, and anal cancer incidence after adjusting for age, sex, race/ethnicity, and geographic residence.

Conclusions: These findings illustrate the independent association between socioeconomic status and increased HPV-associated cancers. The collection, availability, and use of behavioral data that sheds light on sexual practices, patterns, and norms as well as cancer screening, HPV vaccination, and healthcare access and utilization may help inform evidence-based interventions aimed at preventing HPV-associated cancer and detecting these cancers as early as possible. Examining the intersectionality of individual, interpersonal, and structural risk factors for acquiring HPV infection and associated cancer may help identify feasible public health strategies for preventing, detecting, and eventually eliminating these cancers among women and men.

Key words: Human papillomavirus, Rural-urban disparities, HPV-associated cancer, Social determinants of health, Cancer surveillance, Cancer outcomes

Introduction

Human papillomavirus (HPV) is the most common sexually transmitted infection (STI) in the United States and most people acquire the virus by their second or third decade of life through vaginal, anal, or oral sex (CDC, 2017; Kreisel et al., 2021). Persistent HPV infection with high-risk subtypes is associated with an increased risk of cancer. CDC's United States Cancer Statistics (2021a) notes that each year over 46,000 cancers are attributable to HPV types that can be prevented by the current vaccine, and almost 56% of these cancers are diagnosed among women. The International Classification of Diseases for Oncology, 3rd Edition (IACR, 2021; Viens et al., 2016) defines HPV-associated cancers as invasive cancers at anogenital or oropharyngeal sites (cervical adenocarcinoma and squamous cell carcinoma (SCC); vaginal, vulvar, penile, anal, and oropharyngeal SCC) with squamous or glandular cell types containing HPV DNA.

From 2014 through 2018, the incidence rate for HPV-associated cancer among women was 13.9/100,000, with cervical cancer comprising the highest overall incidence followed by anal cancer (7.3/100,000 and 2.4/100,000, respectively). In the same timeframe, the rate of new HPV-associated cancers among men was 11.1/100,000, with oropharyngeal cancer accounting for most of these cancers (8.9/100,000) (CDC USCS, 2021a). Behavioral risk factors such as low HPV vaccine uptake, high-risk sexual activity, and inadequate cervical cancer screening may contribute to increased HPV-associated cancer incidence and later stage at diagnosis among women and men residing in rural versus urban areas (Brisson et al., 2013; CDC, 2019; Drolet et al., 2013; Viens et al., 2016; Walker et al., 2019; Yu et al., 2019; Zahnd et al., 2018a). These risk factors are more pronounced among rural women and men, which increases their vulnerability to HPV infection exposure and a subsequent cancer diagnosis.

Prior studies have investigated differences in HPV-associated cancer incidence by age, sex, race, ethnicity, cancer type, poverty status, and education (Benard et al., 2007; Benard et al., 2008; Reiter et al., 2013; Zahnd et al., 2018a; Zahnd et al., 2019), yet few studies have examined rural-urban differences in HPV-associated cancer after considering both individual variables and indicators of community health care access, insurance status, education level, and economic status. The study's overall purpose is to better understand the impact of rurality on HPV-associated cancers among women and men from 2008 through 2018. We aimed to determine the association between geographic status (rural vs. urban) and HPV-associated cancer incidence among U.S. women and men aged 20 years and older. The principal investigator (PI) adapted a conceptual model created by Brisson and colleagues (2013) for this study, which consists of sociodemographic characteristics, behavioral risk factors, and HPV-related components.

The model (Figure 1.1) demonstrates the relationship between sociodemographic characteristics, behavior and health care access (low HPV vaccine uptake, high-risk sexual activity, low cancer screening, delays in seeking care), and risk for persistent HPV infection with cancer-causing DNA types, which increases HPV-associated cancer incidence and later stage at cancer diagnosis among women and men residing in rural areas (Brisson et al., 2013). Drolet et al. (2013) used an iteration of this framework to explore sociodemographic inequalities in sexual activity and cervical cancer screening among women and implications for the successful uptake of the HPV vaccine.

Methods

We utilized a retrospective, cross-sectional study design to analyze 2008-2018 HPV-associated cancer incidence data from the CDC National Program of Cancer Registries (NPCR) and NCI Surveillance, Epidemiology, and End Results (SEER) program; this data represents about 98% of the U.S. population (CDC USCS, 2021b). HPV-associated cancer incidence data from NPCR/SEER represent all U.S. reported HPV-associated cancer cases based on yearly state and territorial cancer surveillance data submissions to NCI and CDC. NPCR/SEER includes cancer data from all 50 states and Puerto Rico and population denominators based on U.S. Census data for each geographic region. Variables available in the data set for each cancer case include age, sex, race, ethnicity, tumor characteristics, and Rural-Urban Continuum Code (RUCC) describing geographic location (rural or urban county of residence at time of diagnosis) (CDC USCS, 2021b).

Additionally, the NPCR/SEER 2020 U.S. Cancer Statistics incidence analytic database includes a new county-level economic status variable that is a composite of three-year unemployment rate, per capita market income, and poverty rate (ARC, 2022).

Our data set included cancer and community level data for 48 states and one territory (D.C.). Kansas and Minnesota were not included since they do not submit county level data to NPCR or SEER. Furthermore, our data set did not include 2018 cancer incidence data for Nevada, as data encompassing that year did not meet NPCR National Data Quality Standards.

Cervical cancers (International Classification of Diseases for Oncology, 3rd Edition [ICD-0-3] site codes C53.0-C53.9) are limited to carcinomas (ICD-0-3 histology codes 8010-8671, 8940-8941). Vaginal (ICD-0-3 site code C52.9), vulvar (ICD-0-3 site code C51.0-C51.9), anal (ICD-0-3 site code C21.0-C21.9), rectal (ICD-0-3 site code C20.9), penile (ICD-0-3 site code C60.0-60.9), and oropharyngeal (ICD-0-3 site code C01.9, C02.4, C02.8, C05.1, C05.2, C09.0, C09.1, C09.8, C09.9, C10.0, C10.1, C10.2, C10.3, C10.4, C10.8, C10.9, C14.0, C14.2, and C14.8) cancer sites are limited to squamous cell carcinomas (ICD-0-3 histology codes 8050-8084, 8120-8131) (IACR, 2020). Community-level variables (percent some college, percent uninsured, and primary care physicians rate) (Table 4.2) were acquired from County Health Rankings and Roadmaps, which includes data from U.S. Health Resources and Services Administration (HRSA) Area Health Resource Files (AHRF), the American Medical Association (AMA) Physician Master File, American Community Survey (ACS) 5-year estimates, and U.S. Census data (UWPHI, 2021).

U.S. Census collects sociodemographic data through the American Community Survey, which is a yearly household survey that randomly samples addresses in every state, DC, and Puerto Rico. U.S. HRSA AHRF consists of a collection of data from more than 50 agencies and organizations (e.g., American Hospital Association, U.S. Census Bureau, Centers for Medicare and Medicaid Services, Bureau of Labor Statistics, and American Medical Association), is released every year, and available by the Bureau of Health Workforce (HRSA,

2021). County-level data measures of health resources were obtained from AHRF, which publishes the number of primary care physicians per county, based on the American Medical Association Physician Masterfile (AMA, 2021). Primary care physicians (family medicine, internal medicine, pediatrics, obstetrics/gynecology (prior to 2013), and general practice medicine) rate was defined as the number of primary care physicians per 100,000 residents in each county. State-specific data files for 2010-2021 (corresponds to 2008-2018 diagnosis timeframe) were downloaded for each variable, and separate files were created for each variable by state, county, and Federal Information Processing System (FIPS) code.

Separate files were merged into one master community-level file per state, and imported into Stata 17 SE (College Park, TX) for analysis. The quantitative study outcome of interest was: (1) the cancer incidence rate at the county level calculated as: *Number of new HPV-associated cancers / Population x 100,000*. SEER*Stat software version 8.3.9 (NCI, Bethesda, MD) was used to run frequency and rate sessions and acquire case counts and population denominators to calculate age-adjusted incidence rates and incidence rate ratios at 95% confidence intervals (CIs) by county. Incidence rate ratio (IRR) was the measure of association. NPCR/SEER cancer registry data produced HPV-associated cancer (all HPV and cervical, anal, oropharyngeal, vaginal, vulvar, and penile cancer) counts, age-adjusted incidence rates, and rate ratios among women and men 20 years of age and older for the period 2008 through 2018 (NCI, 2019).

Cancer registry data were exported from SEER*Stat using MS Excel. Figure 4.1 depicts the process we used to import and merge data sets in Stata 17 SE including the starting and final number of observations per data set that contributed to the cancer incidence study database. All

individual and community level variables were aggregated up to county level. The PI calculated age-adjusted incidence rates per 100,000 people, which were standardized to the U.S. population.

Bivariate analyses (1 predictor, 1 outcome) were used to explore the association between sociodemographic (individual and community-level) variables and cancer incidence using a negative binomial model. This parametric regression analysis is a type of Poisson regression that can account for overdispersion and approximate the probability distribution of every count (Gardner et al., 1995). Several cancer studies, including those examining trends in incidence, stage at diagnosis, and estimation of cancer cure rate used negative binomial modeling as part of statistical analyses (Benard et al., 2008; Herbert et al., 2018; Li et al., 2003; Rahimzadeh et al., 2014).

A forward, stepwise multivariate model was constructed considering variables with associations in bivariate regression analyses ($p < 0.20$) for model inclusion for all HPV-associated cancer and cervical, vaginal, vulvar, penile, oropharyngeal, and anal cancer. Effect modification was explored by creating interaction terms and stratified analyses by median age, sex, and race/ethnicity in models examining associations between rural or urban and each cancer outcome. During regression model development and testing, collinearity of community level variables (e.g., primary care physicians rate and percent uninsured, percent some college and economic status, percent uninsured and economic status) was assessed by running Spearman's *rho*. Variables were considered collinear if *rho* was > 0.5. Heteroskedasticity in residual distribution was accounted for by using the HUBER/White/Sandwich estimator to estimate the variance-covariance matrix.

Negative binomial models included robust standard errors by using VCE (robust) in the Stata code. Final, multivariate models retained variables with a $p < 0.05$ (Tables 4.6a-d).

Goodness of fit for each model was examined using the *fitstat* command in Stata 17 SE (Long & Freese, 2001). This command generates the log likelihood full model, likelihood ratio, and maximum likelihood R2; the latter was used to calculate the variance inflation factor (VIF). The VIF cut point was set at five. These values, in addition to the Wald Chi-Squared test, were used to compare models, revise model inputs for inclusion, and choose final models.

Results

After merging NPCR/SEER cancer registry data (n = 2,961) with data from U.S. Census and HRSA AHRF (percent uninsured, percent some college, primary care physicians rate, and median age 2017), a total of 2,951 observations or counties were matched for inclusion in the analysis (Figure 4.1).

Descriptive Statistics

Table 4.1 summarizes individual and community level variable study characteristics. Rural counties had a median age of 42.3 years while urban counties exhibited a younger median age (39.8 years). Females and males each contributed about 50% to the total population overall, and within rural counties, while females comprised a slightly higher percentage of the total population in urban counties (51.2%). About 80% of the study population was Non-Hispanic White followed by Non-Hispanic Black (9.2%), Hispanic (7.6%), Non-Hispanic American Indian/Alaska Native (1.9%), and Non-Hispanic Asian/Pacific Islander (1.5%).

Rural counties had a higher percentage of Non-Hispanic American Indian/Alaska Natives (2.5%) while urban counties had a greater proportion of Non-Hispanic Blacks (11%) and Non-Hispanic Asian/Pacific Islanders (2.6%). More than 62% of counties were designated as rural. Urban counties had a greater percentage of individuals with the highest level of some college education (38.7%) while rural counties exhibited the largest percentage of individuals with the

lowest level of some college education (32.4%). When compared with rural counties, urban counties had greater healthcare access (35.7%), but more percent uninsured (32.8%). Rural counties had more counties designated as economically distressed (14.8%) or at-risk (20.2%) while urban areas had more counties designated as transitional (60.2%).

Tables 4.4a-c display mean HPV-associated cancer incidence rates (all HPV and site) by age, sex, race/ethnicity, and geographic residence.

Geographic Disparities in HPV-Associated Cancer Incidence by Age

From 2008 through 2018, 50-79-year-olds had the highest cancer incidence rates for all HPV-associated cancers. Additionally, cancer incidence for all HPV-associated cancers were slightly higher among 20-29, 30-39, and 40-49-year-olds residing in rural areas while incidence among urban residents was higher among individuals aged 50 years and older. Rural females aged 20 years and older experienced higher cervical cancer incidence rates than urban women with the highest overall rates among 30-49-year-old women. Rural and urban women had similar vaginal cancer incidence rates in each age group and incidence was highest among females aged 70 years and older.

Among men, penile cancer incidence increased with elevated age; vulvar cancer incidence among women also rose with increasing age. Like overall HPV-associated cancer incidence, males and females aged 50-79 years experienced the highest oropharyngeal cancer incidence rates. Anal cancer incidence rates were highest among women and men aged 50 years and older. Among females and males aged 40-69 years, rural residents experienced higher anal cancer incidence when compared to urban residents of the same age.

Geographic Disparity in HPV-Associated Cancer Incidence by Sex

Except for oropharyngeal cancer, when compared with males, females had higher all HPV-associated and anal cancer incidence rates. Women residing in rural areas had 60% higher HPV-associated cancer incidence (11.8/100,000) when compared with women from urban areas (11.2/100,000). Rural men experienced almost 48% higher penile cancer incidence (1.7/100,000) and 89% higher anal cancer incidence than urban males. However, urban males had 11% higher oropharyngeal cancer incidence than rural men.

Geographic Disparity in HPV-Associated Cancer Incidence by Race/Ethnicity

Rural, Non-Hispanic White (NHW) males and females had the highest overall HPV-associated cancer incidence rate (22.1/100,000) followed by Non-Hispanic American Indian/Alaska Native (NH AI/AN) men and women (14.6/100,000), and Non-Hispanic Asian/Pacific Islanders (NH A/PI) (10.1/100,000) residing in rural areas. Urban, Non-Hispanic Black (NHB) and Hispanic men and women had higher HPV-associated cancer incidence when compared with rural, NHB and Hispanic residents. NH A/PI females (11.4/100,000) living in rural areas had the highest cervical cancer incidence rate followed by NH AI/AN (11.3/100,000), and NHW (10.4/100,000) women. Rural, NHW female residents had the highest vaginal cancer incidence rates when compared with incidence rates among other racial and ethnic groups included in this study.

NHW males residing in rural areas had the highest penile cancer incidence when compared with urban, NHW men. Oropharyngeal cancer was higher among urban, NHW, NHB, and NH AI/AN men and women when compared with rates among rural residents. Anal cancer was highest among rural, NHW (4.3/100,000) and urban, NH AI/AN (3.4/100,000) males and females.

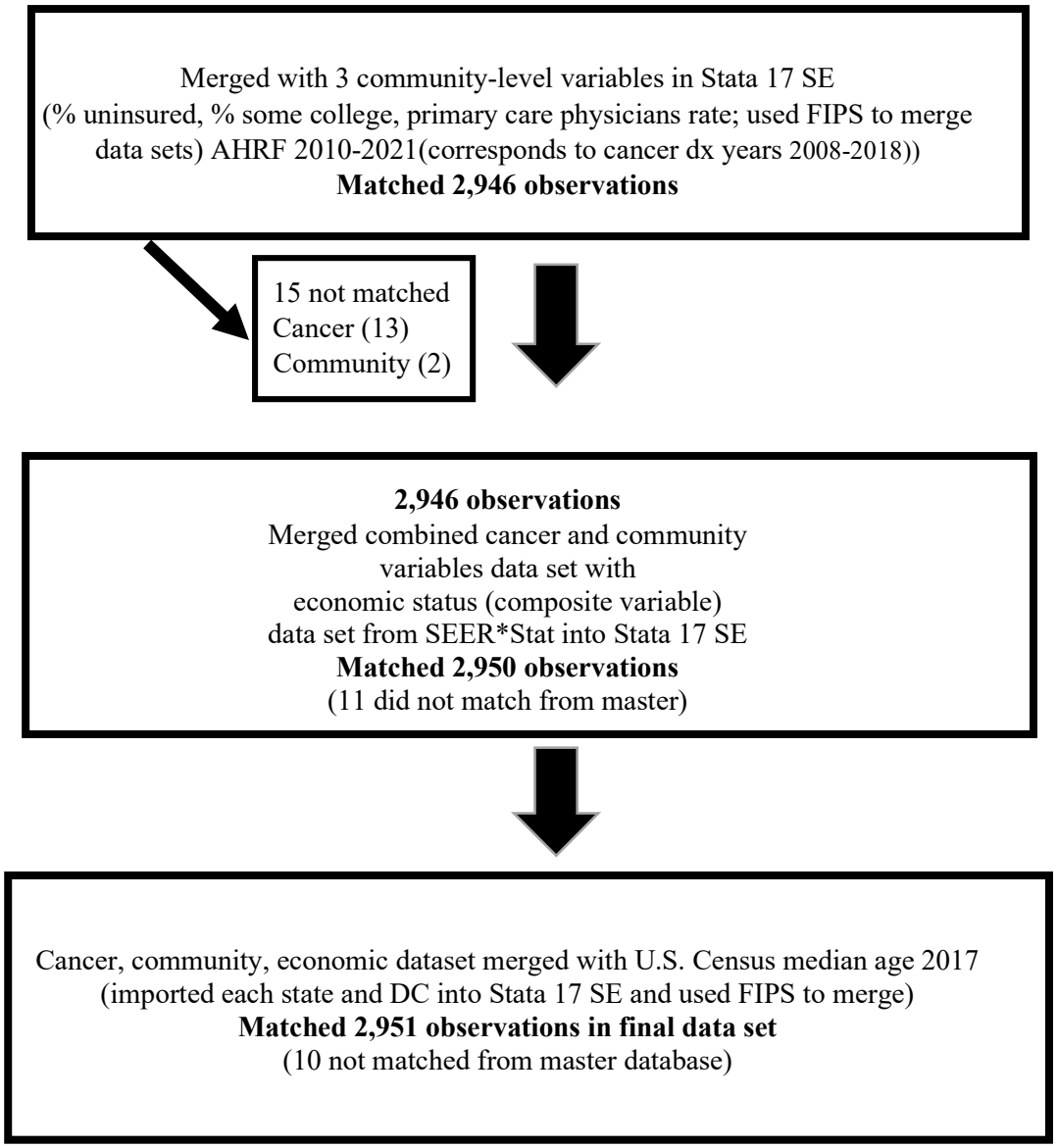

Figure 4.1. *HPV-Associated Cancer Incidence Study Flow Chart for Merging Datasets*

Bivariate Regression Analyses

HPV-associated Cancer Incidence

Tables 4.5a-d illustrate HPV-associated cancer bivariate regression (1 predictor, 1 outcome). In unadjusted analyses, with each year of increasing median age in the county, HPV-associated cancer incidence rates increased by 20 percent (1.02, 95% CI 1.01-1.02). At county

level (unadjusted analyses), a 1% increase in the proportion of females was associated with a 6.4 times higher (6.42, 95% CI 2.72-15.15) incidence rate for all HPV-associated cancers. When we examined race/ethnicity, we found that Non-Hispanic Blacks (NHB) (5.91, 95% CI 3.06-11.39), Non-Hispanic Whites (NHW) (5.37, 95% CI 2.81-10.26), and Non-Hispanic American Indian/Alaska Natives (NH AI/AN) (3.50, 95% CI 1.77-6.91) had the highest HPV-associated cancer incidence rates (Table 4.5a).

When we assigned attainment as the economic status reference quartile, we observed that decreasing county economic status resulted in 29% (transitional), 40% (at-risk), and 35% (distressed) higher HPV-associated cancer incidence rates (county level).

Cervical Cancer Incidence

In unadjusted analyses, when compared with urban counties, counties designated as rural had 4.9 percent higher cervical cancer incidence rates. Among racial and ethnic groups, Non-Hispanic Black (10.29, 95% CI 4.63-22.88) and Hispanic (7.18, 95% CI 2.53-13.42) females had the highest cervical cancer incidence rates. When compared to counties with > 69.89 primary care physicians rate, counties with a lower primary care physicians rate had a 13% (>47.55-69.89% (1.13, 95% CI 1.08-1.18)), 12% (>30.94-47.55% (1.20, 95% CI 1.15-1.25)), and 16% (0-30.94% (1.16, 95% CI 1.10-1.22)) upsurge in cervical cancer incidence. Lastly, decreasing county economic status resulted in 32% (transitional), 50% (at-risk), and 65% (distressed) higher cervical cancer incidence rates when compared to the reference category (attainment).

Vaginal Cancer Incidence

Based on bivariate regression analyses, NHW (8.53, 95% CI 1.89-38.41) and NHB (14.85, 95% CI 3.17-69.54) women had 8.5 and 14.9 times higher vaginal cancer incidence rates. In unadjusted analyses, rurality was not associated with increased vaginal cancer incidence rates.

Moreover, counties designated as having distressed economic status had a 62% increase in vaginal cancer incidence when compared with those that achieved attainment economic status categorization.

Vulvar Cancer Incidence

In unadjusted analyses, with each year of increasing median age in the county, vulvar cancer incidence rates increased by 3 percent (1.03, 95% CI 1.02-1.03). Vulvar cancer incidence was most pronounced among NHWs (26.37, 95% CI 7.65-90.92), NHBs (15.94, 95% CI 4.52-56.25), and NH AI/ANs (9.46 95% CI 2.40-37.34), respectively. Counties located in rural areas had 18% higher (1.18, 95% CI 1.18-1.24) vulvar cancer incidence rates when compared with incidence rates in urban counties. Moreover, when compared to the highest percent college category (>69.89%), counties with >54.60-63.05% (3rd quartile) and >46.88-54.60% (4th quartile) had 13% and 14% increased vulvar cancer incidence, correspondingly.

When attainment (economic status designation) was used as the comparison group, counties categorized as transitional (1.23, 95% CI 1.04-1.45) or at-risk (1.27, 95% CI 1.07-1.51) had higher vulvar cancer incidence rates.

Penile Cancer Incidence

With each year of increasing median age in the county, penile cancer incidence rates increased by 2 percent (1.02, 95% CI 1.01-1.03). When compared with urban areas, rural counties had 42% higher (1.42, 95% CI 1.31-1.54) penile cancer incidence. Furthermore, when compared with counties at the attainment economic status level, counties categorized as economically at-risk (1.34, 95 % CI 1.03-1.73) or distressed (1.47, 95% CI 1.12-1.92) had higher penile cancer incidence rates.

Oropharyngeal Cancer Incidence

With each year of increasing median age in the county, oropharyngeal cancer incidence rates increased by 3 percent (1.03, 95% CI 1.02-1.03). Regarding race and ethnicity, Non-Hispanic Blacks, Non-Hispanic Whites, and Non-Hispanic American Indian and Alaska Natives had 39.2% (3.92, 95% CI 2.08-7.40), 38.6% (3.86, 95% CI 2.07-7.20), and 23.2% (2.32, 95% CI 1.12-4.81) higher oropharyngeal cancer incidence rates. Furthermore, we found that when compared to the lowest percent uninsured quartile (0-13.10%), counties with >13.10-16.56 and >16.56-19.95% uninsured had 4% (1.04, 95% CI 1.01-1.08) and 7% higher (1.07, 95% CI 1.02 - 1.11) oropharyngeal cancer incidence rates. However, unadjusted analyses demonstrated that counties with >19.95% uninsured had a 5% lower (0.95, 95% CI .91-1.00) oropharyngeal cancer incidence compared with counties in the highest quartile (1.04, 95% CI 1.01-1.08).

Lastly, counties categorized as distressed had a 24% increase (1.24, 95% CI 1.12-1.37) in oropharyngeal cancer incidence when compared with the attainment economic status category.

Anal Cancer Incidence

At county level (unadjusted analyses), each 1% increase in the proportion of females was associated with a 14.6 times higher (14.57, 95% CI 5.12-41.48) incidence rate for anal cancer. When we examined race/ethnicity, we found that Non-Hispanic Whites and Non-Hispanic Blacks had 2.8 (2.79, 95% CI 1.61-4.83) and 2.2 times higher (2.24, 95% CI 1.27-3.97) anal cancer incidence rates, correspondingly. We concluded that compared to counties with the highest economic status (attainment), counties designated as transitional (1.35, 95% CI 1.20-1.53), at-risk (1.42, 95% CI 1.25-1.61), and distressed (1.20, 95% CI 1.04-1.38) had increased anal cancer incidence rates.

Multivariate Regression Analyses

Tables 4.6a-d display final multivariate models for all HPV-associated cancer and each site-specific cancer.

HPV-Associated Cancer

Our final model for HPV-associated cancer incidence (outcome variable) included median age, percent female, race/ethnicity, rural, and economic status (VIF= 1.32). Increasing median age was associated with a 1% increase in county-level all HPV-associated cancer incidence after adjusting for confounding variables. Every 1% increase in percent females resulted in a 3.6-fold increase (3.65, 95% CI 1.01-1.02) in HPV-associated cancer incidence at county level after adjusting for age, race/ethnicity, geographic residence, and economic status. We examined race/ethnicity and found that an increasing proportion of Non-Hispanic Whites (NHWs) and Non-Hispanic Blacks (NHBs) in a county was associated with 84% (1.84, 95% CI 1.29-2.64) and 75% higher (1.75, 95% CI 1.21-2.53) all HPV-associated cancer incidence rates, respectively, after adjusting for median age, sex, geographic residence, and economic status.

After accounting for confounding factors, rural counties had a decreased incidence (.97, 95% CI .95-.99) of all HPV-associated cancer, which demonstrated that residing in a rural area had a protective effect. Additionally, compared to counties at the highest economic status (attainment), counties in the lowest 3 quartiles had 29-40% higher (1.29, 95% CI 1.22-1.37; 1.40, 95% CI 1.31-1.48; 1.40 . 95% CI 1.31-1.51) HPV-associated cancer incidence rates after adjusting for median age, sex, rural residence, race/ethnicity, and geographic residence.

Cervical Cancer

The cervical cancer incidence multivariate model included sex, age, race/ethnicity, rural, primary care physicians rate, and economic status variables (VIF= 1.13). An increasing proportion of NHBs in a county was associated with 73% higher (1.73, 95% CI 1.03-2.91) cervical cancer incidence rates after accounting for median age, sex, geographic residence, PCP rate, and economic status. Compared to the highest level of PCP rate (>69.89%), a lower PCP rate (0-69.89%) was associated with 7-12% higher (1.07, 95% CI 1.04-1.20; 1.12, 95% CI 1.07-1.17; 1.10, 95% CI 1.04-1.17) cervical cancer incidence after adjusting for confounders. Cervical cancer was the only HPV-associated cancer that was independently associated with PCP rate.

Counties designated as economically transitional, at-risk, or distressed had 27-51% higher cervical cancer incidence when compared to the highest economic status level after adjusting for age, sex, race/ethnicity, geographic residence, and PCP rate.

Vulvar Cancer

The vulvar cancer incidence model included age, sex, race/ethnicity, rural residence, and economic status (VIF=1.12). Every 1% increase in county median age was associated with a 1% increase in vulvar cancer incidence rates after adjusting for confounding variables. Each 1% increase in percent females at county level was associated with 9.2 times higher (9.21, 95% CI 2.10-40.32) vulvar cancer incidence rates among females after adjusting for age, race/ethnicity, geographic residence, and economic status. Increasing proportions of NHWs and NHBs in a county was associated with 5.4 (5.45, 95% CI 2.18-13.7) and 2.8 times (2.80, 95% CI 1.09-7.17) higher vulvar cancer incidence, respectively, after adjusting for confounding variables.

Additionally, rural residence was associated with 10% higher (1.10, 95% CI 1.04-1.16) vulvar cancer incidence after adjustment for age, sex, race/ethnicity, and economic status.

Like HPV-associated and cervical cancer findings, lower designations of economic status at county level were associated with 26-34% higher vulvar cancer incidence rates after adjusting for confounders (Table 4.6b).

Vaginal Cancer

When compared with the highest economic status level, attainment, women who resided in counties designated as distressed had a 61% higher risk (1.61, 95% CI 1.11-2.35) of vaginal cancer incidence after adjustment for age, sex, race/ethnicity, and geographic residence (Table 4.6b).

Penile Cancer

Increasing median age at county level was associated with a 1% increase in penile cancer incidence, after adjustment for confounders. Increased proportions of Hispanics, Non-Hispanic Whites, and Non-Hispanic American Indian/Alaska Natives in a county was associated with 48, 37, and 29 times higher incidence of penile cancer, correspondingly, after adjusting for age, sex, geographic residence, and economic status. Please note the very wide confidence intervals for race/ethnicity variables. This is due to very few cases of penile cancer diagnosed and reported over the 2008-2018 timeframe. Rural counties had a 24% higher (1.24, 95% CI 1.13-1.36) penile cancer incidence after adjustment for age, race/ethnicity, and economic status.

When compared to attainment, counties designated as distressed had 43% higher (1.43, 95% CI 1.07-1.91) penile cancer incidence after accounting for confounding variables.

Oropharyngeal Cancer

The oropharyngeal cancer incidence multivariate model included sex, age, race/ethnicity, rural, primary care physicians rate, and economic status variables (VIF= 1.26). A 1% increase in median age at county level was associated with 2% higher (1.02, 95% CI 1.02-1.03)

oropharyngeal cancer incidence after accounting for confounding variables. Multivariate analyses showed that an increasing proportion of NHBs and NHWs in a county was associated with 1.6 times higher (1.59, 95% CI 1.04-2.42; 1.56, 95% CI 1.04-2.34) oropharyngeal cancer incidence after adjusting for age, sex, geographic residence, primary care physicians rate, and economic status. Rural residence was associated with a 10% reduction (.90, 95% CI .87-.92) in oropharyngeal cancer incidence at county level after adjusting for confounding variables.

The lowest PCP rate level (0-30.94%) was associated with a 6% reduction (.94, 95% CI .90-.99) in oropharyngeal cancer at county level after adjusting for age, sex, race/ethnicity, geographic residence, and economic status. When compared with attainment as the reference, a lower economic status designation including transitional, at-risk, and distressed designations was associated with 31-40% higher (transitional: 1.31, 95% CI 1.21-1.41; at-risk: 1.40, 95% CI 1.28-1.53; distressed: 1.33, 95% CI 1.19-1.48) oropharyngeal cancer incidence at county level after accounting for age, sex, race/ethnicity, geographic residence, and PCP rate.

Anal Cancer

The anal cancer incidence multivariate model included sex, age, race/ethnicity, rural, and economic status variables (VIF= 1.10). A 1% increase in median age at county level was associated with a 2% increase in anal cancer incidence after adjusting for confounding variables. With every 1% increase in females at county level, there was a 7.4 times (7.38, 95% CI 2.46-22.2) higher incidence of anal cancer among women after adjusting for age, sex, race/ethnicity, geographic residence, and economic status. Per 1% increase of Hispanics in a county was associated with an almost 50% decreased risk (.51, 95% CI .29-.91) of anal cancer incidence after adjusting for confounding variables.

Rural residence was associated with 6% less (.94, 95% CI .90-.99) anal cancer incidence at county level, after adjusting for age, sex, race/ethnicity, and economic status.

Additionally, lower economic status including transitional, at-risk, and distressed status, was associated with 35-47% higher anal cancer incidence at county level after adjusting for age, sex, race/ethnicity, and geographic residence.

Discussion

Researchers evaluated NPCR/SEER 2008 through 2018 cancer registry and healthcare access, insurance status, and socioeconomic status (SES) data (PCP rate, percent some college, percent uninsured, and economic status) to examine the association between rurality and HPV-associated cancer incidence among U.S. women and men. Our multivariate regression analyses demonstrated an association between rural county designation, lower economic status, and increased vulvar cancer incidence after adjustment for age, sex, and race/ethnicity.

While prior studies examined geographic residence and cervical or HPV-associated cancer incidence using NPCR/SEER cancer registry data, these studies accounted for age, sex, and race/ethnicity without adjustment for economic status (Henley et al., 2017; Yu et al., 2019; Zahnd et al., 2019). Additionally, we found an association between residing in a rural county, lower economic status, and increased penile cancer incidence after adjusting for age, sex, and race/ethnicity.

Our study results validate findings from a study conducted by Benard and colleagues (2008), which examined 1998-2003 NPCR/SEER cancer and select SES data (high school education, income, and poverty status), and rural-urban residence. The 2008 study found an association between increased poverty, lower education level, and elevated HPV-associated penile cancer. While this study included percent ≥ high school education, income, and poverty

status as community-level variables, we utilized economic status only, as inclusion of percent some college and economic status in the regression model resulted in predictor variable collinearity. Boscoe and colleagues (2014; 2016) analyzed 2005-2009 national cancer registry data from 16 states (about 42% of the U.S. population) as well as data on poverty status, age, and race/ethnicity, and concluded that cervical and penile cancer represented the HPV-associated cancer sites most strongly associated with increased poverty.

In contrast, our study included 48 states and DC, which is more representative of the U.S. population aged 20 years and older. Our study did not find a significant association between residing in a rural county and elevated all HPV-associated, cervical, vaginal, oropharyngeal, or anal cancer incidence after adjusting for age, sex, race/ethnicity, PCP rate (cervical cancer and oropharyngeal cancer only), and economic status. However, we found that decreasing economic status was independently associated with increased all HPV-associated, cervical, vulvar, oropharyngeal, and anal cancer after adjusting for confounding factors. Benard et al. (2008) examined HPV-associated cancer incidence and education, income, and poverty status at the county level and found an association between decreased household income and higher incidence of male oral cavity and oropharyngeal cancers and cervical cancers after adjusting for age, sex, and race/ethnicity.

The same study concluded that increased vaginal, cervical, female anal cancer, and male oropharyngeal and oral cavity cancer incidence was associated with higher levels of poverty. These findings further support the substantive roles low educational attainment, poverty, lack of employment, and lower income play in elevating county-level HPV-associated cancer incidence rates. Future studies should examine the intersection of these social determinants of health with healthcare access, rurality, sex, race, and ethnicity, which may compound HPV infection and

associated cancer risk in some geographic areas where state HPV vaccination coverage remains low (Zahnd et al., 2021). Furthermore, our findings demonstrated an association between decreasing county PCP rate and elevated cervical cancer incidence after accounting for age, race/ethnicity, sex, and economic status.

Similarly, Campbell and colleagues (2003) examined the relationship between primary care physician supply and cervical cancer incidence and mortality rates in Florida using state cancer registry and AMA Physician Masterfile data and found an association between increased primary care physicians rate and lower cervical cancer incidence and mortality at county level after adjusting for median household income, education, marital status, white race, and urban/non-urban residence. Campbell's study focused on one state, used 1993-1995 cancer incidence data, examined cervical cancer only, did not account for all races and ethnicities, and focused on percent of the population having less than a high school education and median household income to assess county level SES. In contrast, our study incorporated a more representative (96% of states) and current (2008-2018) cancer incidence data set, focused on all HPV-associated cancers, explored percent some college and percent uninsured to understand the roles of education level and insurance status, and included five race/ethnicity categories. In prior studies, higher physician (primary and specialized care) density has been associated with earlier detection and lower incidence of screening amenable cancers (Adams et al., 2015; Ananthakrishnan et al., 2010; Daley et al, 2011; Ferrante et al, 2000; Nguyen et al., 2018).

To our knowledge, our study is the first to examine the relationship between PCP rate, rurality, and all HPV-associated cancers. We found racial/ethnic differences in HPV-associated cancer, as NHWs and NHBs had 84% and 75% higher rates of HPV-associated cancer incidence after adjustment for confounding variables. Additionally, counties with a higher proportion of

NHBs had 73% higher cervical cancer incidence after adjusting for age, sex, PCP rate, and economic status. Higher proportions of NHWs and NHBs in a county was also associated with elevated oropharyngeal and vulvar cancer incidence after adjusting for confounders.

Some previous studies have demonstrated similar HPV-associated cancer racial disparities. However, prior studies found cervical cancer disparities among NH AI/AN and Hispanics, which I did not find in my study (Melkonian et al., 2020; Ortiz et al., 2021; Watson et al., 2014). Implementation of culturally tailored and population-based cancer prevention and early detection interventions focused on improving adolescent HPV vaccine uptake and increasing cervical cancer screening may begin to address these racial and ethnic cancer disparities in communities that experience the greatest HPV-associated cancer burden (Benard et al., 2007; Benard et al., 2008; Zahnd et al., 2018a; Zahnd et al., 2019).
This can be accomplished by making state or territorial policy revisions that promote equitable access to health insurance, HPV vaccination, and primary care.

Cancer registries do not collect behavioral data which is critical to understanding the root causes of low HPV vaccine uptake, high risk sexual activity (unprotected oral, anal, and vaginal sex, multiple sex partners), low cancer screening, and delays in seeking care. Collecting and acquiring behavioral data using a mixed-methods, community-based participatory approach may help identify the structural drivers of poor health outcomes. This data may be leveraged to revise public health policies and fund culturally appropriate, tailored, and sustainable public health interventions aimed at reducing health inequities at interpersonal, community, and structural levels.

Limitations

Our study methods have several limitations worth noting. Since our study design was ecological, this limited our ability to establish causality. Our results may be subject to ecologic fallacy, as the associations we found related to HPV-associated cancers at the county level may not necessarily reflect associations at the individual level for all HPV-associated and the six site-specific cancers (Greenland and Robins, 1994). Moreover, as part of routine cancer surveillance, state and territorial registries record and submit cancer cases, not individuals. The same individual may appear multiple times in a cancer registry, if they are diagnosed with multiple primary cancers (Izquierdo and Schoenbach, 2000).

Nonetheless, cancer registries conduct several quality assurance and quality control activities, which consist of data quality audits, case consolidation, follow-back to hospitals, facilities, and labs, and manual data review, which may reduce the likelihood of duplicate case reporting. Since NPCR/SEER captures HPV-associated cancer cases reported by hospitals, facilities, and labs, our data set was missing unreported, undiagnosed HPV-associated cancers among women and men, especially among individuals lacking access to routine healthcare. However, there is a high likelihood that every chronic and infectious disease surveillance system is missing a small percentage of undiagnosed cases of disease. Furthermore, the primary outcome of incidence rates is based on data derived from state and territorial cancer registries that use population estimates in the denominator, and these estimates may be incomplete, imprecise, and result in under- or overestimation of populations (Boscoe and Miller, 2004).

Nevertheless, state cancer incidence data collected by registries and submitted to NPCR and SEER represent some of the most complete, high quality surveillance data available in the

U.S. Our study dataset included a decade of data representing about 98% of the U.S. population and 96% of states. The cross-sectional study design did not allow researchers to conduct a longitudinal cancer study, which follows individuals over 20-30 years to assess the impact of disease. However, it would be quite expensive to prospectively follow people for 25 years to assess cancer outcomes. Since several cancers take approximately 10-15 years to develop, a shorter timeframe using the cross-sectional design is more practical and economically feasible for public health studies used to inform programs and state policies, and to target resources.

The cross-sectional design and data source does not permit researchers to account for variability in residential status since the rural or urban assignment is based on where an individual lives at the time of diagnosis. Additionally, HPV-associated cancers may be underestimated due to delays in cancer data reporting or inaccuracies in the data. Yet, both CDC NPCR and NCI SEER use 24-month data to account for delays and to ensure completeness and quality of cancer surveillance data, so underestimating HPV-associated cancer cases seems unlikely. The data does not allow for examination of confounders such as HPV vaccine uptake or cervical cancer screening because these variables are not included in the NPCR/SEER cancer data set.

We were unable to ascertain the association between rural-urban residence and cancer stage at diagnosis for HPV-associated cancers, which is critical for examining disease severity and health outcomes by geography. Future studies should examine HPV-associated and site-specific cancer stage at diagnosis by geographic residence, insurance status, economic status, and healthcare access to identify any racial/ethnic, age-specific, and geographic disparities, especially for oropharyngeal, vulvar, and anal cancers, which are on the rise.

Additionally, penile and vaginal cancer results were based on a small number of cases over the study timeframe, so findings should be interpreted with caution.

Our community-level variables also posed limitations. The median age variable reflected one year within the study timeframe (2017) instead of the entire study period (2008-2018), which limited us from examining age for each reported HPV-associated cancer comprehensively. Moreover, the percent some college variable only accounted for a portion of our study population (25-44-year-olds) instead of all males and females 20 years and older. Additionally, the percent uninsured variable did not include data for individuals aged 65 years and older. Lastly, we used primary care physicians rate to assess healthcare access, which does not include the number of nurses, nurse practitioners, or physician assistants practicing within each county.

Future studies should utilize a comprehensive variable that includes several healthcare professions because this will provide a more accurate measure of true healthcare access (e.g., primary healthcare professionals per 100,000 population by county). Despite these limitations, to our knowledge, this is the first study to consider the roles of PCP rate, lack of insurance, economic status (using a composite variable), and some college education in examining the relationship between geographic residence and HPV-associated (all HPV-associated, cervical, vaginal, vulvar, penile, oropharyngeal, and anal cancer) cancer incidence.

Implications

Our study results may inform state comprehensive cancer control plan, cancer, and immunization program priorities funded through state and federal resources. Public health leaders, policymakers, healthcare professionals, and researchers may use study findings to develop tailored, culturally appropriate, and acceptable public health and clinical interventions (e.g., health education, cancer screening, HPV vaccination). Future research should include

studies aimed at exploring effective and sustainable methods for collecting behavioral data (e.g., sexual patterns, practices, and norms; history of sexual abuse; cancer screening; substance use; and mental health), as no surveillance system routinely collects this critical information. Data linkage with HPV immunization and cervical cancer screening surveillance systems may provide a complete picture of the association between risk factors and cancer outcomes among rural and urban women.

Future research should examine the relationships between behavior, culture, geography, and increased risk for cervical, vulvar, oropharyngeal, and anal cancer. Currently, cervical cancer is the only HPV-associated cancer that has a standard screening protocol for the detection of pre-cancer and cancer (USPSTF, 2018). Our **s**tudy findings may inform community-level interventions aimed at improving access and acceptance of HPV-associated cancer screening for cervical, vulvar, anal, and oropharyngeal cancers through partnerships between public health departments, healthcare systems, and primary care professionals. Standardizing and normalizing screening practices for vulvar, anal and oropharyngeal cancer is imperative for primary healthcare professionals to detect these HPV-associated cancers as early as possible.

Since HPV is the most common sexually transmitted infection, pilot studies that assess the feasibility of vulvar, oropharyngeal, and anal cancer screening in varied settings (e.g., community-based clinic settings, teaching hospitals, home-based self-testing with healthcare professional virtual consultation prior to testing) may facilitate early detection of these pre-cancers and cancers. Because our findings describe the HPV-associated disease burden, states and territories can utilize these results to design multi-faceted HPV-associated cancer prevention interventions aimed at increasing adolescent HPV vaccine coverage in rural and urban areas through schools, community centers, pharmacies, and mobile clinics. Additional behavioral

studies are warranted to examine the root causes of sexual risk behavior, poor access to health care, and vaccine and cancer screening hesitancy in rural and urban populations.

Conclusion

The results of our study validate the important roles rurality (for penile and vulvar cancer), sex, race/ethnicity, PCP rate, and economic status play in elevating HPV-associated cancer incidence among men and women. Lower economic status, rurality, and lack of healthcare access represent proxies for larger, systemic issues such as structural racism, intergenerational poverty, and gender discrimination, including discrimination due to sexual orientation. These systemic barriers may include incarceration, residential segregation, lack of effective public health policies focused on improving social determinants of health, and lack of opportunities for economic advancement in financially depressed communities within rural and urban areas (Bailey et al., 2017; Bailey et al., 2021). The collection, availability, and use of behavioral data that sheds light on sexual practices, patterns, and norms as well as cancer screening, HPV vaccination, and healthcare access and utilization may help inform evidence-based interventions aimed at preventing HPV-associated cancer and detecting these cancers as early as possible.

Examining the intersectionality of individual, interpersonal, and structural risk factors for acquiring HPV infection and associated cancer may help identify feasible and sustainable public health strategies for preventing, detecting, and eventually eliminating these cancers among women and men.

Table 4.1. *NPCR/SEER Cancer Registry Individual Level Variables*

Variable Name	Variable definition	Variable type	Role of variable in analysis
HPV-associated cancer incidence	# of new HPV-associated cancers among men and women/100,000 population	Ratio (continuous)	Primary outcome variable
Rural or urban residence (USDA RUCC, 2013)	Metro counties: 1) Counties in metro areas of 1 million population or > 2) Counties in metro areas of 250,000 to 1 million population 3) Counties in metro areas of fewer than 250,000 people Non-metro counties: 4) Urban population of 20,000 or more, adjacent to a metro area 5) Urban population of 20,000 or more, not adjacent to a metro area 6) Urban population of 2,500 to 19,999, adjacent to a metro area 7) Urban population of 2,500 to 19,999, not adjacent to a metro area 8) Completely rural or < 2,500 urban population, adjacent to a metro area 9) Completely rural or < 2,500 urban population, not adjacent to a metro area 88) Unknown-Alaska/Hawaii State/not official USDA Rural-Urban Continuum code 99) Unknown/not official USDA Rural-Urban Continuum code	Categorical (dichotomous)	Primary predictor variable
Age (SEER*Stat cancer data) **U.S. Census median age (2017)**	Age by 10-year age bands beginning at age 20 (20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80+) Median age by county	Interval (continuous) Continuous	Covariable
Race and ethnicity	Non-Hispanic White, Non-Hispanic Black, Non-Hispanic American Indian and Alaska Native, Non-Hispanic Asian and Pacific Islander, and Hispanic	Nominal (categorical)	Covariable
Sex	Female or Male	Nominal (categorical)	Covariable

Table 4.2. *Study Community Variables Assessing Social Determinants of Health*

Variable name	Variable definition	Variable type	Role of variable in analysis
Percent some college (ACS 5-year estimates, AHRF, 2021)	Adults aged 25-44 years with some post-secondary education	Ordinal (categorical)	Community-level covariable
Percent uninsured (U.S. Census, 2021)	Percent of people under age 65 without health insurance	Percentage (continuous)	Community-level covariable
Primary care physicians (PCP) rate (AHRF, AMA, 2021)	PCP number/County population	Percentage (continuous)	Community-level covariable
Economic status (Appalachian Regional Commission, 2021; USCS, 2021)	Composite: 3-year average unemployment rate, per capita market income, and poverty rate (Each county categorized as distressed, at-risk, transitional, competitive, attainment)	Ordinal (categorical)	Community-level covariable

Table 4.3. *Individual and Community Level Variable Study Characteristics*

Characteristic	Total	Rural	Urban
Age (yrs.)	**Median, IQR**	**Median, (IQR)**	
Median age	41.3 (44.5-38.1)	42.3 (45.7-39.3)	39.8 (42.7-36.9)
Sex	**Percent (SD)**	**Percent (SD)**	
Female	50.4 (.03)	50.0 (.03)	51.2 (.02)
Male	49.6 (.03)	50.0 (.03)	48.8 (.02)
Race/Ethnicity	**Percent (SD)**	**Percent (SD)**	
Non-Hispanic White	79.8 (.19)	81.2 (.20)	77.4 (.04)
Non-Hispanic Black	9.2 (.14)	8.2 (.15)	11.0 (.13)
Non-Hispanic American Indian/Alaska Native	1.9 (.07)	2.5 (.09)	.80 (.03)
Non-Hispanic Asian/Pacific Islander	1.5 (.04)	.80 (.02)	2.6 (.05)
Hispanic	7.6 (.13)	7.3 (.13)	8.2 (.12)
Geographic residence	**n (%)**		
Rural	1,838 (62.1)		
Urban	1,120 (37.9)		
Educational attainment			
Percent some college	**n (%)**	**n (%)**	
> 63.05	749 (25.3)	315 (17.1)	433 (38.7)
> 54.60-63.05	737 (24.9)	407 (22.1)	329 (29.4)
> 46.88-54.60	738 (24.9)	520 (28.3)	218 (19.5)
0-46.88	737 (24.9)	596 (32.4)	140 (12.5)
Healthcare access			
***Primary care physicians (PCP) rate**	**n (%)**	**n (%)**	
> 69.89	749 (25.3)	349 (19.0)	400 (35.7)
> 47.55-69.89	737 (24.9)	457 (24.9)	279 (24.9)
> 30.94-47.55	738 (24.9)	516 (28.1)	221 (19.7)
0-30.94	737 (24.9)	516 (28.1)	220 (19.6)
Health insurance status			
Percent uninsured	**n (%)**	**n (%)**	
> 19.95	748 (25.3)	370 (20.1)	367 (32.8)
> 16.56-19.95	739 (25.0)	445 (24.2)	290 (25.9)
> 13.10-16.56	737 (24.9)	458 (24.9)	281 (25.1)
0-13.10	737 (24.9)	565 (30.7)	182 (16.3)
Economic status	**n (%)**	**n (%)**	
Distressed	310 (10.6)	270 (14.8)	40 (3.6)
At-Risk	464 (15.9)	367 (20.2)	97 (8.8)
Transitional	1,482 (50.8)	821 (45.1)	661 (60.2)
Competitive	393 (13.5)	207 (11.4)	186 (16.9)
Attainment	271 (9.3)	156 (8.6)	115 (10.5)

Abbreviations- IQR= interquartile range, SD= standard deviation

*PCP rate= PCP number/county population

Note: 30 counties were missing economic status data; 3 counties were missing PCP rate, percent uninsured, and percent some college data. These counties were not included in analysis.

Table 4.4a. *Mean All HPV, Cervical, and Vaginal Cancer Incidence by Age, Sex, Race/Ethnicity, U.S., 2008-2018*

Characteristic	All HPV-Associated Cancers (per 100,000)			Cervical Carcinoma (per 100,000)			Vaginal SCC (per 100,000)		
	Total (SD)	Rural (SD)	Urban (SD)	Total (SD)	Rural (SD)	Urban (SD)	Total (SD)	Rural (SD)	Urban (SD)
Age (yrs.)									
20-29	1.9 (3.4)	1.9 (4.0)	1.8 (2.0)	3.6 (7.0)	3.7 (8.3)	3.4 (4.1)	.01 (.28)	.01 (.30)	.09 (.23)
30-39	8.3 (7.5)	8.5 (8.8)	8.0 (4.7)	13.9 (13.6)	14.4 (15.9)	13.0 (8.5)	.10 (.90)	.09 (.98)	.12 (.75)
40-49	16.7 (10.5)	16.8 (12.0)	16.6 (7.2)	15.3 (13.8)	15.6 (16.1)	14.8 (8.5)	.43 (1.8)	.44 (2.1)	.4103 (1.2)
50-59	29.4 (13.8)	29.3 (16.1)	29.7 (9.0)	12.7 (12.8)	13.2 (15.4)	12.0 (6.7)	.89 (4.7)	.97 (5.8)	.77 (1.6)
60-69	35.1 (15.3)	34.5 (17.8)	36.1 (10.0)	10.7 (11.3)	11.0 (13.5)	10.3 (6.3)	1.3 (3.5)	1.3 (4.1)	1.3 (2.3)
70-79	32.5 (17.8)	31.7 (20.4)	34.0 (12.6)	8.8 (13.4)	9.0 (15.3)	8.6 (9.7)	1.9 (5.2)	1.8 (6.0)	2.0 (3.2)
80+	27.8 (21.5)	27.1 (25.2)	28.9 (13.4)	6.7 (12.5)	6.4 (14.5)	7.2 (8.3)	2.4 (6.7)	2.4 (7.6)	2.6 (4.7)
Sex									
Female	11.6 (4.2)	11.8 (4.9)	11.2 (2.9)	10.7 (5.2)	11.0 (6.1)	10.2 (3.4)	.83 (1.4)	.86 (1.6)	.77 (.71)
Male	8.9 (3.9)	8.9 (4.4)	8.8 (2.7)						
Race/Ethnicity									
Non-Hispanic White	22.1 (7.2)	22.2 (8.2)	22.0 (5.2)	10.2 (5.8)	10.4 (6.8)	9.9 (3.7)	.86 (1.6)	.90 (2.0)	.80 (.81)
Non-Hispanic Black	11.9 (28.6)	10.82 (33.4)	13.7 (18.3)	8.5 (37.1)	7.7 (43.1)	9.8 (24.0)	.50 (3.8)	.41 (4.5)	.6437 (2.1)
Non-Hispanic American Indian/Alaska Native	13.6 (50.8)	14.6 (56.6)	12.0 (39.5)	10.4 (79.4)	11.3 (88.6)	8.9 (1.7)	.29 (6.0)	.36 (7.4)	.1788 (2.1)
Non-Hispanic Asian/Pacific Islander	9.6 (47.7)	10.1 (56.3)	8.7 (28.4)	10.2 (64.3)	11.4 (78.7)	8.1 (27.9)	.45 (9.5)	.41 (9.7)	.5102 (9.1)
Hispanic	8.6 (19.8)	8.4 (23.5)	8.9 (11.6)	8.7 (22.6)	8.5 (26.7)	9.0 (13.6)	.29 (2.8)	.22 (2.3)	.38 (3.4)

Abbreviations- SCC= squamous cell carcinoma, SD= standard deviation
Incidence rates are per 100,000 persons and are age-adjusted to the 2000 U.S. standard population (19 age groups, Census P25-1130).
National Program of Cancer Registries and Surveillance, Epidemiology, and End Results Program SEER*Stat Database: U.S. Cancer Statistics Incidence Analytic File- 1998-2018. United States Department of Health and Human Services. Centers for Disease Control and Prevention. Released June 2021, based on 2020 submission.

Table 4.4b. *Mean Vulvar and Penile Cancer Incidence by Age, Sex, Race/Ethnicity, U.S., 2008-2018*

Characteristic	Vulvar SCC (per 100,000)			Penile SCC (per 100,000)		
	Total (SD)	Rural (SD)	Urban (SD)	Total (SD)	Rural (SD)	Urban (SD)
Age (yrs.)						
20-29	.12 (1.0)	.12 (1.1)	.12 (.80)	.01 (.22)	.01 (.27)	.01 (.07)
30-39	.93 (2.9)	.93 (3.3)	.93 (2.1)	.13 (.99)	.13 (1.2)	.12 (.49)
40-49	3.0 (7.7)	3.3 (9.4)	2.6 (3.4)	.65 (3.0)	.70 (3.1)	.55 (2.8)
50-59	4.4 (7.0)	4.6 (8.4)	4.1 (3.5)	1.2 (3.5)	1.3 (4.2)	1.1 (2.0)
60-69	5.7 (8.2)	5.8 (9.3)	5.7 (6.0)	2.6 (5.6)	2.9 (6.6)	2.2 (3.2)
70-79	8.4 (12.3)	8.3 (13.8)	8.5 (9.3)	5.2 (11.0)	5.6 (13.2)	4.4 (5.9)
80+	12.6 (19.0)	13.1 (22.7)	11.8 (10.3)	6.4 (15.4)	6.7 (18.2)	6.0 (9.1)
Sex						
Female	4.2 (3.5)	4.5 (4.1)	3.8 (2.0)			
Male				1.5 (2.0)	1.7 (2.4)	1.2 (1.1)
Race/Ethnicity						
Non-Hispanic White	4.6 (3.9)	4.8 (4.6)	4.3 (2.3)	1.7 (2.9)	1.9 (3.5)	1.3 (1.2)
Non-Hispanic Black	2.0 (16.7)	1.7 (17.4)	2.5 (15.6)	.83 (8.1)	.87 (9.9)	.78 (3.5)
Non-Hispanic American Indian/Alaska Native	2.3 (30.3)	2.8 (37.6)	1.5 (10.3)	1.2 (21.9)	1.5 (27.0)	.69 (8.1)
Non-Hispanic Asian/Pacific Islander	.55 (8.0)	.24 (4.2)	1.1 (11.8)	.19 (3.9)	.13 (2.6)	.29 (5.3)
Hispanic	1.2 (9.0)	1.1 (9.9)	1.2 (7.2)	.75 (6.2)	.70 (6.6)	.83 (5.3)

Abbreviations- SCC= squamous cell carcinoma, SD= standard deviation
Incidence rates are per 100,000 persons and are age-adjusted to the 2000 U.S. standard population (19 age groups, Census P25-1130).
National Program of Cancer Registries and Surveillance, Epidemiology, and End Results Program SEER*Stat Database: U.S. Cancer Statistics Incidence Analytic File- 1998-2018. United States Department of Health and Human Services. Centers for Disease Control and Prevention. Released June 2021, based on 2020 submission.

Table 4.4c. *Mean Oropharyngeal and Anal Cancer Incidence by Age, Sex, Race/Ethnicity, 2008-2018*

Characteristic	**Oropharyngeal SCC (per 100,000)**			**Anal SCC (per 100,000)**		
Characteristic	Mean (SD)	Rural (SD)	Urban (SD)	Mean (SD)	Rural (SD)	Urban (SD)
Age (yrs.)						
20-29	.07 (.79)	.08 (.99)	.06 (.24)	.08 (.30)	.10 (.46)	.07 (.16)
30-39	.61 (2.6)	.64 (3.3)	.56 (.96)	.11 (.20)	.04 (.20)	.15 (.19)
40-49	5.0 (5.3)	4.9 (6.2)	5.1 (3.3)	1.8 (3.3)	2.5 (5.5)	1.5 (.87)
50-59	15.2 (9.2)	14.8 (10.5)	15.8 (6.5)	4.8 (3.0)	5.5 (4.5)	4.4 (1.6)
60-69	19.3 (11.3)	18.7 (13.1)	20.5 (7.4)	6.3 (3.0)	6.7 (4.1)	6.1 (2.3)
70-79	14.7 (12.2)	13.9 (14.0)	16.1 (8.2)	5.8 (4.0)	5.1 (6.0)	6.1 (2.1)
80+	7.1 (9.7)	6.5 (10.9)	8.1 (7.3)	5.4 (4.3)	4.6 (6.0)	5.8 (2.9)
Sex						
Female	1.6 (1.3)	1.6 (1.5)	1.6 (.84)	4.0 (2.2)	4.7 (3.2)	3.6 (1.3)
Male	7.2 (3.5)	7.2 (4.0)	7.3 (2.4)	2.1 (1.6)	2.7 (2.2)	1.8 (.94)
Race/Ethnicity						
Non-Hispanic White	10.0 (4.5)	9.7 (5.3)	10.3 (3.0)	4.2 (1.8)	4.3 (2.6)	4.2 (.98)
Non-Hispanic Black	4.9 (16.7)	4.6 (18.7)	5.5 (12.8)	1.9 (4.4)	1.8 (7.1)	2.0 (1.6)
Non-Hispanic American Indian/Alaska Native	4.6 (23.1)	4.5 (24.0)	4.8 (21.5)	2.7 (4.3)	1.5 (4.6)	3.4 (4.0)
Non-Hispanic Asian/Pacific Islander	2.4 (22.6)	2.4 (25.3)	2.4 (17.4)	.44 (1.2)	.36 (1.7)	.49 (.82)
Hispanic	2.6 (10.3)	2.6 (11.9)	2.5 (6.7)	1.1 (2.0)	1.3 (3.3)	.98 (.49)

Abbreviations- SCC= squamous cell carcinoma, SD= standard deviation
Incidence rates are per 100,000 persons and are age-adjusted to the 2000 U.S. standard population (19 age groups, Census P25-1130).
National Program of Cancer Registries and Surveillance, Epidemiology, and End Results Program SEER*Stat Database: U.S. Cancer Statistics Incidence Analytic File- 1998-2018. United States Department of Health and Human Services. Centers for Disease Control and Prevention. Released June 2021, based on 2020 submission.

Table 4.5a. *All HPV and Cervical Cancer Incidence Rate Ratios, U.S., 2008-2018*

Characteristic	All HPV-associated Cancers (per 100,000)		Cervical Carcinoma (per 100,000)	
	IRR (95% CI)	**p-value**	**IRR (95% CI)**	**p-value**
Age (yrs.)				
Median Age (2017)	1.02 (1.01-1.02)	p < 0.00	1.00 (.99-1.00)	p < 0.09
Sex				
Percent Female	6.42 (2.72-15.15)	p < 0.00	10.93 (5.04-23.7)	p < 0.00
Race/Ethnicity				
Non-Hispanic White	5.37 (2.81-10.26)	p < 0.00	5.72 (2.60-12.57)	p < 0.00
Non-Hispanic Black	5.91 (3.06-11.39)	p < 0.00	10.29 (4.63-22.88)	p < 0.00
Non-Hispanic American Indian/Alaska Native	3.50 (1.77-6.91)	p < 0.00	5.83 (2.53-13.42)	p < 0 .00
Hispanic	2.81 (1.42-5.59)	p < 0.00	7.18 (2.53-13.42)	p < 0.00
Non-Hispanic Asian/Pacific Islander	Omitted		Omitted	
Geographic residence				
Rural	1.04 (1.04-1.06)	p < 0.00	1.05 (1.02-1.08)	p < 0.00
Urban	Ref		Ref	
Educational attainment				
Percent some college (%)				
> 63.05				
> 54.60-63.05	1.17 (1.13-1.21)	p < 0.00	1.20 (1.14-1.26)	p < 0.00
> 46.88-54.60	1.23 (1.188-1.265)	p < 0.00	1.30 (1.23-1.38)	p < 0.00
0-46.88	1.23 (1.19-1.28)	p < 0.00	1.47 (1.39-1.55)	p < 0.00
Healthcare access (%)				
***Primary care physicians (PCP) rate**				
> 69.89	Ref		Ref	
> 47.55-69.89	1.05 (1.02-1.08)	p < 0.00	1.13 (1.08-1.18)	p < 0.00
> 30.94-47.55	1.08 (1.05-1.11)	p < 0.00	1.20 (1.15-1.25)	p < 0..00
0-30.94	1.06 (1.02-1.10)	p < 0.00	1.16 (1.10-1.22)	p < 0.00
Health insurance status				
Percent uninsured				
0-13.10%	Ref		Ref	
> 13.10-16.56	1.06 (1.03-1.09)	p < 0.00	1.11 (1.06-1.16)	p < 0.00
> 16.56-19.95	1.08 (1.04-1.11)	p < 0.00	1.18 (1.13-1.24)	p < 0.00
>19.95	1.00 (.97-1.03)	p < .97	1.18 (1.12-1.24)	p < 0.00
Economic Status				
Attainment	Ref	Ref	Ref	Ref
Competitive	1.10 (1.03-1.17)	p < 0.00	1.08 (.96-1.21)	p < .19
Transitional	1.29 (1.22-1.37)	p < 0.00	1.32 (1.19-1.47)	p < 0.00
At-risk	1.41 (1.33-1.49)	p < 0.00	1.50 (1.35-1.68)	p < 0.00
Distressed	1.35 (1.26-1.45)	p < 0.00	1.65 (1.47-1.85)	p < 0.00

Abbreviations- SCC= squamous cell carcinoma, SD= standard deviation
Incidence rates are per 100,000 persons and are age-adjusted to the 2000 U.S. standard population (19 age groups, Census P25-1130).
National Program of Cancer Registries and Surveillance, Epidemiology, and End Results Program SEER*Stat Database: U.S. Cancer Statistics Incidence Analytic File- 1998-2018. United States Department of Health and Human Services. Centers for Disease Control and Prevention. Released June 2021, based on 2020 submission.

Table 4.5b. *Vaginal and Vulvar Cancer Incidence Rate Ratios, U.S., 2008-2018*

Characteristics	Vaginal SCC (per 100,000)		Vulvar SCC (per 100,000)	
	IRR (95% CI)	**p-value**	**IRR (95% CI)**	**p-value**
Age (yrs.)				
Median Age (2017)	1.02 (1.00-1.03)	p < 0.02	1.03 (1.02-1.03)	p < 0.00
Sex				
Percent Female	5.75 (.22-149.97)	p < 0.29	15.10 (3.70-61.62)	p < 0.00
Race/Ethnicity				
Non-Hispanic White	8.53 (1.89-38.41)	p < 0.01	26.37 (7.65-90.92)	p < 0 .00
Non-Hispanic Black	14.85 (3.17-69.54)	p < 0.00	15.94 (4.52-56.25)	p < 0.00
Non-Hispanic American Indian/Alaska Native	3.75 (.70-20.00)	p < 0.12	9.46 (2.41-37.34)	p < 0.00
Hispanic	4.80 (.77-29.77)	p < 0.09	4.46 (1.14-17.49)	p < 0.03
Non-Hispanic Asian/Pacific Islander	Omitted		Omitted	
Geographic residence				
Rural	1.09 (.99-1.20)	p < 0.10	1.18 (1.18-1.24)	p < 0.00
Urban	Ref		Ref	
Educational attainment				
Percent some college (%)				
> 63.05	Ref		Ref	
> 54.60-63.05	1.03 (.88-1.19)	p < 0.73	1.13 (1.03-1.24)	p < 0.01
> 46.88-54.60	1.27 (1.08-1.49)	p < 0.00	1.14 (1.04-1.24)	p < 0.00
0-46.88	1.40 (1.18-1.67)	p < 0.00	1.12 (1.02-1.23)	p < 0.02
Healthcare access (%)				
*Primary care physicians (PCP) rate				
> 69.89	Ref		Ref	
> 47.55-69.89	1.19 (1.04-1.36)	p < 0.01	1.10 (1.01-1.17)	p < 0.03
> 30.94-47.55	1.12 (.97-1.29)	p < 0.12	1.07 (.99-1.15)	p < 0.11
0-30.94	1.12 (.92-1.36)	p< 0.25	1.08 (.98-1.19)	p < 0.11
Health insurance status				
Percent uninsured				
0-13.10%	Ref		Ref	
> 13.10-16.56	.97 (.86-1.11)	p < 0.68	1.02 (.95-1.09)	p < 0.68
> 16.56-19.95	1.06 (.93-1.21)	p < 0.40	.90 (.84-.97)	p < 0.00
>19.95	1.02 (.84-1.23)	p < 0.87	.79 (.72-.87)	p < 0.00
Economic Status				
Attainment	Ref		Ref	
Competitive	.87 (.61-1.23)	p < 0.43	1.15 (.96-1.38)	p < 0.13
Transitional	1.20 (.87-1.66)	p < 0.26	1.23 (1.04-1.45)	p < 0.02
At-risk	1.32 (.95-1.83)	p < 0.10	1.27 (1.07-1.51)	p < 0.01
Distressed	1.62 (1.15-2.28)	p < 0.01	1.20 (1.00-1.44)	p < 0.06

Abbreviations- SCC= squamous cell carcinoma, SD= standard deviation

Incidence rates are per 100,000 persons and are age-adjusted to the 2000 U.S. standard population (19 age groups, Census P25-1130).National Program of Cancer Registries and Surveillance, Epidemiology, and End Results Program SEER*Stat Database: U.S. Cancer Statistics Incidence Analytic File- 1998-2018. United States Department of Health and Human Services. Centers for Disease Control and Prevention. Released June 2021, based on 2020 submission

Table 4.5c. *Penile and Oropharyngeal Cancer Incidence Rate Ratios, U.S., 2008-2018*

Characteristics	Penile SCC (per 100,000)		Oropharyngeal SCC (per 100,000)	
	IRR (95% CI)	**p-value**	**IRR (95% CI)**	**p-value**
Age (yrs.)				
Median Age (2017)	1.02 (1.01-1.03)	p < 0.00	1.03 (1.02-1.03)	p < 0.00
Sex				
Percent Female			3.67 (.85-15.86)	p < 0.08
Race/Ethnicity				
Non-Hispanic White	2185.66 (155.16-30789.45)	p < 0.00	3.86 (2.07-7.20)	p < 0.00
Non-Hispanic Black	2058.60 (140.35-30194.46)	p < 0.00	3.92 (2.08-7.40)	p < 0.00
Non-Hispanic American Indian/Alaska Native	1988.43 (126.43-31273.12)	p < 0.00	2.32 (1.12-4.81)	P< 0.02
Hispanic	2551.25 (155.97-41732.57)	p < 0.00	1.28 (.65-2.54)	p < 0.48
Non-Hispanic Asian/Pacific Islander	Omitted		Omitted	
Geographic residence				
Rural	1.42 (1.31-1.54)	p < 0.00	.99 (.96-1.02)	p < 0.40
Urban	Ref		Ref	
Educational attainment				
Percent some college (%)				
> 63.05	Ref		Ref	
> 54.60-63.05	1.18 (1.02-1.36)	p < 0.03	1.15 (1.10-1.20)	p < 0.00
> 46.88-54.60	1.47 (1.27-1.71)	p < 0.00	1.18 (1.13-1.24)	p < 0.00
0-46.88	1.65 (1.43-1.91)	p < 0.00	1.13 (1.08-1.19)	p < 0.00
Healthcare access (%)				
*Primary care physicians (PCP) rate				
> 69.89	Ref		Ref	
> 47.55-69.89	1.09 (.97-1.23)	p < 0.16	1.01 (.97-1.05)	p < 0.61
> 30.94-47.55	1.16 (1.03-1.31)	p < 0.02	1.03 (.99-1.07)	p < 0.12
0-30.94	1.33 (1.15-1.54)	p < 0.00	1.00 (.95-1.05)	p < 0.99
Health insurance status				
Percent uninsured				
0-13.10%	Ref		Ref	
> 13.10-16.56	1.10 (.98-1.23)	p < 0.11	1.04 (1.01-1.08)	p < 0.03
> 16.56-19.95	1.09 (.97-1.23)	p < 0.17	1.07 (1.02 -1.11)	p < 0.00
>19.95	1.17 (1.02-1.34)	p < 0.02	.95 (.91-1.00)	p < 0.04
Economic Status				
Attainment	Ref		Ref	
Competitive	.98 (.74-1.29)	p < 0.87	1.11 (1.01-1.21)	p < 0.03
Transitional	1.07 (.84-1.37)	p < 0.60	1.29 (1.19-1.40)	p < 0.00
At-risk	1.34 (1.03-1.73)	p < 0.03	1.39 (1.28-1.52)	p < 0.00
Distressed	1.47 (1.12-1.92)	p < 0.01	1.24 (1.12-1.37)	p < 0.00

Abbreviations- SCC= squamous cell carcinoma, SD= standard deviation

Incidence rates are per 100,000 persons and are age-adjusted to the 2000 U.S. standard population (19 age groups, Census P25-1130).

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Table 4.5d. *Anal Cancer Incidence Rate Ratios, U.S., 2008-2018*

Characteristics	**Anal SCC (per 100,000)**	
	IRR (95% CI)	**p-value**
Age (yrs.)		
Median Age (2017)	1.02 (1.02-1.03)	p < 0.00
Sex		
Percent Female	14.57 (5.12-41.48)	p < 0.00
Race/Ethnicity		
Non-Hispanic White	2.79 (1.61-4.83)	p < 0.00
Non-Hispanic Black	2.24 (1.27-3.97)	p < 0.01
Non-Hispanic American Indian/Alaska Native	1.37 (.53-3.59)	p < 0.52
Hispanic	1.14 (.59-2.21)	p < 0.69
Non-Hispanic Asian/Pacific Islander	Omitted	
Geographic residence		
Rural	1.00 (.95-1.04)	p < 0.80
Urban	Ref	
Educational attainment		
Percent some college (%)		
> 63.05	Ref	
> 54.60-63.05	1.25 (1.17-1.33)	p < 0.00
> 46.88-54.60	1.23 (1.16-1.31)	p < 0.00
0-46.88	1.12 (1.04-1.20)	p < 0.00
Healthcare access (%)		
*Primary care physicians (PCP) rate		
> 69.89	Ref	
> 47.55-69.89	.99 (.94-1.04)	p < 0.75
> 30.94-47.55	1.01 (.95-1.07)	p < 0.76
0-30.94	.98 (.91-1.05)	p < 0.54
Health insurance status		
Percent uninsured		
0-13.10%		
> 13.10-16.56	1.07 (1.01-1.13)	p < 0.01
> 16.56-19.95	1.06 (1.00-1.12)	p < 0.04
>19.95	.97 (.90-1.04)	p < 0.35
Economic Status		
Attainment	Ref	
Competitive	1.14 (.99-1.31)	p < 0.06
Transitional	1.35 (1.20-1.53)	p < 0.00
At-risk	1.42 (1.25-1.61)	p < 0.00
Distressed	1.20 (1.04-1.38)	p < 0.01

Abbreviations- SCC= squamous cell carcinoma, IRR= incidence rate ratio, CI= confidence interval
Incidence rates are per 100,000 persons and are age-adjusted to the 2000 U.S. standard population (19 age groups, Census P25-1130).
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Table 4.6a. *All HPV-Associated and Cervical Cancer Incidence Multivariate Regression Models, U.S. 2008-2018*

Characteristic	All HPV-associated Cancers (per 100,000)		Cervical Carcinoma (per 100,000)	
Age (Yrs.)	**IRR (95% CI)**	**p-value**	**IRR (95% CI)**	**p-value**
Median Age (2017)	1.01 (1.01-1.02)	p < 0.00	1.00 (.99-1.00)	p < 0.18
Sex				
Percent Female	3.65 (1.62-8.20)	p < 0.00	11.92 (5.71-24.86)	p < 0.22
Race/Ethnicity				
Non-Hispanic White	1.84 (1.29-2.64)	p < 0.00	1.44 (.87-2.38)	p < 0.15
Non-Hispanic Black	1.75 (1.21-2.53)	p < 0.00	1.73 (1.03-2.91)	p < 0.04
Non-Hispanic American Indian/Alaska Native	1.31 (.86-2.01)	p < 0.21	1.08 (.60-1.95)	p < 0.80
Hispanic	1.14 (.77-1.69)	p < 0.51	1.68 (1.03-1.12)	p < 0.06
Geographic residence				
Rural	.97 (.95-.99)	p < 0.01	1.02 (.99-1.06)	p < 0.00
Educational attainment				
Percent some college (%)				
> 63.05				
> 54.60-63.05				
> 46.88-54.60				
0-46.88				
Healthcare access (%)				
*Primary care physicians (PCP) rate				
> 69.89			Ref	
> 47.55-69.89			1.07 (1.04- 1.20)	p < 0.00
> 30.94-47.55			1.12 (1.07-1.17)	p < 0.00
0-30.94			1.10 (1.04-1.17)	p < 0.00
Health insurance status				
Percent uninsured				
0-13.10%				
> 13.10-16.56				
> 16.56-19.95				
>19.95				
Economic Status				
Attainment	Ref		Ref	
Competitive	1.10 (1.03-1.17)	p < 0.00	1.07 (.95-1.20)	p < 0.27
Transitional	1.29 (1.22-1.37)	p < 0.00	1.27 (1.15-1.42)	p < 0.00
At-risk	1.40 (1.31-1.48)	p < 0.00	1.41 (1.25-1.58)	p < 0.00
Distressed	1.40 (1.31-1.51)	p < 0.00	1.51 (1.33-1.72)	p < 0.00

Abbreviations- SCC= squamous cell carcinoma, IRR= incidence rate ratio, CI= confidence interval
Incidence rates are per 100,000 persons and are age-adjusted to the 2000 U.S. standard population (19 age groups, Census P25-1130).
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Table 4.6b. *Vulvar and Vaginal Cancer Incidence Multivariate Regression Models, U.S., 2008-2018*

Characteristic	Vulvar SCC (per 100,000)		Vaginal SCC (per 100,000)	
Age (Yrs.)	**IRR (95% CI)**	**p-value**	**IRR**	**p-value**
Median Age (2017)	1.01 (1.00- 1.02)	p < 0.05	1.01 (1.00-1.03)	p < 0.14
Sex				
Percent Female	9.21 (2.10-40.32)	p < 0.00	3.83 (.19-79.94)	p < 0.38
Race/Ethnicity				
Non-Hispanic White	5.41 (2.18-13.65)	p < 0.00	.67 (.31-1.47)	p < 0.32
Non-Hispanic Black	2.80 (1.09-7.17)	p < 0.03	.70 (.27-1.80)	p < 0.46
Non-Hispanic American Indian/Alaska Native	1.82 (.58-5.77)	p < 0.31	.86 (.10-7.58)	p < 0.89
Hispanic	1.07 (.39-2.98)	p < 0.89	.86 (.07-10.94)	p < 0.91
Geographic residence				
Rural	1.10 (1.04-1.16)	p < 0.00	1.43 (.69-2.98)	p < 0.34
Educational attainment				
Percent some college (%)				
> 63.05				
> 54.60-63.05				
> 46.88-54.60				
0-46.88				
Healthcare access (%)				
*Primary care physicians (PCP) rate				
> 69.89				
> 47.55-69.89				
> 30.94-47.55				
0-30.94				
Health insurance status				
Percent uninsured				
0-13.10%				
> 13.10-16.56				
> 16.56-19.95				
>19.95				
Economic Status				
Attainment	Ref		Ref	
Competitive	1.18 (.99-1.40)	p < 0.07	.87 (.51-1.23)	p < 0.43
Transitional	1.26 (1.08-1.48)	p < 0.00	1.18 (.85-1.64)	p < 0.33
At-risk	1.30 (1.09-1.55)	p < 0.00	1.27 (.89-1.80)	p < 0.18
Distressed	1.34 (1.11-1.62)	p < 0.00	1.61 (1.11-2.35)	p < 0.01

Abbreviations- SCC= squamous cell carcinoma, IRR= incidence rate ratio, CI= confidence interval
Incidence rates are per 100,000 persons and are age-adjusted to the 2000 U.S. standard population (19 age groups, Census P25-1130).
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Table 4.6c. *Penile and Oropharyngeal Cancer Incidence Multivariate Regression Models, U.S., 2008-2018*

Characteristic	Penile SCC (per 100,000)		Oropharyngeal SCC (per 100,000)	
Age (Yrs.)	**IRR (95% CI)**	**p-value**	**IRR (95% CI)**	**p-value**
Median Age (2017)	1.01 (1.00-1.03)	p < 0.03	1.02 (1.02-1.03)	p < 0.00
Sex				
Percent Female	n/a		1.10 (.26-4.61)	p < 0.90
Race/Ethnicity				
Non-Hispanic White	36.83 (5.45-249.08)	p < 0.00	1.56 (1.04-2.34)	p < 0.03
Non-Hispanic Black	26.78 (3.77-190.17)	p < 0.00	1.59 (1.04-2.42)	p < 0.03
Non-Hispanic American Indian/Alaska Native	29.09 (3.51-241.32)	p < 0.00	1.33 (.75-2.36)	p < 0.33
Hispanic	47.73 (6.12-372.12)	p < 0.00	.68 (.43-1.09)	p < 0.11
Geographic residence				
Rural	1.24 (1.13-1.36)	p < 0.00	.90 (.87-.92)	p < 0.00
Educational attainment				
Percent some college (%)				
> 63.05				
> 54.60-63.05				
> 46.88-54.60				
0-46.88				
Healthcare access (%)				
*Primary care physicians (PCP) rate				
> 69.89			Ref	
> 47.55-69.89			.99 (.95-1.02)	p < 0.44
> 30.94-47.55			.99 (.95-1.03)	p < 0.68
0-30.94			.94 (.90-.99)	p < 0.02
Health insurance status				
Percent uninsured				
0-13.10%				
> 13.10-16.56				
> 16.56-19.95				
>19.95				
Economic Status				
Attainment	Ref		Ref	
Competitive	.98 (.75-1.30)	p < 0.91	1.10 (1.01-1.20)	p < 0.03
Transitional	1.06 (.83-1.36)	p < 0.65	1.31 (1.21-1.41)	p < 0.00
At-risk	1.25 (.96-1.63)	p < 0.10	1.40 (1.28-1.53)	p < 0.00
Distressed	1.43 (1.07-1.91)	p < 0.02	1.33 (1.19-1.48)	p < 0.00

Abbreviations- SCC= squamous cell carcinoma, IRR= incidence rate ratio, CI= confidence interval
Incidence rates are per 100,000 persons and are age-adjusted to the 2000 U.S. standard population (19 age groups, Census P25-1130).
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Table 4.6d. *Anal Cancer Incidence Multivariate Regression Model, U.S., 2008-2018*

Characteristic	**Anal SCC (per 100,000)**	
Age (yrs.)	**IRR (95% CI)**	**p-value**
Median Age (2017)	1.02 (1.01-1.02)	p < 0.00
Sex		
Percent Female	7.38 (2.46—22.18)	p < 0.00
Race/Ethnicity		
Non-Hispanic White	.97 (.60-1.56)	p < 0.89
Non-Hispanic Black	.72 (.43-1.21)	p < 0.21
Non-Hispanic American Indian/Alaska Native	.64 (.24-1.72)	p < 0.38
Hispanic	.51 (.29-.91)	p < 0.02
Geographic residence		
Rural	.94 (.90-.99)	p < 0.01
Educational attainment		
Percent some college (%)		
> 63.05		
> 54.60-63.05		
> 46.88-54.60		
0-46.88		
Healthcare access (%)		
*Primary care physicians (PCP) rate		
> 69.89		
> 47.55-69.89		
> 30.94-47.55		
0-30.94		
Health insurance status		
Percent uninsured		
0-13.10%		
> 13.10-16.56		
> 16.56-19.95		
>19.95		
Economic Status		
Attainment	Ref	
Competitive	1.15 (1.00-1.31)	p < 0.05
Transitional	1.38 (1.20-1.56)	p < 0.00
At-risk	1.47 (1.28-1.69)	p < 0.00
Distressed	1.35 (1.16-1.56)	p < 0.00

Abbreviations- SCC= squamous cell carcinoma, IRR= incidence rate ratio, CI= confidence interval
Incidence rates are per 100,000 persons and are age-adjusted to the 2000 U.S. standard population (19 age groups, Census P25-1130).
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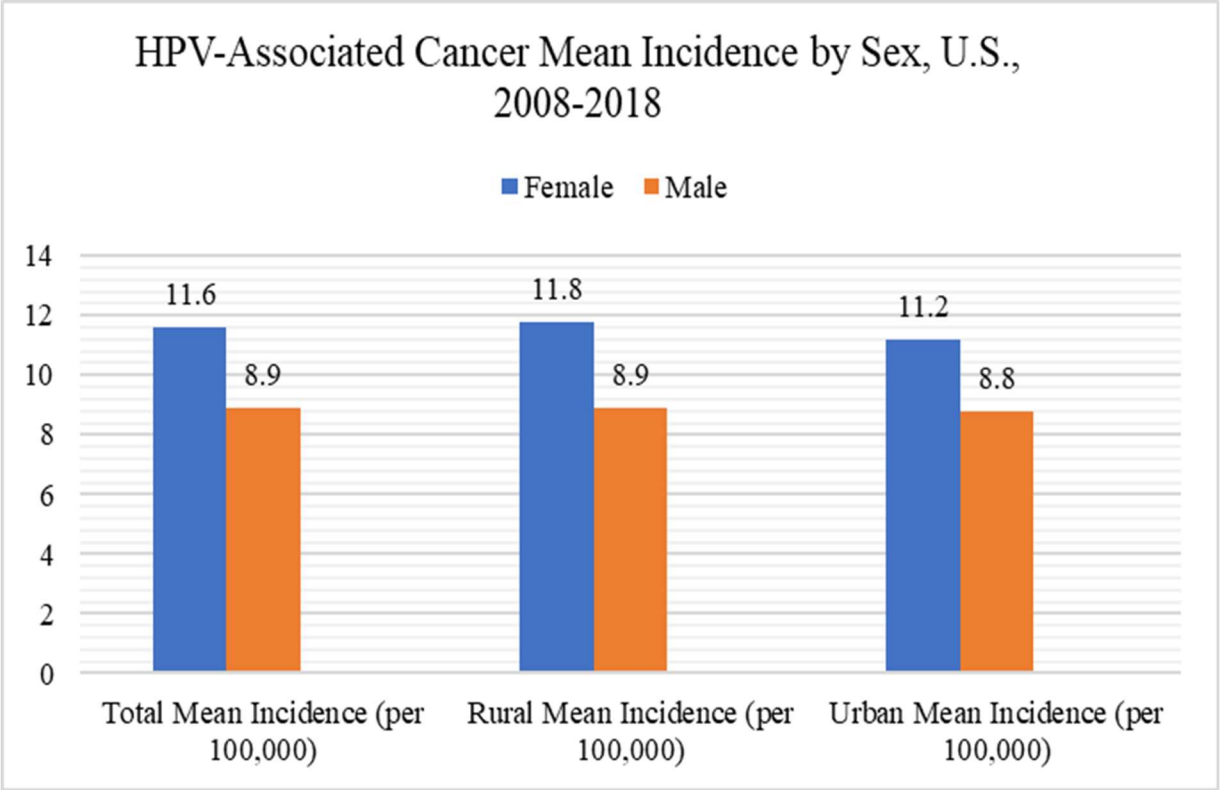

Figure 4.2. *HPV-Associated Cancer Mean Incidence by Sex, U.S., 2008-2018*

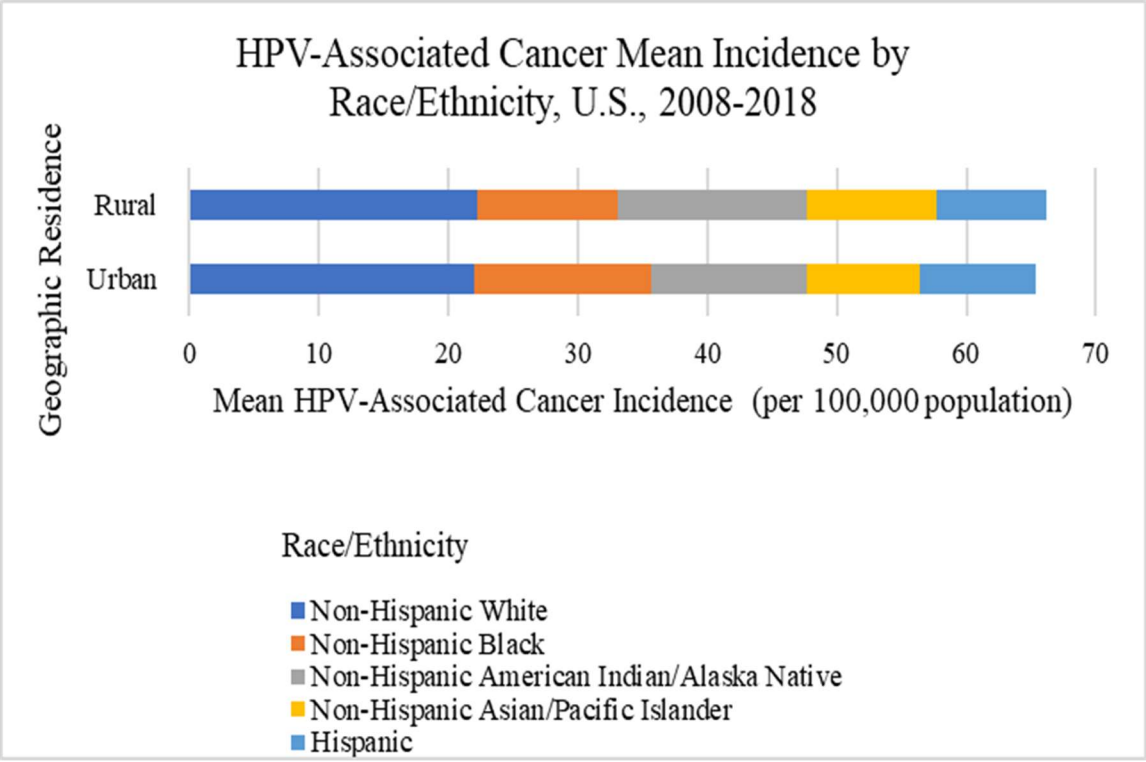

Figure 4.3. *HPV-Associated Cancer Mean Incidence by Race/Ethnicity, U.S., 2008-2018*

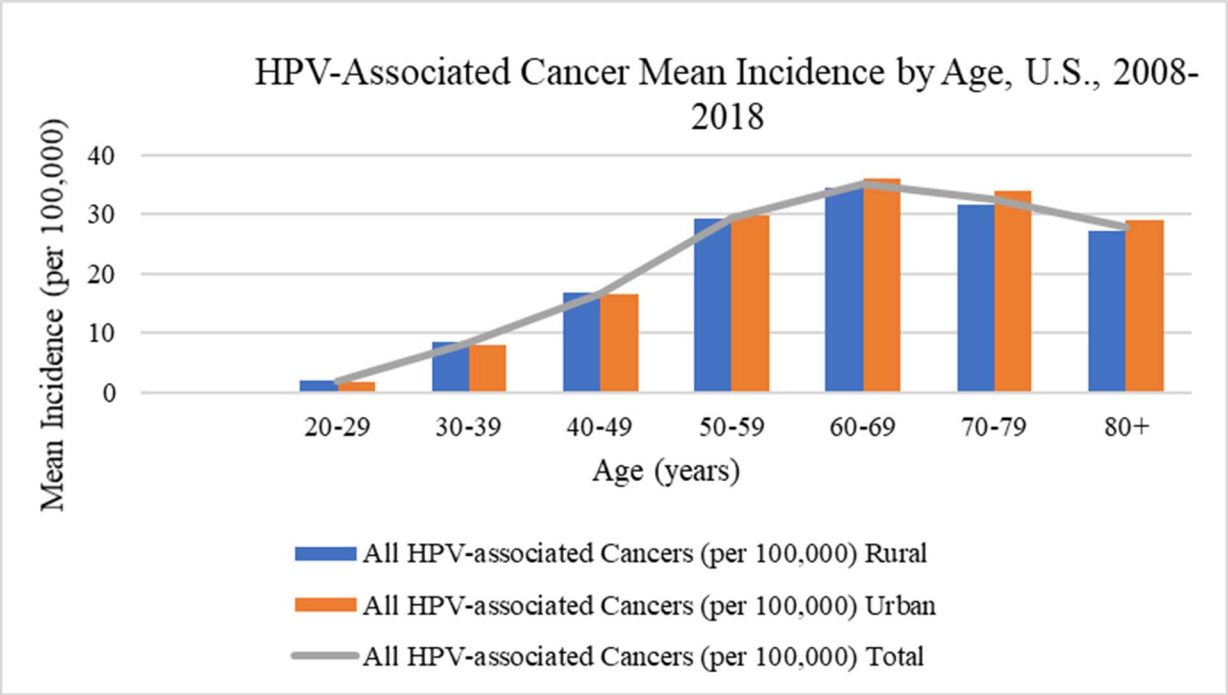

Figure 4.4. *HPV-Associated Cancer Mean Incidence by Age, U.S., 2008-2018*

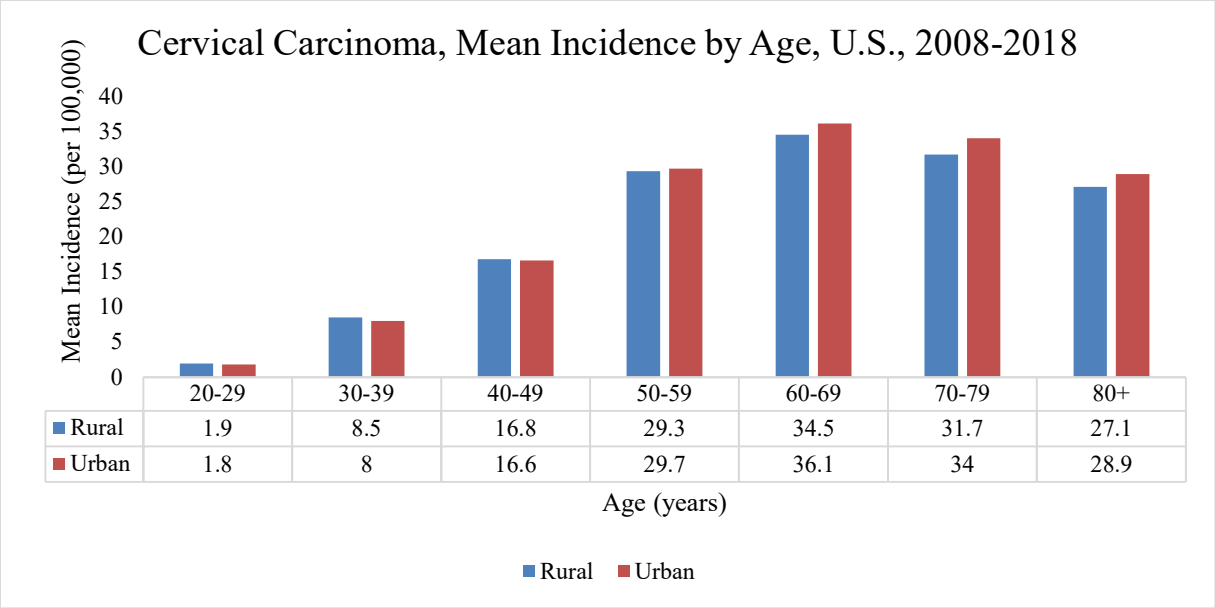

Figure 4.5. *Cervical Carcinoma Mean Incidence by Age, U.S., 2008-2018*

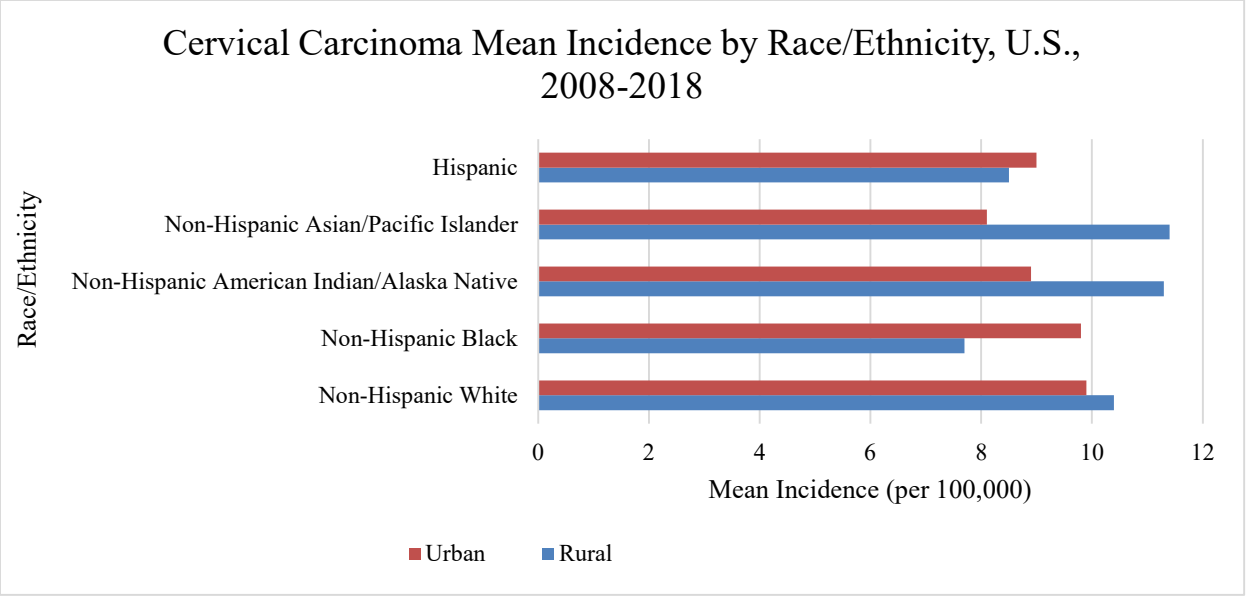

Figure 4.6. *Cervical Carcinoma, Mean Incidence by Race/Ethnicity, U.S., 2008-2018*

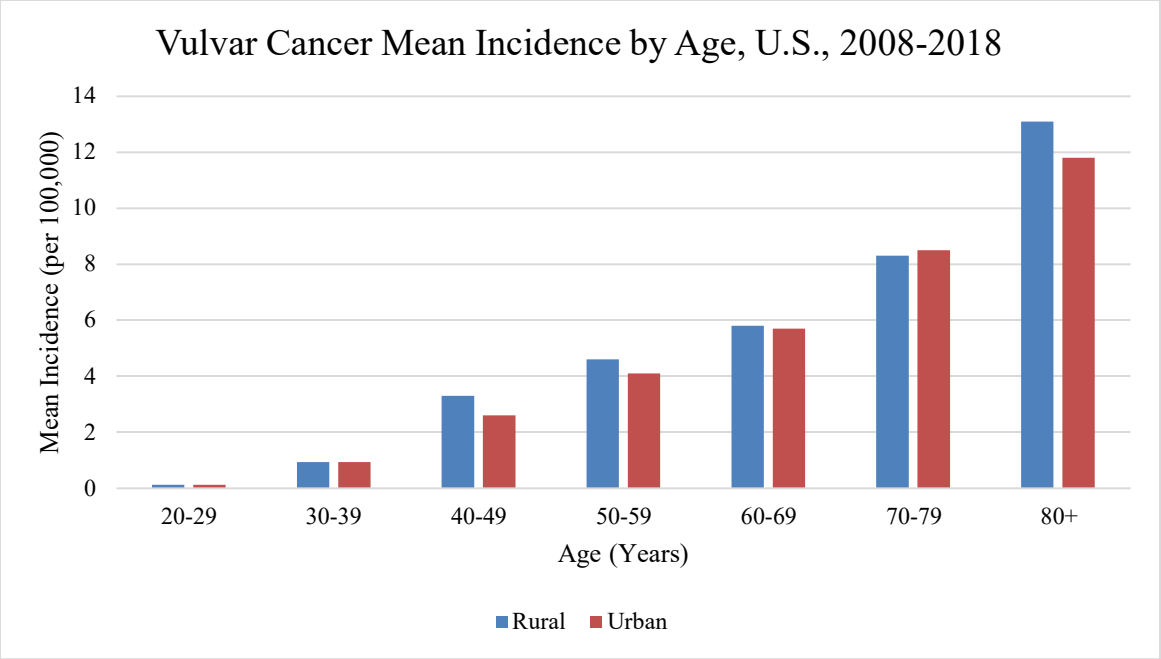

Figure 4.7. *Vulvar Cancer Mean Incidence by Age, U.S., 2008-2018*

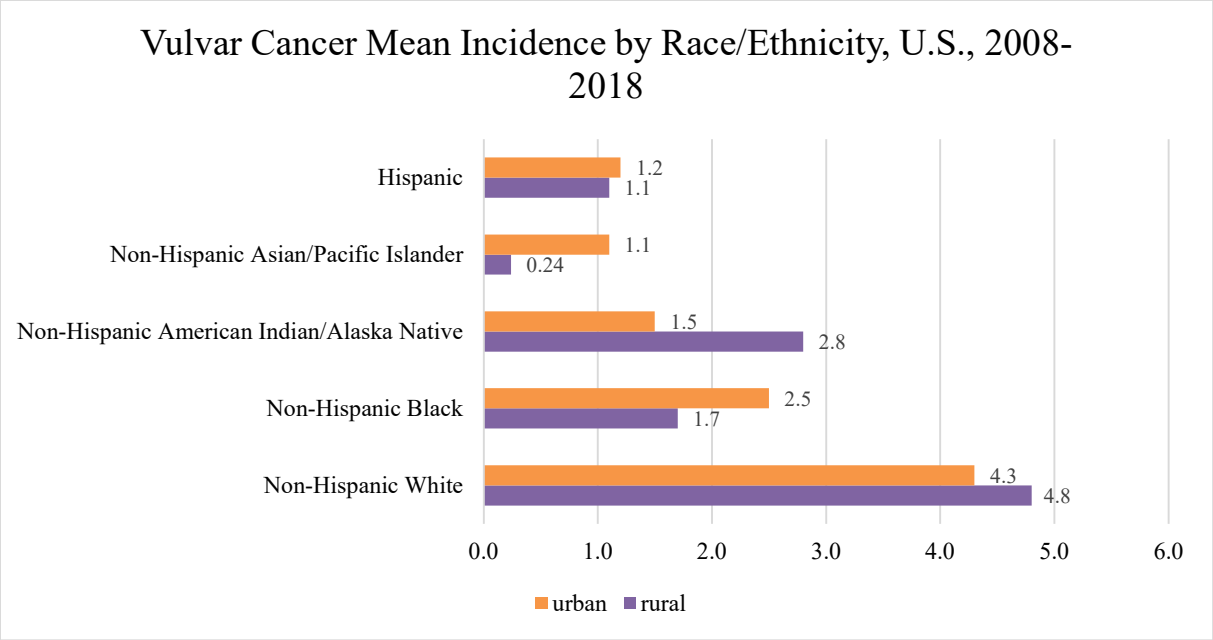

Figure 4.8. *Vulvar Cancer Mean Incidence by Race/Ethnicity, U.S., 2008-2018*

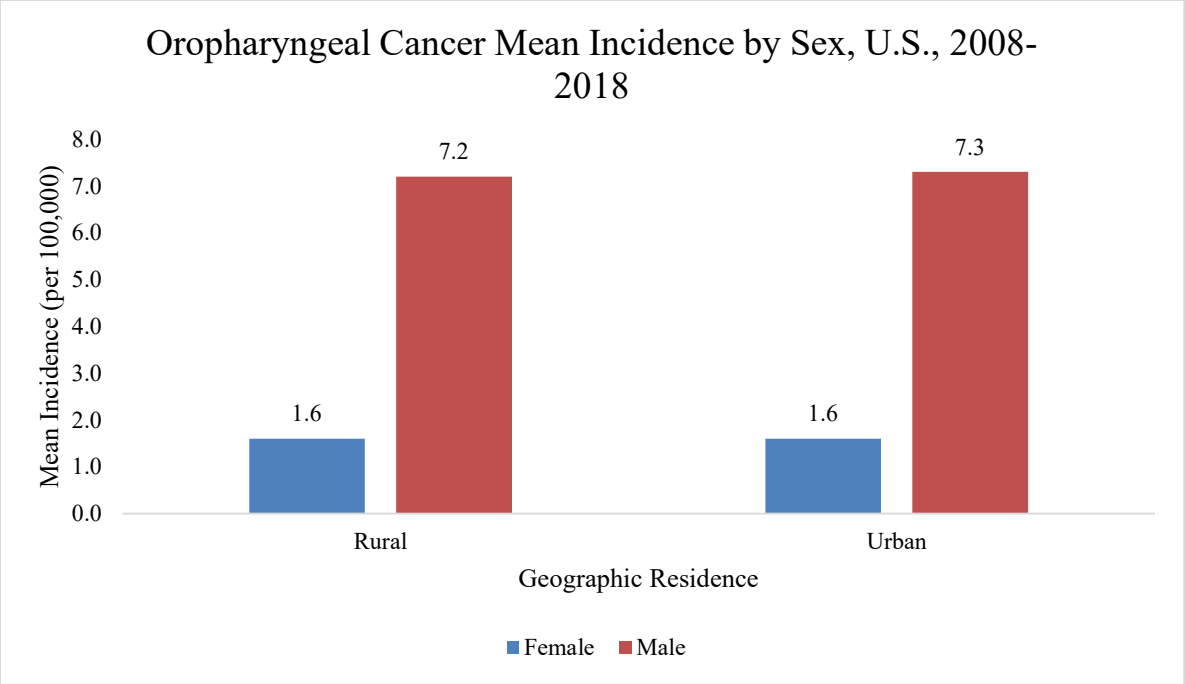

Figure 4.9. *Oropharyngeal Cancer Mean Incidence by Sex, U.S., 2008-2018*

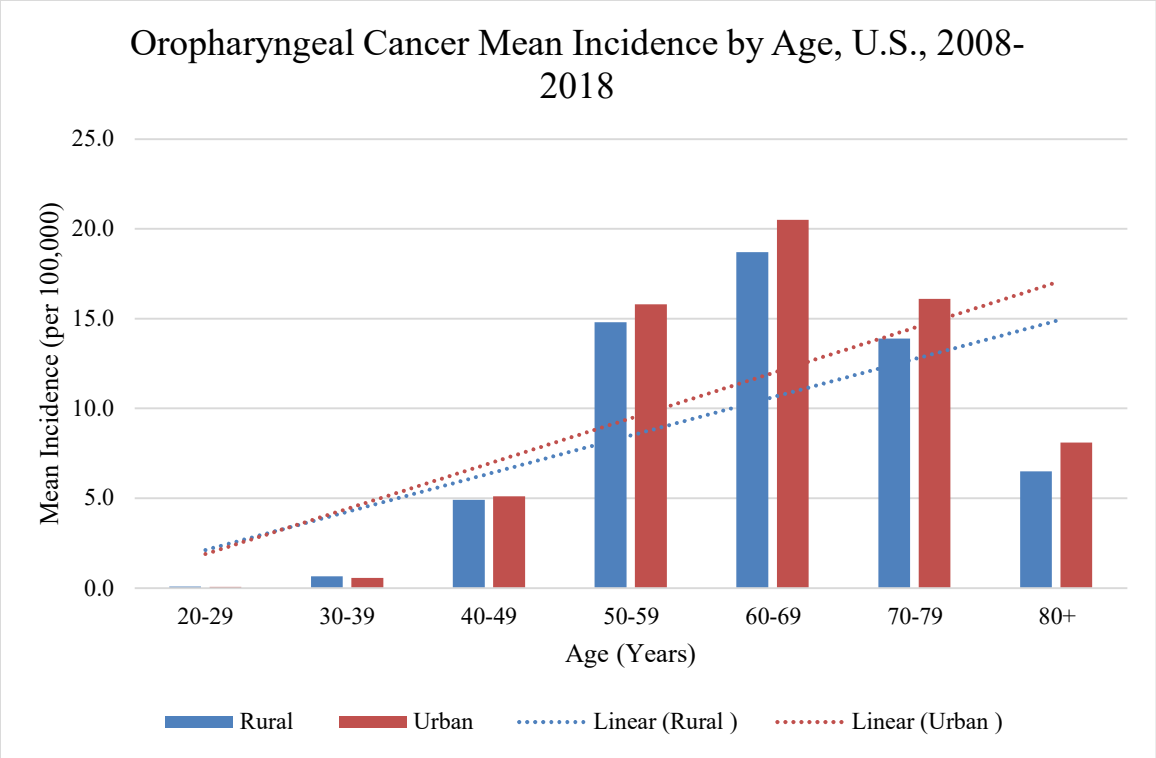

Figure 4.10. *Oropharyngeal Cancer Mean Incidence by Age, U.S., 2008-2018*

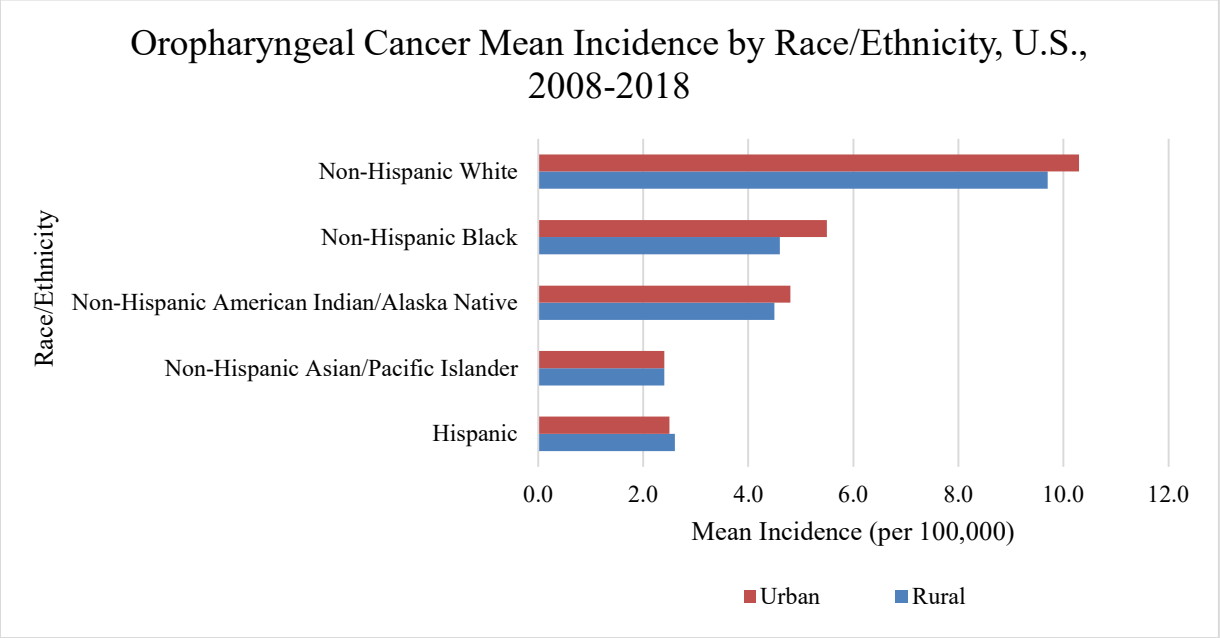

Figure 4.11. *Oropharyngeal Cancer Mean Incidence by Race/Ethnicity, U.S., 2008-2018*

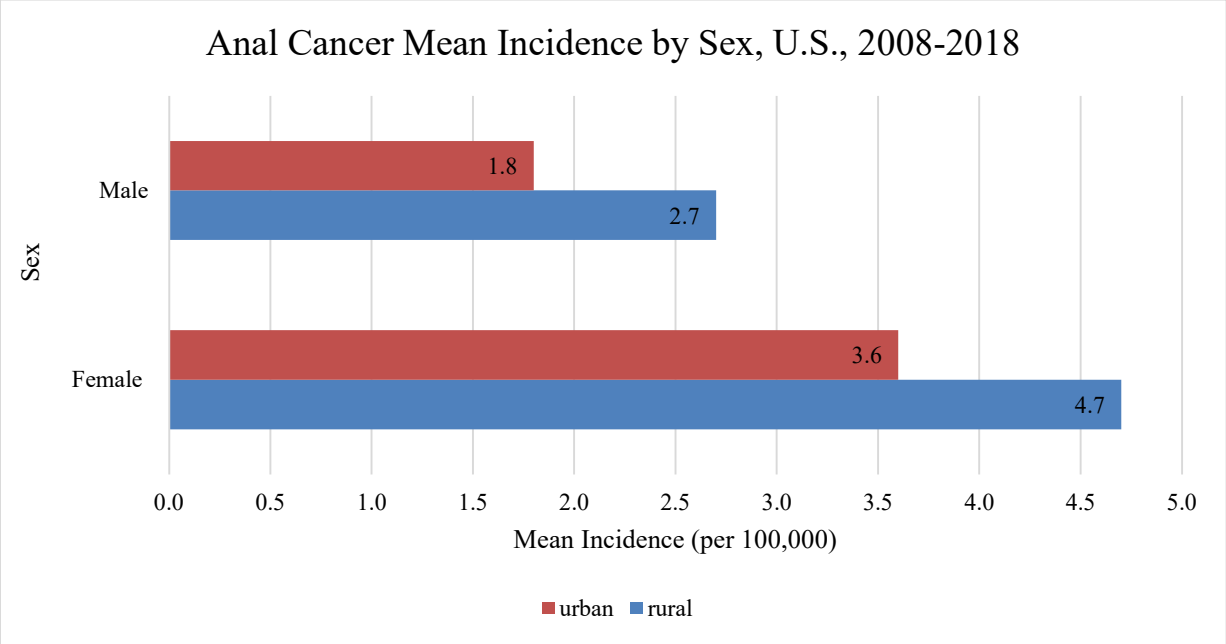

Figure 4.12. *Anal Cancer Mean Incidence by Sex, U.S., 2008-2018*

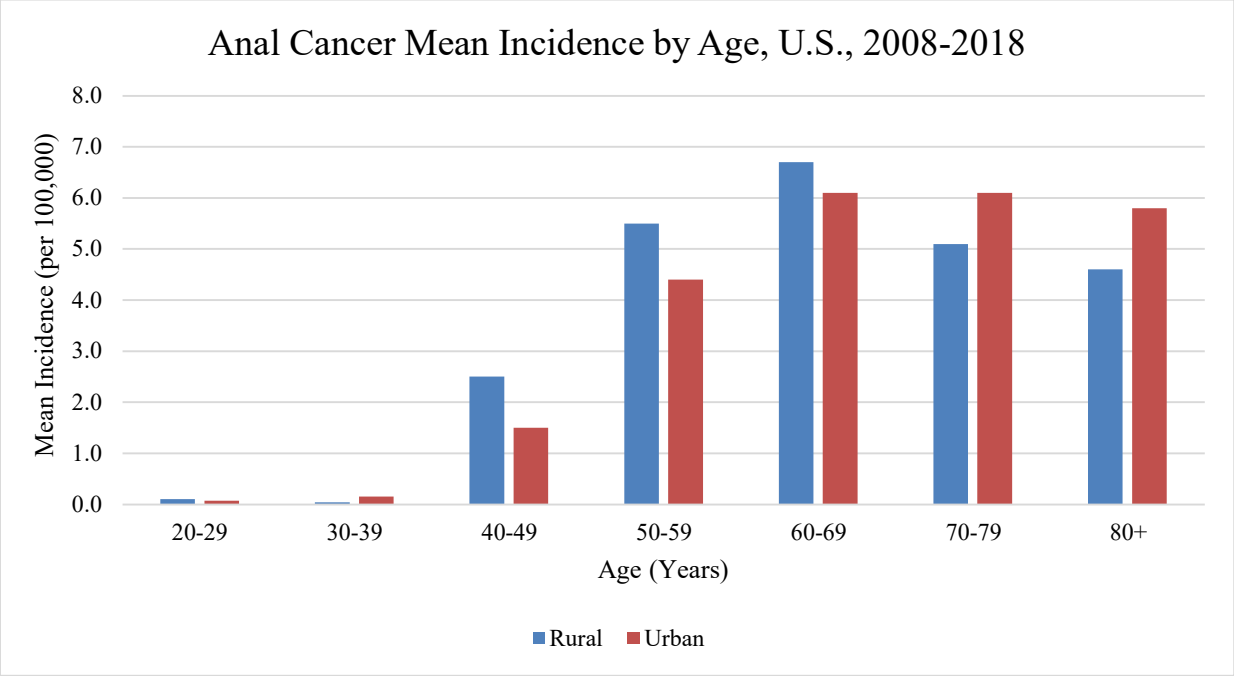

Figure 4.13. *Anal Cancer Mean Incidence by Age, U.S., 2008-2018*

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CHAPTER 5

DISCUSSION, PUBLIC HEALTH IMPLICATIONS, CONCLUSION, AND RECOMMENDATIONS

Discussion

This study utilized a convergent, parallel mixed methods design to answer three research questions and test three hypotheses (Table 1.1). The project's overall purpose was to better understand the impact of rurality on HPV-associated cancers among women and men and the impact of state immunization policies on adolescent HPV vaccine uptake. The project study aims entailed: (1) determining the association between geographic status (rural vs. urban) and HPV-associated cancer incidence among U.S. women and men aged 20 years and older; (2) exploring the policy environment, process, and stakeholder involvement in states that passed HPV vaccine legislation as part of immunization policy; and (3) assessing HPV and cancer risk knowledge, attitudes, beliefs, and perceptions among state stakeholders and how this may impact rejection or passage of HPV vaccine legislation. Based on the quantitative study findings, which analyzed 2008-2018 NPCR/SEER data and community-level healthcare access and SES data, rural residence among women and men aged 20 years and older was only associated with a higher incidence of vulvar and penile cancer, respectively, after adjusting for age, sex, race/ethnicity, and economic status.

While prior studies examined geographic residence and cervical or HPV-associated cancer incidence using NPCR/SEER cancer registry data, these studies accounted for age, sex, and race/ethnicity without adjustment for economic status (Henley et al., 2017; Yu et al., 2019; Zahnd et al., 2019). Current findings validate prior cancer registry study results that examined the relationship between HPV-associated cancers and geographic residence with and without adjustment for poverty (Benard et al., 2008; Reiter et al., 2012; Zahnd et al., 2019). However, our findings are counter to results shared by Zahnd et al. (2018a; 2019), which found higher incidence rates of overall HPV-associated, cervical, vaginal, and anal cancer among rural women, and higher rates of oropharyngeal cancer among rural men. Past studies have found an association between poverty and higher HPV-associated cancer incidence (Benard et al., 2008; Boscoe et al., 2016; Boscoe et al., 2014; Zahnd et al, 2018a).

This was also a significant finding from our study. Multivariate regression analyses demonstrated that decreasing economic status was independently associated with increased all HPV-associated, cervical, vulvar, oropharyngeal, and anal cancer after adjusting for age, sex, race/ethnicity, and geographic residence. Benard et al. (2008) examined HPV-associated cancer incidence and education, income, and poverty status at the county level and found an association between decreased household income and higher incidence of male oral cavity and oropharyngeal cancers and cervical cancers after adjusting for age, sex, and race/ethnicity. The same study concluded that increased vaginal, cervical, female anal cancer, and male oropharyngeal and oral cavity cancer incidence was associated with higher levels of poverty.

These findings further support the substantive roles low educational attainment, poverty, lack of employment, and lower income play in elevating county-level HPV-associated cancer incidence rates. Future studies should examine the intersection of these social determinants of

health with healthcare access, rurality, sex, race, and ethnicity, which may compound HPV infection and associated cancer risk in some geographic areas where state HPV vaccination coverage remains low (Zahnd et al., 2021). Additionally, we examined whether there was a relationship between lack of healthcare access and increased HPV-associated cancer incidence by including county-level primary care physicians (PCP) rate as a predictor variable. Our study uncovered an association between decreasing county PCP rate and elevated cervical cancer incidence after accounting for age, race/ethnicity, sex, and economic status.

Similarly, Campbell and colleagues (2003) examined the relationship between primary care physician supply and cervical cancer incidence and mortality rates in Florida using state cancer registry and American Medical Association (AMA) Physician Masterfile data and found an association between increased primary care physicians rate and lower cervical cancer incidence and mortality at county level after adjusting for median household income, education, marital status, white race, and urban/non-urban residence. Campbell's study focused on one state, used 1993-1995 cancer incidence data, examined cervical cancer only, did not account for all races and ethnicities, and focused on percent of the population having less than a high school education and median household income to assess county level SES. In contrast, our study incorporated a more representative (96% of states) and current (2008-2018) cancer incidence data set, focused on all HPV-associated cancers, explored percent some college and percent uninsured to understand the roles of education level and insurance status, and included five race/ethnicity categories. In prior studies, higher physician (primary and specialized care) density has been associated with earlier detection and lower incidence of screening amenable cancers (Adams et al., 2015; Ananthakrishnan et al., 2010; Daley et al, 2011; Ferrante et al, 2000; Nguyen et al., 2018).

To our knowledge, our study is the first to examine the relationship between PCP rate, rurality, and all HPV-associated cancers. In the U.S., some HPV-associated cancers disproportionately impact persons who are Black, Indigenous, or People of Color (BIPOC) (Hirth, 2019; Jemal et al., 2013; Megwalu and Ma, 2017; Melkonian et al., 2020; Yoo et al., 2017). We found racial/ethnic differences in HPV-associated cancer, as Non-Hispanic Whites (NHWs) and Non-Hispanic Blacks (NHBs) had 84% and 75% higher rates of HPV-associated cancer after adjusting for confounders. CDC United States Cancer Statistics (2021) notes that HPV-associated cancer incidence was highest among White, Black, Non-Hispanic, and Hispanic females and males from 2014 through 2018 ranging from 14.4-13.2/100,000 among females and 11.8-6.9/100,000 among males. Unlike our study, this analysis did not adjust for community-level confounders and categorized race and ethnicity separately to calculate incidence.

Based on our multivariate regression analysis**,** NHB had 73% higher cervical cancer incidence after adjusting for age, sex, geographic residence, PCP rate, and economic status. Although cervical cancer incidence rates steadily declined over the last 40 years among most racial and ethnic groups due to the development of the Pap test and availability of other cervical cancer screening modalities (e.g., HPV DNA test), NHB women experience lower 5-year relative cervical cancer survival rates at every stage when compared with NHW women (localized: 87% vs. 92%; regional: 49% vs. 57%; distant: 11% vs. 19%) (Collins et al., 2014; Siegel et al., 2020). del Carmen and colleagues (1999) examined 1990-1995 NCI SEER data from 11 cancer registries and found that NHB women continued to experience sub-optimal cervical cancer health outcomes (19% higher mortality risk) even after adjusting for age, stage, initial treatment type, and histology when compared with NHW females.

Our study concluded that vulvar cancer was highest among NHWs followed by NHBs, which is consistent with a vulvar cancer incidence study conducted by Liao and colleagues that examined 2001-2017 NPCR/SEER registry data (2021). Lastly, oropharyngeal cancers were highest among NHBs followed by NHWs after adjusting for age, sex, geographic residence, PCP rate, and economic status. Interestingly, Lenze and colleagues (2019) conducted a systematic review of racial disparities and HPV status in oropharyngeal cancer and concluded that the cancer survival disparity among NHB and NHW patients was not statistically significant after adjusting for HPV status. However, inclusion of additional population-based studies in future meta-analyses and systematic reviews may validate their study findings, as the study team's meta-analysis only included five studies.

The implementation of culturally tailored and population-based cancer prevention and early detection interventions focused on improving adolescent HPV vaccine uptake and increasing cervical cancer screening may begin to address some of the racial and ethnic cancer disparities in communities that experience the greatest HPV-associated cancer burden (Benard et al., 2007; Benard et al., 2008; Zahnd et al., 2018a; Zahnd et al., 2019). This can be accomplished by making state or territorial policy revisions that promote equitable access to health insurance, HPV vaccination, and primary care. Cancer registries do not collect behavioral data which is critical to understanding the root causes of low HPV vaccine uptake, high risk sexual activity (unprotected oral, anal, and vaginal sex, multiple sex partners), low cancer screening, and delays in seeking care. Collecting and acquiring behavioral data using a mixed-methods, community-based participatory approach may help identify the structural drivers of poor health outcomes.

This data may be leveraged to revise public health policies and fund culturally appropriate, tailored, and sustainable evidence-based public health interventions aimed at

reducing health inequities at interpersonal, community, and structural levels. Qualitative study results identified barriers and facilitators to HPV vaccine uptake and policy introduction at individual, interpersonal, community, and structural social ecological levels in five, geographic and culturally diverse states. Qualitative in-depth interviews explored the policy environment, process, and RI and HI stakeholder involvement in passing HPV vaccine school mandate legislation as part of immunization policy. Additionally, I assessed HPV and cancer risk knowledge, attitudes, beliefs, and perceptions among state stakeholders and how this may impact rejection or passage of HPV vaccine legislation.

This study provides valuable insight into the role of state vaccine policy in increasing adolescent HPV vaccine uptake from stakeholders embedded in different policy environments. In-depth interview results underscore the critical roles of the healthcare professional, parent, and state in adolescent HPV vaccine initiation and completion and how each of their shared responsibilities as vaccine advocate, educator, and champion can be utilized to improve vaccine coverage. By treating HPV vaccine like Tdap, meningococcal, or other routine adolescent vaccines, their collective agency, operating at interpersonal, community, and structural social ecological model (SEM) levels, enables the normalization of HPV vaccine. Clear and consistent communication between the health care professional and parent about the risks and benefits of HPV vaccine and a strong provider recommendation reinforces the healthcare professional as vaccine advocate, educator, and champion, and empowers the parent to make an informed decision about adolescent immunization against HPV (Gilkey et al., 2015; Gilkey and McRee, 2016; Malo et al., 2016).

Parent, healthcare professional, and state roles can be leveraged through community engagement, partnerships, and collaborations between stakeholder organizations to increase

adolescent HPV vaccine uptake in rural communities across the U.S. Their inclusion on cancer and immunization coalitions, advisory groups, and during policy development is essential to implementing effective HPV vaccine policy and non-policy strategies. The state plays a critical role in adolescent HPV vaccine uptake as educator, advocate, and champion by managing immunization information systems, increasing access to HPV vaccine through policies, and disseminating HPV vaccine education and awareness campaigns. While parents and healthcare professionals represent decision makers at the interpersonal level, the state serves as the decision maker at the community and structural levels, which yields the greatest public health impact.

Stakeholders identified a strong provider recommendation, healthcare professional training, community-based health education and promotion, stakeholder support, and structural strategies such as vaccine mandates for school entry and adolescent vaccination in pharmacy settings as the main facilitators to HPV vaccine uptake. These results mirror findings from previous studies that examined facilitators and barriers to HPV vaccine uptake from different stakeholder perspectives including nurses, physicians, health department staff, and advocacy groups. Moreover, stakeholders discussed a lack of HPV knowledge, lack of strong provider recommendation, parental hesitancy, vaccine misinformation and mistrust, anti-vaccine groups, lack of school requirement, and less frequent adolescent healthcare visits as major barriers to HPV vaccine uptake, which validate prior study findings (Cartmell et al., 2018; Carhart et al., 2018; Holman et al., 2014; Mansfield et al., 2021; Newcomer et al., 2020). Study participants described the COVID-19 pandemic as a deterrent to routine adolescent immunization (individual, interpersonal, community, and structural levels), as COVID-19 overwhelmed most health systems and Departments of Health, which focused on testing, treatment, or vaccination rollout to diagnose, manage, or prevent COVID-19 infection for over two years.

Delays in vaccination may leave some adolescents unvaccinated or partially vaccinated due to a missed opportunity to acquire their subsequent vaccine dose(s) on time. This decline in state HPV vaccine coverage has long-term consequences for cancer and STI prevention and incidence (Gilkey et al., 2020). Furthermore, COVID-19 vaccine hesitancy and anti-vaccine sentiment may negatively impact the uptake of routine adolescent vaccinations, (e.g., Tdap and meningococcal conjugate vaccine) which may lead to future statewide outbreaks of these vaccine preventable diseases. Adolescent vaccine bundling represents a practical public health strategy to ensure optimal levels of vaccine coverage for all recommended adolescent vaccines post-COVID-19 (Farmar et al., 2016; Pingali et al., 2021).

Policy stakeholders shared that COVID-19 vaccine implementation may cause further vaccine mistrust among some parents while also presenting an opportunity for health care professionals and vaccine advocates to promote resumption of routine adolescent immunization. A recent study of clinics implementing the Vaccines for Children program found that increases in telehealth visits, patient fear of acquiring COVID-19, and an understaffed and overburdened healthcare workforce negatively impacted HPV vaccination rates in a rural state (Ryan et al., 2022). Stakeholders told us that HPV vaccine was not a priority for healthcare professionals or parents because of the focus on staying home, COVID-19 testing and vaccination, and staff reassignments to COVID-19 response. States, healthcare professionals, and parents have an obligation to reinvest in promoting adolescent HPV vaccination to prevent future HPV-associated pre-cancers and cancers.

To increase vaccination rates, a potential solution is to begin the HPV vaccination series at age 9, which is the recommended age based on the American Cancer Society HPV

Vaccination Guidelines (Saslow et al., 2020). A 2016 population-based cohort study concluded that on-time completion of the HPV vaccine series (2-3 doses) between the ages of 13 to 15 years was significantly associated with an adolescent receiving the first dose by age 9 or 10 as opposed to initiating HPV vaccine at age 11 or 12. Researchers adjusted for insurance status, sex, race, year the first dose was received, and frequent healthcare visits (St. Sauver et al., 2016). Immunizing adolescents earlier may result in less missed opportunities, less need for multiple vaccines in one visit, and allows for adolescents to receive their vaccine doses prior to the onset of puberty.

Furthermore, a Swedish study of more than 1.6 million females who were followed over 11 years found that females vaccinated against HPV before age 17 had a significantly lower risk of acquiring cervical cancer by age 31 after adjusting for confounding variables (Lei et al., 2020). While prior studies examined facilitators and barriers to HPV vaccine uptake from a stakeholder standpoint, very few have explored stakeholder perspectives in multiple states and included HPV vaccine policy introduction. A multi-state qualitative study explored stakeholder perspectives about the politics behind HPV vaccine policy formation and found that supporters who invested substantial time and resources to promote or oppose state HPV vaccine legislation (policy entrepreneurs) played a significant role in influencing which public health policies were prioritized for consideration and approval (Abiola et al., 2013). Our study found that focusing on cancer prevention when explaining or introducing HPV vaccine policy (community and structural levels), incorporating vaccine champions in the policy creation, introduction, and approval process (community and structural levels), and revising an existing policy or regulation (structural) represented facilitators to HPV vaccine policy introduction at the state level.

Stakeholders discussed the importance of strong community involvement such as engagement of cancer or immunization coalitions, advocacy groups, or advisory committees as an additional community level facilitator. Stakeholders cited a lengthy review and approval process, a lack of policy opportunity (structural level), and opposition from anti-vaccine groups (community level) as barriers to policy introduction. Nonetheless, Rhode Island and Hawaii successfully passed rules and regulations mandating HPV vaccine for 7th grade school entry through the Department of Health and both revised existing rules and regulations instead of creating a new policy and submitting it to the Legislature. Both states had strong community involvement and backing from vaccine workgroups, advisory committees, and cancer and immunization coalitions. Members of these community groups served as advocates and subject matter experts who provided testimony, reviewed policy language, researched immunization policy in other states, or took the lead in introducing regulatory changes to existing immunization policy.

The RI and HI Department of Health spearheaded and managed policy change efforts until regulation approval and played a significant role in rollout and enforcement of new school immunization policies. States who are considering passing HPV vaccine policy may benefit from speaking with states implementing regulations, as this provides an invaluable opportunity to learn about feasible policy models and implementation successes and challenges. Stakeholders ranked reporting of vaccine doses into immunization information systems and vaccine bundling (providing more than one age-recommended vaccine in a single clinic visit) as required policy components while they identified school mandates and policies that improve vaccine access as high priority.

Quantitative Study Limitations

Our quantitative study had several limitations worth noting. Since the study design was ecological, this limited our ability to establish causality. Study results may be subject to ecologic fallacy, as the associations we found related to HPV-associated cancers at the county level may not necessarily reflect associations at the individual level for all HPV-associated and the six site-specific cancers (Greenland and Robins, 1994). Moreover, as part of routine cancer surveillance, state and territorial registries record and submit cancer cases, not individuals.

The same individual may appear multiple times in a cancer registry, if they are diagnosed with multiple primary cancers (Izquierdo and Schoenbach, 2000). Nonetheless, cancer registries conduct several quality assurance and quality control activities, which consist of data quality audits, case consolidation, follow-back to hospitals, facilities, and labs, and manual data review, which may reduce the likelihood of duplicate case reporting. Since NPCR/SEER captures HPV-associated cancer cases reported by hospitals, facilities, and labs, our data set was missing unreported, undiagnosed HPV-associated cancers among women and men, especially among individuals lacking access to routine healthcare. However, there is a high likelihood that every chronic and infectious disease surveillance system is missing a small percentage of undiagnosed cases of disease.

Furthermore, the primary outcome of incidence rates is based on data derived from state and territorial cancer registries that use population estimates in the denominator, and these estimates may be incomplete, imprecise, and result in under- or overestimation of populations (Boscoe and Miller, 2004).

However, state cancer incidence data collected by registries and submitted to NPCR and SEER represent some of the most complete, high quality surveillance data available in the U.S. Our study dataset included a decade of data representing about 98% of the U.S. population and 96% of states. The cross-sectional study design did not allow researchers to conduct a longitudinal cancer study, which follows individuals over 20-30 years to assess the impact of disease. Additionally, this study design does not allow researchers to establish causality or pinpoint the sequence in which events or exposures take place (Fos et al.,2018).

However, it would be quite expensive to prospectively follow people for 25 years to assess cancer outcomes. Since several cancers take approximately 10-15 years to develop, a shorter timeframe using the cross-sectional design is more practical and economically feasible for public health studies used to inform programs and state policies, and to target resources. The cross-sectional design and data source does not permit researchers to account for variability in residential status since the rural or urban assignment is based on where an individual lives at the time of diagnosis. Additionally, HPV-associated cancers may be underestimated due to delays in cancer data reporting or inaccuracies in the data.

Yet, both CDC NPCR and NCI SEER use 24-month data to account for delays and to ensure completeness and quality of cancer surveillance data, so underestimating HPV-associated cancer cases seems unlikely. The data does not allow for examination of confounders such as HPV vaccine uptake or cervical cancer screening because these variables are not included in the NPCR/SEER cancer data set. We were unable to ascertain the association between rural-urban residence and cancer stage at diagnosis for HPV-associated cancers, which is critical for examining disease severity and health outcomes by geography. Future studies should examine HPV-associated and site-specific cancer stage at diagnosis by geographic residence, insurance

status, economic status, and healthcare access to identify any racial/ethnic, age-specific, and geographic disparities, especially for oropharyngeal, vulvar, and anal cancers, which are on the rise.

Additionally, penile and vaginal cancer results were based on a small number of cases over the study timeframe, so findings should be interpreted with caution. Our community-level variables also posed limitations. The median age variable reflected one year within the study timeframe (2017) instead of the entire study period (2008-2018), which limited us from examining age for each reported HPV-associated cancer comprehensively. Moreover, the percent some college variable only accounted for a portion of our study population (25-44-year-olds) instead of all males and females 20 years and older.

Additionally, the percent uninsured variable did not include data for individuals aged 65 years and older. Lastly, we used primary care physicians rate to assess healthcare access, which does not include the number of nurses, nurse practitioners, or physician assistants practicing within each county. Future studies should utilize a comprehensive variable that includes several healthcare professions because this will provide a more accurate measure of true healthcare access (e.g., primary healthcare professionals per 100,000 population by county). Despite these limitations, to our knowledge, this is the first study to consider the roles of PCP rate, lack of insurance, economic status (using a composite variable), and some college education in examining the relationship between geographic residence and HPV-associated (All HPV-associated, cervical, vaginal, vulvar, penile, oropharyngeal, and anal cancer) cancer incidence.

Qualitative Study Limitations

The qualitative study component has several limitations. Each state did not have the same number of study participants (range: 2-4) interviewed, so findings may not reflect all

participating states equally. Additionally, stakeholder in-depth interview results represented viewpoints from five states, so results are not transferable to other settings in the U.S. Furthermore, all stakeholders interviewed were vaccine proponents, so we were unable to capture viewpoints from HPV vaccine opponents. Lastly, study results may not represent stakeholder perspectives from health insurance companies, schools, federally qualified health centers, or anti-vaccine groups, as recruitment targeted public health professionals and clinicians representing Departments of Health, academic institutions, and a national cancer advocacy organization.

Public Health Implications

HPV-associated cancer incidence study results may inform state comprehensive cancer control plan, cancer, and immunization program priorities funded through state and federal resources. Public health leaders, policymakers, healthcare professionals, and researchers may use study findings to develop tailored, culturally appropriate, and acceptable public health and clinical interventions (e.g., health education, cancer screening, HPV vaccination). Future research should include studies aimed at exploring effective and sustainable methods for collecting behavioral data (e.g., sexual patterns, practices, norms, history of sexual abuse, cancer screening, substance use, and mental health), as no surveillance system routinely collects this critical information. Data linkage with HPV immunization and cervical cancer screening surveillance systems may provide a complete picture of the association between risk factors and cancer outcomes among rural women.

Future research should examine the relationships between behavior, culture, geography, and increased risk for cervical, vulvar, oropharyngeal, and anal cancer. Currently, cervical cancer is the only HPV-associated cancer that has a standard screening protocol for the detection of pre-

cancer and cancer (USPSTF, 2018). Quantitative **s**tudy findings may inform community-level interventions aimed at improving access and acceptance of HPV-associated cancer screening for cervical, vulvar, anal, and oropharyngeal cancers through partnerships between public health departments, healthcare systems, and primary care professionals. A first step may entail conducting pilot anal, vulvar, and oropharyngeal cancer screening studies to assess feasibility, potential modalities, and screening frequency in populations at increased risk for HPV-associated infection and cancer.

Standardizing and normalizing screening practices for vulvar, anal and oropharyngeal cancer is imperative for primary healthcare professionals to detect these HPV-associated cancers as early as possible. Since HPV is the most common sexually transmitted infection, pilot studies that assess the feasibility of vulvar, oropharyngeal, and anal cancer screening in varied settings (e.g., community-based clinic settings, teaching hospitals, home-based self-testing with healthcare professional virtual consultation prior to testing) may facilitate early detection of these pre-cancers and cancers. Since our findings describe the HPV-associated disease burden, states and territories can utilize these results to design multi-faceted HPV-associated cancer prevention interventions aimed at increasing adolescent HPV vaccine coverage in rural areas through schools, community centers, pharmacies, and mobile clinics.

Additional behavioral studies are warranted to examine the root causes of sexual risk behavior, poor access to health care, and vaccine and cancer screening hesitancy in rural and urban populations.

Imminent research should examine policy and non-policy strategies that increase adolescent HPV vaccine uptake such as adolescent vaccine bundling, community engagement, temporary school-based vaccine clinics, facility reminder/recall systems, or the use of

community health workers and physicians as HPV vaccine advocates and communicators of accurate vaccine information to parents. This is especially important due to significant declines in routine adolescent vaccinations over the last two years because of the COVID-19 pandemic (Pingali et al., 2021). Some of the prior or existing COVID-19 immunization infrastructure in communities may help inform novel approaches to augmenting adolescent HPV vaccine coverage, so that adolescents can catch up on missed vaccine doses that may prevent them from acquiring HPV-associated cancer later in life. Additionally, since Hawaii is the latest state to successfully implement a school vaccine mandate for 7th grade entry (2020), a future study should focus on using a Difference-in-Differences method to examine National Immunization Survey-Teen HPV vaccine coverage data before (2017) and after (2023) immunization policy implementation to assess policy impact using two states exhibiting similar vaccine coverage rates as comparisons in the model.

Conclusion

Quantitative study results validate the important roles rurality (for penile and vulvar cancer), sex, race/ethnicity, PCP rate, and economic status play in elevating HPV-associated cancer incidence among men and women. These factors represent proxies for larger, systemic issues such as gender discrimination, including discrimination based on sexual orientation, intergenerational poverty, and structural racism. These systemic barriers may include incarceration, residential segregation, lack of effective public health policies focused on improving social determinants of health, and lack of opportunities for economic advancement in financially depressed communities within rural and urban areas (Bailey et al., 2017; Bailey et al., 2021). The collection, availability, and use of behavioral data that sheds light on sexual practices, patterns, and norms as well as cancer screening, HPV vaccination, and healthcare access and

utilization may help inform evidence-based interventions aimed at preventing HPV-associated cancer and detecting these cancers as early as possible.

Examining the intersectionality of individual, interpersonal, and structural risk factors for acquiring HPV infection and associated cancer may help identify feasible and sustainable public health strategies for preventing, detecting, and eventually eliminating these cancers among women and men. Qualitative study results offer critical insight into the role of HPV vaccine policy in improving adolescent vaccine uptake from several stakeholder points of view. Moreover, some of the stakeholders we interviewed actively participated in the immunization policy change process by providing testimony, drafting policy revisions, or engaging in early policy discussions and advocacy efforts to propose changes. Future research could entail the use of focus group discussions and inclusion of state policymakers from the Legislature because they may have interesting and potentially opposing viewpoints about introducing and approving HPV vaccine policy within their respective state.

Additionally, utilizing a focus group discussion method may glean more detailed information and provide a greater level of understanding about the state policy process since responses build upon one another and gaps in details are filled in as the discussion unfolds. Future studies could also examine stakeholder perspectives from other geographic areas within the U.S. and focus on a combination of states with high (75% and higher), medium (60-74%), and low (59% or less) HPV vaccine coverage rates using 80% HPV vaccine coverage as the reference point for success.

Recommendations

Mixed methods study findings generated the following public health recommendations for federal government, states, healthcare professionals, health departments, medical schools, policymakers, and parents.

1. State: policymakers and health departments: Collaborate with the state comprehensive cancer control and immunization coalitions, advocacy groups, health insurance plans, and the American Cancer Society HPV Vaccine Roundtable to improve state HPV vaccination rates, especially in rural areas.

- Review existing state immunization policies and assess the feasibility of revising policy to increase equitable access to healthcare and HPV vaccine. Consider proposing policies such as adolescent vaccination without parental consent, vaccine mandates for school entry, and universal purchase.
- Aim to increase adolescent HPV vaccine coverage to 85 percent by 2025.
- Ensure that adolescent HPV vaccine goals, objectives, and targets are embedded in state cancer control, chronic disease prevention, and immunization program plans.

2. State: policymakers and health departments; healthcare professionals, parents: Promote and support the initiation of the HPV vaccine series at age 9 years.

- If an existing immunization policy does not allow for HPV vaccination prior to age 11 years, support pilot projects to implement early vaccine initiation (ages 9-10 years) in school-based, pharmacy, clinical, and community settings.
- Consider revising state policy to include HPV vaccination beginning at age 9 years.

3. Federal, state: health departments; healthcare professionals, researchers: Facilitate the collection of behavioral data (sexual patterns, partnering, practices, and norms that increase HPV

infection risk; history of sexual abuse; healthcare use and access; insurance status; substance use; and mental health) by creating multi-year funding opportunities that promote community-based participatory research and collaborations across cancer prevention and control partners.

- Behavioral data can be used in conjunction with cancer surveillance, immunization, and cancer screening data to tailor public health interventions aimed at preventing and detecting HPV-associated cancer.

4. Federal, state: health department; researchers: Create funding opportunities to explore the feasibility and sustainability of linking immunization registries with state and territorial cancer registries to understand the impact of HPV vaccine on HPV-associated cancer incidence.

5. Healthcare professionals, medical associations, medical schools: Standardize and normalize screening practices for vulvar, anal and oropharyngeal cancer in clinical settings to detect these HPV-associated cancers as early as possible.

- Create training for healthcare professionals and a required teaching module for nursing and medical students on screening strategies for HPV-associated anal, vulvar, and oropharyngeal cancer.

6. Federal, state: health departments: Create health education and awareness campaigns using social media and podcasts to educate the public about the different types of HPV-associated cancer that can be transmitted through unprotected vaginal, anal, and oral sex. Feature physicians, parents, policymakers, health department leaders, and advocates as vaccine champions.

- Create a health education module for middle and high school students about HPV infection, risk behaviors, and HPV-associated cancers to increase knowledge and awareness. Include a section about HPV vaccine as cancer prevention.

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CHAPTER 6

UNDERSTANDING THE CANCER BURDEN TO TARGET ADOLESCENT HPV VACCINE EFFORTS: IMMUNIZATION AS OUR BEST DEFENSE AGAINST HPV-ASSOCIATED CANCER

The intent of this mixed methods study was to better understand the impact of rurality on HPV-associated cancers among women and men and the impact of state immunization policies on adolescent HPV vaccine uptake. The project study aims were to: (1) determine the association between geographic status (rural vs. urban) and HPV-associated cancer incidence among U.S. women and men aged 20 years and older; (2) explore the policy environment, process, and stakeholder involvement in states that passed HPV vaccine legislation as part of immunization policy; and (3) assess HPV and cancer risk knowledge, attitudes, beliefs, and perceptions among state stakeholders and how this may impact rejection or passage of HPV vaccine legislation. I found that rural residence among women and men aged 20 years and older was associated with a higher incidence of vulvar and penile cancer (partially confirms hypothesis 1: Rural residence among women and men aged 20 years and older is associated with a higher incidence of HPV-associated cancers). Rurality was not associated with increased all HPV-associated, cervical, vaginal, oropharyngeal, and anal cancer incidence after adjusting for age, sex, race/ethnicity, and economic status.

Based on results from 13 state stakeholder in-depth interviews and a content analysis of state immunization policies in five states, it was clear that adopting HPV vaccine and related

public health policy that improved access to healthcare and vaccine increased adolescent vaccine uptake, which significantly reduces the risk of acquiring HPV-associated cancer in adulthood (confirms hypothesis 2). State (CA, GA, HI, MA, and RI) HPV vaccine policy sub-components included: HPV vaccine administration in pharmacy settings (all states); school vaccine mandates for 7th grade entry (HI and RI); adolescent HPV vaccination without parental consent (CA); implementation of immunization surveillance systems to collect immunization data for monitoring vaccine safety and uptake (all states); universal purchase (MA and RI), required sex education in schools (CA, GA, RI), and Medicaid expansion through the Affordable Care Act (CA, HI, MA, RI) (Table 3.4). Although states adopted different sub-components that supported HPV vaccine uptake, the common thread among all states was the focus on increasing access to HPV vaccine and healthcare.

Stakeholders were very aware of the link between HPV infection and cancer risk. Among some interview participants, this knowledge and awareness made them more likely to advocate for inclusion of state HPV immunization legislation (partially confirms hypothesis 3- HI, RI, and GA). Several respondents shared that immunization against HPV infection was the best defense against acquiring HPV-associated cancer. Improving adolescent HPV vaccine uptake statewide requires the implementation of targeted and culturally appropriate public health strategies at individual, interpersonal, community, and structural levels. Implementing local and state policies that increase vaccine and healthcare access will impart the most sustainable and effective impact in preventing HPV-associated cancer.

While manuscript one focused on preventing HPV-associated cancer by increasing uptake and implementing multi-component policies, manuscript two examined the current HPV-

associated cancer burden in the U.S. by age, sex, race/ethnicity, percent uninsured, primary care physicians (PCP) rate, and economic status using national cancer registry and publicly available, county-level data. The quantitative study component provided me with the opportunity to analyze complete, high-quality data to understand individual and structural level cervical, vulvar, vaginal, penile, oropharyngeal, and anal cancer disparities. Since sound public health and policy decision making begins with acquiring and analyzing the most current data, manuscript two created the foundation for identifying and recommending public health interventions based on the best available evidence. Routine analysis of HPV-associated cancer surveillance data will allow states and government agencies to monitor the cancer burden for each HPV-associated cancer and examine trends in cancer incidence and mortality.

Bi-annual data monitoring and analysis may help target cervical cancer screening programs where they are needed most. Additionally, results from data analyses may help secure funding and support for pilot studies that examine the feasibility of anal, oropharyngeal, and vulvar cancer screening in populations that may be at increased risk for acquiring HPV infection and subsequent cancer. Multi-phase behavioral studies that examine sexual practices, partnering, and norms may help inform these efforts. Quantitative study results reinforced the critical need to improve adolescent HPV vaccine coverage statewide, as analyses identified racial and ethnic, geographic, gender-based, healthcare access, and economic HPV-associated cancer disparities.

Utilizing a mixed methods design allowed qualitative study findings to inform recommendations generated from quantitative findings. State policy change is a powerful strategy to increase health equity and improve health outcomes among adults and adolescents. While few states approved policies that allow adolescents to receive HPV vaccine without parental consent, Colorado recently passed Senate Bill 21-016, which permits minors to seek

preventive care (including HPV vaccine) independently (CO General Assembly, 2021). States that are contemplating vaccine policy revisions may benefit from learning about the successes and obstacles experienced by states that recently proposed or passed vaccine policy sub-components.

Results from HPV vaccine efficacy and impact studies may be utilized to prioritize viable policy options in states striving to increase adolescent HPV vaccine completion rates. Rosenblum and colleagues (2022) analyzed National Health and Nutrition Examination Survey (NHANES) pre-vaccine (2003-2006) and vaccine (2007 onward) era data and concluded that compared with HPV prevalence before vaccine was available, by 2015 through 2018, quadrivalent HPV vaccine type (6, 11, 16, and 18) prevalence among 14-24-year-old females declined by 74%, 90% and 85%, respectively in the female unvaccinated study group, among the vaccinated female group, and among sexually experienced female survey participants. The potential for widespread herd immunity against HPV infection due to high adolescent vaccine coverage statewide is plausible based on these recent vaccine impact findings (Rosenblum, 2021). Additionally, recent HPV vaccine clinical trial results from Kenya demonstrated over 97% efficacy in women 18 months after receiving a single dose of bivalent or nonavalent HPV vaccine (Barnabas et al., 2022).

Although additional clinical trials are necessary to assess single dose HPV vaccine efficacy over a longer timeframe (36-months or more post-vaccination), these results may prompt cancer prevention and immunization experts to reconsider alternate strategies for improving adolescent HPV vaccine uptake.

As adolescent HPV vaccine coverage is currently at 59%, a one-dose regimen may allow states with suboptimal completion rates to catch up and states above 70% coverage to meet or surpass the Healthy People 2030 goal of 80% HPV vaccine completion (Pingali et al., 2021).

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APPENDICES

APPENDIX A

UNIVERSITY OF GEORGIA
CONSENT FORM
Examining Geographic Differences in HPV-Associated Cancer among Women and Men, Adolescent HPV Vaccine Uptake, and State Immunization Policy

State HPV Vaccine Policy Stakeholder In-Depth Interviews

You are being asked to take part in a research study. The information in this form will help you decide if you want to be in the study. Please ask the researcher below if there is anything that is not clear or if you need more information.

Principal Investigator: Paran Pordell, M.P.H.
College of Public Health
Department of Health Policy and Management
Email: paran.pordell@uga.edu
Phone: (917) 447-4390

I am conducting this research study to learn more about the effect of state immunization policies on HPV vaccine uptake among 13-17-year-olds in select parts of the U.S. I'm also interested in learning more about how knowledge, attitudes, beliefs, and perceptions about HPV and cancer risk affects the immunization policy proposal or revision process.

You are being invited to be in this research study because your work or volunteer role meets the definition of a state public health stakeholder (e.g., state health department staff member, state policymaker, member of comprehensive cancer control coalition, or advocacy group). You also meet the study eligibility criteria of being a state resident, serving in your role for two or more years or had prior HPV-related public health and/or policy work or volunteer experience within the last 5 years, and being 21 years of age or older.

If you agree to participate in this study:

- I will ask you questions about your knowledge, attitudes, beliefs and perceptions about HPV and cancer risk among females and males and your perspective about HPV vaccine policy.
- The virtual interview will take about 60 minutes and be conducted through MS Teams or Zoom for your safety and convenience.

- With your permission, I will also record the interview, so that I can capture your responses accurately. Do I have your consent to record our interview? ___YES ___NO
- I will follow up in 1-2 months by email to give you an opportunity to review my interview notes, so that I captured our discussion accurately.

You can choose to skip a question at any time and your participation in this study is completely voluntary. You can also end our interview at any time. If one of my questions is unclear, please stop me and I'll ask it a different way. There is very minimal risk to participating in this study. Some interview questions about HPV, cancer, or risk behavior may make you slightly uncomfortable.

There are no direct benefits to participating in this study. However, your responses may help me understand the state immunization policy and HPV vaccine advocacy environment from a stakeholder perspective.

All information collected from these interviews will be stored securely on a password protected computer or in a locked file cabinet that is accessible only to me or a designated research assistant. None of the comments you make during today's discussion will be linked with your name in any way.

De-identified study information and findings will only be shared with other researchers as part of the manuscript writing, review, and submission for publication process.

Please contact Paran Pordell if you have any questions about the research or participant rights. Please feel free to ask questions about this research at any time. You can contact the Principal Investigator, Paran Pordell, at 917-447-4390 or by email at ppordell@uga.edu Additionally, you can contact Dr. Mark Ebell, Lead Principal Investigator, by email at ebell@uga.edu.

If you agree to participate in this research study, please sign below

_____

Name of Researcher Signature Date

_____

Name of Participant Signature Date

_____

Please submit an electronic copy and keep a copy for your records.

APPENDIX B

HPV IMMUNIZATION POLICY AND VACCINE UPTAKE STAKEHOLDER IN-DEPTH INTERVIEW (IDI) GUIDE

A. Introductions: Hi, my name is Paran Pordell and I am a doctoral student in public health at the University of Georgia. As part of my dissertation, I am carrying out a project to learn more about perspectives on strategies that may be most effective in improving adolescent HPV vaccination coverage. I am also seeking to understand critical components of proposal and adoption of programs or policies for HPV vaccines. The interview will take about 60 minutes. To help me remember what we discussed, I'd like to tape-record the interview if that is alright with you. All of the information learned from our interview will be kept confidential and your name will not be used in any way. The results will be summarized across all the interviews. Do I have your permission to record the interview? Do you have any questions before we begin?

B. Stakeholder Information

1a. To begin, could you briefly describe where you work and your main duties?

1b. How long have you worked in this position or a similar (prior) position?

C. Stakeholder knowledge, attitudes, beliefs, and perceptions about HPV, cancer risk, and immunization

2a. What do you know about HPV infection?

[PROBE as needed: Cervical, head and neck cancer, anal cancer]

2b. What things can individuals do to prevent HPV infection and potentially prevent HPV-associated cancers?

2c. Please describe what you know and have heard about HPV vaccination.

D. Barriers and Facilitators to Achieving High Adolescent HPV Vaccine Uptake

3a. What do you think are the greatest barriers to achieving high HPV vaccination rates among adolescents in your state?

[PROBE: Anti-vaccine groups, conservative legislature and governor, economic expense, etc.)

3b. What do you think are key things that facilitate or help improve HPV vaccination rates among adolescents in your state?

[PROBE: Champions, governor, cancer control coalition involvement, feasibility, etc.]

3c. What do you think are some effective policy and non-policy-related strategies to increase HPV vaccine uptake?

[PROBE: Educating legislators, educating public, holding community advisory meetings, primary care clinician involvement as stakeholder, etc.]

E. Legislation/Regulation

Now I'm going to ask a few questions about HPV policy in your state.

Answer 4b-g if state introduced and rejected or approved HPV vaccine policy or regulation.

4a. Did your state propose HPV vaccination as part of state immunization policy/regulation?

__Yes __ No __ I don't know. **If response is NO or I DON'T KNOW, skip to Q7.**

4b. If yes, in what year?

4c. What were the key facilitators to introducing HPV vaccine policy/regulation?

4d. What were the key barriers to introducing HPV vaccine policy/regulation?

4e. How was HPV vaccination policy/regulation introduced?

[PROBE: Tell me a little bit more about your policy process]

4f. What organizations or stakeholders were involved in the initial advocacy and policy/regulatory discussions?

4g. What role did your organization have during the HPV vaccine policy/regulatory discussion and development process?

5. What were the main concerns raised about inclusion of HPV vaccine policy within state immunization rules and regulations? Are these concerns still applicable today?

6. I'm interested in learning about how you integrated perspectives of different stakeholder groups during the policy proposal, rejection and/or adoption process. I'm going to read a list of different groups and would like you to share from your experience how these perspectives were considered or included.

6a. Health care professionals?

6b. Parents?

6c. Advocacy groups?

6d. Health insurance providers ?

6e. School administrators?

7. I'm going to read a list of sub-components of policy/regulation. I'd like to understand which you would consider priorities for inclusion in a comprehensive or model state HPV vaccination policy/regulation.

Priority response options rated from 0-5, where 0 means you don't think it is an essential component for inclusion, <u>1 is not a priority</u> and <u>5 is essential</u>

0 – Not recommended to include
1- Not a priority
2- Low priority
3- Medium priority
4- High Priority
5- Essential

__ Policies permitting HPV vaccination in pharmacy settings
__ Medicaid expansion through the Affordable Care Act (Section 317 of the Public Health Services Act)
__Universal Purchase (local government purchases the vaccine for all children, including those who are fully insured)
__ School entry requirements for HPV vaccination in elementary and/or middle school (depends on when adolescent receives first dose)
__ Sex education requirement in schools
__ Reporting of HPV vaccination data through immunization information systems
__ Religious exemption
__ Medical exemption
__ Philosophical exemption

__ Adolescents can receive vaccination without parental consent
__ HPV vaccination is available through school health clinics, community health events, through mobile or temporary clinics
__ Include language about utility of adolescent vaccine bundling as strategy to increase uptake [HPV vaccine administered with other required adolescent vaccines such as Tdap and meningococcal vaccines]
__ Other _____

F. Stakeholder Attitudes, Beliefs, and Perceptions about HPV Vaccine Roles and Responsibilities

Let's talk about some different roles and responsibilities people may have in preventing HPV infection.

8a. What do you think is the parent's role in HPV vaccination?

8b. What do you think is the health care professional's (e.g., physician, nurse) role in immunization against HPV?

8c. What role do you think the state should have concerning adolescent HPV vaccination?

8d. How does your state support adolescent HPV vaccine uptake?

[PROBE: Vaccines for Children, health education campaign, requirements for school entry, etc.]

If time permits, ask Q9 *(optional)*

9. For states who are considering introducing HPV vaccination policy/regulations, what are three lessons learned worth sharing that may facilitate the policy/regulatory proposal and approval process?

Is there anything else you would like to share with me about HPV vaccination policy/regulation?

We have reached the end of the interview. Do you have any questions?

Thank you so much for your willingness to spend some time talking with me today.

APPENDIX C

IMMUNIZATION POLICY ANALYSIS: CA, GA, HI, MA, and RI

(Potential manuscript)

HPV Vaccine Policy Sub-Components

Table 1 summarizes the health policy sub-components adopted by each state. After review of immunization and health-related policies or regulations for CA, GA, HI, MA, and RI, all states adopted the following three policy sub-components: (1) policies permitting HPV vaccination in a pharmacy setting; (2) reporting of HPV vaccination data through immunization information systems; and (3) medical exemption. MA and RI adopted universal purchase for adolescent vaccines while only CA passed legislation that allows adolescents to receive HPV vaccine without parental consent. All states except CA allow school immunization exemption based on religious beliefs. HI and RI mandated HPV vaccine for 7th grade school entry. Making HPV vaccine available at pharmacies, adopting Medicaid expansion through the Affordable Care Act, and enacting legislation to become a universal purchase state represent regulatory facilitators to HPV vaccine access.

Adopting access-related policy sub-components may increase convenience for parents/guardians and adolescents, eliminate financial and geographic barriers, and improve state HPV vaccine coverage rates (vaccine dose initiation and completion). The myriad factors impacting HPV vaccine policy change include state policymakers prioritizing HPV-associated cancer prevention as an issue, involvement of immunization and comprehensive cancer control

coalitions, the availability of fiscal and operational resources, and maintaining strong partnerships, collaborations, and networks among governmental and non-governmental entities. Furthermore, during in-depth interviews, stakeholders shared that gaining buy-in from physicians, health insurance plans, the health department, policymakers, parents, pharmacists, advocacy groups, and school administrators, and ensuring involvement from HPV vaccine champions creates an ideal environment for policy change (open policy window) (Kingdon, 1984). We evaluated key vaccine policy sub-components displayed in Table 2 (school immunization requirements with and without mandates, policies permitting vaccination in pharmacy settings, universal purchase, and adolescent vaccination without parental consent) and focused on examining similarities and differences between state legislation.

Policy Evaluation Criteria

I utilized 4-6 of the following criteria to evaluate state immunization policies: (1) *Equity* defined as social justice or fairness in the distribution of a policy's costs, benefits, and risks; (2) b*eneficence* as an obligation to minimize harm and maximize possible benefits; (3) e*fficacy* or the extent to which the proposed policy will attain the goals set forth in the problem statement (e.g., adopting HPV vaccine policy will improve annual HPV vaccine rates among adolescents); (4) *liberty/freedom as* the power to make your own choices and the quality or state of being free; (5) *political feasibility* or the likelihood that the policy will be adopted; and (6) a*dministrative feasibility* or the likelihood that a department or agency can implement the policy or deliver the program well with adequate resources (e.g., staffing, expertise, finances, etc.) (Caputo, 2013; HHS OHRP, 2018).

Adolescent Immunization Requirements for School Entry

Political Feasibility

CA Health and Safety Codes for school immunizations (120325, 120400, 120405, 120410, and 120415), the GA Department of Public Health (GDPH) Chapter 511-2-2 and GA State Laws O.C.G.A. § 20-2-771, 31-2A-6, 31-12-3, and 49-5-12, the Department of Health Title 11, Chapter 157 of the Hawaii Administrative Rules (HAR 11-157), MA 105 CMR 220.000 and MA General Law, Part I, Title XII, Chapter 76 , Section 15, and RI General Laws §16-38-2 and §23-1-18 are *politically feasible* because legislators and health departments revised sections of these regulations or laws and passed policies due to a concern for public health and safety, to promote electronic reporting of immunization data for enhanced vaccine-preventable disease surveillance, and because of changes in religious and medical exemption request processes (CDPH, 2021; CA Legislature, 2016; GA State Legislature, 2021; HDOH, 2021; Commonwealth of MA, 2021a; RIDOH, 2014). These states did not experience major political opposition to regulatory revisions because changes were made to general immunization policies and health department rules and regulations that covered prevention of numerous infectious diseases instead of being specifically focused on HPV vaccine. This normalization strategy made HPV vaccine inclusion in policies more acceptable and feasible.

Administrative Feasibility

I found all state policies for immunization school requirements *administratively feasible* because Departments of Health and schools possessed adequate staffing, resources, and systems in place to implement regulatory changes, track immunizations, exemption forms, and immunization reporting by schools. The health departments in each state provided specific guidance to schools, health care professionals, and parents/guardians about required

immunizations for school entry and reporting. All states used Department of Health websites to inform the public of changes to legislation and created press releases, and updated school immunization requirements and guidelines. Additionally, they provided vaccine questions and answers (Q&As) documents and other resources to inform the public, health care professionals, and school administrators about school immunization policy changes.

This gave stakeholders the opportunity to review, understand, and adopt the changes by the regulatory start date.

Freedom/Liberty

CA Health and Safety Code immunization sections, GA immunization laws, and Massachusetts General Laws (immunization-related) promote *freedom/liberty* because there is no HPV vaccine school entry requirement, which provides an opportunity for students, parents, and guardians to make informed decisions about vaccination against HPV infection autonomously. Moreover, the CA Health and Safety Code for immunization allows new unvaccinated students to conditionally attend school, if they receive the required vaccines within the specified timeframe. Furthermore, RI immunization laws and regulations allow for temporary immunization exemption only if the adolescent scheduled an appointment to obtain the required immunization. More lenient than CA immunization requirements, GA State Law O.C.G.A. § 20-2-771 allows unvaccinated students to conditionally attend school for 30 days, which may be extended up to 90 days from the first day of attendance provided that the student proves they are in the process of acquiring the required immunizations.

Additionally, MA, RI, HI, and GA immunization regulations and laws enable *freedom/liberty* for parents, guardians, and students because the immunization regulations allow for religious and

medical exemptions. Lastly, CA Health and Safety Codes promote *freedom/liberty* by allowing for medical exemption from required immunizations for adolescent school entry.

Beneficence

GA immunization laws, CA Health and Safety Codes, the Hawaii Administrative Rules, MA General Laws, and Rhode Island State Immunization Regulations exhibit *beneficence* by excluding unvaccinated students from school during a public health emergency, as this reduces harm to community health and well-being and promotes the greatest good for the most Georgia, California, Hawaii, Rhode Island, and Massachusetts residents by reducing infectious disease transmission. MA General Law provides the MA Department of Public Health (MDPH) with the authority to revise vaccine requirements to protect against communicable diseases as needed, which promotes *beneficence* because providing this flexibility lets MDPH include necessary vaccines in case of a public health emergency or due to changing ACIP recommendations (MA Legislature, 2021). The inclusion of this section in the legislation provides the health department with authority and autonomy, which may prevent extensive disease transmission in all ages across communities.

Consequently, because MA included this language in immunization policy, written legislation may save lives, which does the greatest good for all MA residents.

Equity

The Hawaii Administrative Rules 11-157 (HAR 11-157**)** promote *equity* by providing required vaccines free of charge to indigent and medically indigent students and requiring adolescent boys and girls to be vaccinated against HPV. By including HPV vaccine as a school entry requirement for seventh graders, the Hawaii Department of Health (HDOH) equalizes the requirement, which facilitates vaccine access through state and federal programs, health insurers,

and other immunization program strategies (HDOH, 2021). Additionally, Rhode Island R23-1-IMM and RI General Laws §16-38-2, and §23-1-18 promote equity by including HPV vaccine as a school entry requirement for 7th graders and high school students. This requirement also facilitates access through state mechanisms including the implementation of a community clinic to vaccinate uninsured children, RI's Vaccinate Before You Graduate (for 12th graders to catch up on their vaccinations), and via universal purchase programs (RIDOH, 2022).

The HPV vaccine school entry requirement was written into the Department of Health Rules and Regulations in both states as part of a comprehensive update of immunization and other adolescent school health requirements (e.g., In Hawaii, physical exams for 7th graders). This inclusion of HPV vaccine as part of the regular school immunization requirements facilitates vaccine normalization and acceptance,

Efficacy

Hawaii Administrative Rules HAR-11-157 embody *efficacy* because they include an HPV vaccine requirement, which may protect adolescents from infection and HPV-associated cancers in adulthood. Furthermore, this vaccine *efficacy* may also reduce future health care costs associated with diagnosing, managing, and treating HPV-associated cancers (Chesson et al., 2012; HDOH, 2021). Similarly, R23-1-IMM and RI General Laws §16-38-2, and §23-1-18 are *efficacious* because they include an HPV vaccine requirement for 7th grade and high school entry, which may increase adolescent vaccination coverage and help RI achieve herd immunity against HPV infection (RIDOH, 2014). This achievement may protect adolescents from HPV-associated cancer morbidity and mortality in adulthood.

Massachusetts General Laws related to immunization exhibit *some efficacy*, as demonstrated by HPV vaccination completion rates comparable to Hawaii rates (Table 2: 73.4% and 73.9%

respectively). It is important to note that HAR-11-157 went into effect during the COVID-19 pandemic (July 1, 2020), which caused declines in routine adolescent vaccinations (Patel et al., 2021). It will take several years to see the true impact of passing HPV vaccine legislation for 7th grade school entry under the Hawaii Administrative Rules (Ron Balajadia, personal communication, November 30, 2021).

Policies Permitting HPV Vaccine in Pharmacy Settings

Political Feasibility

In 2013, California passed SB 493, which allows pharmacists to administer routine vaccines recommended by The Advisory Committee on Immunization Practices (ACIP) and authorized by the Food and Drug Administration (FDA) to individuals aged 3 years and older (CA Legislature, 2013). Similarly, Georgia's SB 46 allows for the administration of vaccines in pharmacy settings (GA Legislature, 2021). In 2017, Hawaii State Legislature passed SB 514 which allows pharmacists to administer HPV, Tdap, meningococcal, and influenza vaccines to 11-17-year-old adolescents (HI Legislature, 2017). Section 216 of the Rhode Island Code of Regulations-40-15-1.11 authorizes pharmacists and pharmacy interns delegated by pharmacists to administer vaccinations to individuals aged 9 years and older with a written protocol or prescription from a prescriber. This regulation also includes a training and continuing education requirement (RIDOH, 2021).

In 2015, pharmacists in Massachusetts were permitted to provide vaccines to individuals 18 years and older under MA 105 CMR 700.004(B)(6) with standing orders from a physician. This regulation was revised in 2020 allowing pharmacists and pharmacy interns to administer CDC ACIP recommended vaccines to individuals aged 3 years and older (Commonwealth of MA, 2021b).

These immunization policy sub-components are *politically feasible* because the Legislature and Governor in the respective states signed these bills into laws, which resulted in implementation throughout rural and urban pharmacy settings.

Administrative Feasibility

All state laws/regulations exhibit *administrative feasibility*, as each state has a process in place to receive immunization data from pharmacists, has specific guidelines for prescriptions, standing orders, or protocols, and includes training components for pharmacist continuing education and/or refresher training on vaccines.

Liberty/Freedom

California's SB 293 promotes *freedom/liberty* because while it permits pharmacists to administer adolescent vaccination through a protocol provided by a prescriber, it also allows them to administer ACIP recommended vaccines independently. Alternatively, GA's SB 46 only permits pharmacists to administer vaccine through a vaccine protocol issued by a physician, which limits pharmacist *freedom/liberty*. Moreover, there is no mention in the legislative language of pharmacists being able to independently vaccinate for all ACIP recommended vaccines within the target age group of 11-13 years. Hawaii's SB 514 lets pharmacists administer HPV, Tdap, meningococcal, and influenza vaccines to 11-17-year-old adolescents (Hawaii State Legislature, 2017).

However, a physician or advanced practice registered nurse must provide a prescription, which limits the *liberty/freedom* of a pharmacist to independently administer adolescent vaccines (Hawaii State Legislature, 2017). Massachusetts 105 CMR 700.004(B)(6) requires a prescription or standing orders from a physician, includes continuing education and training requirements, and reporting of vaccine doses into the MA immunization information system (Commonwealth

of MA, 2021). Like HI and GA, this regulation limits the *liberty/freedom* of the pharmacist to administer HPV vaccine independently. Lastly, section 216-Rhode Island Code of Regulations-40-15-1.11 authorizes pharmacists and pharmacy interns delegated by pharmacists to administer vaccinations to individuals aged 9 years and older with a written protocol or prescription from a prescriber (RI Dept. of State, 2021). Not unlike GA, HI, and MA, this regulation limits the *liberty/freedom* of the pharmacist to administer HPV vaccine independently.

Equity

CA SB 493 supports *equity* because it allows for a broad age range to receive immunizations (including 11-13-year-olds) in a rural or urban pharmacy setting. However, GA SB 46 is *not equitable* because it allows pharmacists to immunize based on the adult ACIP recommended vaccines for individuals 18 years and older, permits influenza vaccine and any vaccine necessary due to a public health emergency beginning at age 13 years (e.g., COVID-19 vaccine). It does not allow for a broad range of ages to be vaccinated as recommended by ACIP including adolescents aged 9-13 years. On the contrary, Hawaii SB 514 promotes *equity* because it broadens the adolescent age range allowed to receive HPV and other age-appropriate vaccinations.

Additionally, SB 514 facilitates adolescent HPV vaccine uptake and promotes vaccine bundling among 11-13-year-olds because it includes Tdap, meningococcal, HPV, and influenza vaccines. Like HI and CA, MA 105 CMR 700.004(B)(6) is *equitable* due to the broad age range for vaccine eligibility, which increases access for adolescents statewide. Furthermore, Rhode Island Regulation 40-15-1.11 is *equitable* because it includes adolescents aged 9 years and older for vaccine eligibility, which increases access for adolescents residing in rural and urban regions of the state.

Universal Purchase

Equity

Rhode Island and Massachusetts immunization legislation includes universal purchase sub-components. Passed in 2015, Rhode Island General Law §§ 23-1-45-47 created a state childhood immunization account within the general fund, which authorizes RIDOH to provide no-cost immunizations to children. Rhode Island General Law §§ 23-1-46 requires insurers to contribute to the childhood immunization account to cover the costs of childhood vaccinations not covered by the CDC Vaccines for Children program. This legislation provides access to vaccine for all RI infants, children, and adolescents regardless of health insurance status, income, or geography, which exemplifies *equity* by expanding access to vaccines required for school entry, including HPV vaccine (RIDOH, 2022).

Massachusetts passed universal purchase legislation in 2019 under M.G.L. Part I, Title XVI, Chapter 111, Section 24N, which established a childhood vaccine program, a vaccine purchase trust fund, and a vaccine program advisory council. MA utilizes the vaccine purchase trust fund to purchase, store, and distribute vaccines for routine childhood immunizations in the state (Commonwealth of MA, 2019). Resembling RI, the Department of Public Health oversees the fund. Additionally, this legislation established a vaccine program advisory council consisting of physicians, public health experts, health insurance and managed care organization representatives, a health information specialist, and representatives of medical societies. MA General Law also embodies *equity* because it expands access to adolescent vaccines in rural and urban areas, which aids in curbing disease transmission.

MA legislation is also *equitable* because universal purchase removes any required copayment, coinsurance, deductible, or dollar limit provisions in a health insurance policy or contract (MDPH, 2021).

Political and Administrative Feasibility

MA General law for universal purchase is *politically feasible* because the bill was signed into law in 2019 and *administratively feasible* because there is a specific process in place to collect the universal purchase funds, store and distribute the vaccines, provide oversight through MDPH, and convene the vaccine program advisory council (MA Legislature, 2019). The RI General Laws are *politically feasible* because the law was approved by the legislature and Governor and implemented in 2016. The laws are *administratively feasible* because RI created a process for the collection of funds from insurers into a general childhood immunization fund managed by the Department of Health who is required to report on immunization programs and costs to the General Assembly yearly to monitor vaccine coverage and spending (RIVAP, 2015).

Efficacy

RI and MA universal purchase laws are *efficacious* because by eliminating financial and geographic barriers to vaccine access for all infants, children, and adolescents, upsurges in vaccine initiation and completion are likely, which may result in a significant decline in vaccine-preventable diseases, notably during disease outbreaks (e.g., measles).

Improving Access and Increasing Adolescent Health Care Autonomy: Adolescent Vaccination without Parental Consent

California is the only state in our analysis that passed legislation allowing adolescents to be vaccinated against HPV without parental consent. Passed in 2011 and implemented in 2012, AB 499 amended Section 6926 of the CA Family Code, which provides legal authority to individuals

12 years and older to consent to confidential medical services to diagnose, treat, or prevent any sexually transmitted infections (STIs), including HPV (CA Legislature, 2011). AB 499 empowers adolescents by providing *freedom/liberty* to make their own decisions to prevent, diagnose, and treat STIs, and exemplifies *efficacious* public health policy. The law is *politically feasible* because the Legislature successfully amended the CA Family Code 6926 to include medical care related to the prevention of STIs including hepatitis B and HPV.

Additionally, it is *administratively feasible* because AB 499 updated an existing policy under Chapter 652 of CA law permitting confidential medical services for STI testing and treatment services by including STI prevention. Lastly, AB 499 is *efficacious* because the law provides adolescents with a mechanism to take care of their sexual health without involving their parents or guardians, which may detect and/or treat STIs and potentially halt the chain of infectious disease transmission to other sexually active adolescents. AB 499 has two loopholes worth noting. As written, the law does not cover STI health care costs, nor does it prevent insurance companies from sharing health care claims information related to STI services, which may be sent to parents or guardians who may be the primary policy holders. This may compromise adolescent confidentiality. Moreover, parents or guardians are not liable for any STI health care costs.

Policy Recommendation

Based on the evaluation criteria *political feasibility, administrative feasibility, freedom/liberty, equity, beneficence, and efficacy* utilized to analyze state policies, the following immunization policy sub-components represent a comprehensive, model HPV vaccine policy:

- Immunization requirements for school entry including HPV vaccine school mandate for 7th grade and medical exemption
- Administration of HPV vaccine in pharmacy settings for adolescents 9 years and older
- State universal purchase programs

- Adolescent vaccine bundling based on age
- HPV vaccine access for adolescents without parental consent

Based on analysis findings, updating general immunization and related health policy sub-components inclusive of HPV vaccine are most feasible to introduce, pass, and implement in CA, GA, HI, MA, and RI. The last section of the policy analysis focuses on examining religious and medical exemption processes and documentation in each state.

Table 1.

HPV Vaccine-Related Health Policy Sub-Components Implemented by States and HPV Vaccine Coverage Among 13-17-Year-Olds

State	Policies Permitting HPV Vaccination in Pharmacy Settings	Medicaid Expansion Through the Affordable Care Act	Universal Purchase	Vaccine Mandate for School Entry	Sex Education Requirement in Schools	Reporting of HPV Vaccination Data through Immunization Information Systems	Religious Exemption	Medical Exemption	Philosophical Exemption	Adolescents can Receive Vaccine without Parental Consent	*≥ 1 HPV Vaccine Dose among Adolescents (2020) %	*HPV Vaccine Coverage among Adolescents (Up-to-Date, 2020) %
California	X	X			X	X		X		X	78.2	62.3
Georgia	X				X	X	X	X			73.1	54.9
Hawaii	X	X		X		X	X	X			84.9	73.9
Massachusetts	X	X	X			X	X	X			87.4	73.4
Rhode Island	X	X	X	X	X	X	X	X			93	83

*CDC National Immunization Survey-Teen, 2021

Religious Exemption

Table 2 summarizes religious exemption policies for CA, GA, HI, MA, and RI. CA Senate Bill 277 removed religious exemption as an adolescent vaccine opt out option for public and private school entry in 2015 (CA Legislature, 2015). Governor Jerry Brown approved SB 277 to substantially reduce the number of vaccine exemptions requested by parents/guardians and improve vaccine coverage rates. The 2015 measles outbreak in Disneyland that infected over 150 people served as the catalyst and provided the opportune policy window for revising school immunization policy (Zipprich et al., 2015). GA's religious exemption policy requires that a parent/guardian sign the exemption form in front of a notary public for the exemption to be deemed valid (GA Legislature, 2021).

Hawaii and Rhode Island have similar religious exemption forms and processes and require a parent or guardian signature. A student aged 18 years and older can also sign the exemption form. MA requires a written statement from a parent or guardian stating that vaccination is against the student's religious beliefs.

Table 2.

Religious Exemption Policies for School Immunization Requirements in CA, GA, HI, MA, and RI

State	Religious exemption included?	Date of latest exemption form available on DOH website	Immunization Legislation	Exemption form contains information about vaccine benefits/risks, risk of contracting disease, and transmitting disease to others
California	No	Not applicable	SB 277 amended Section 120325 of CA Health and Safety Code (passed in 2015) removed personal belief and religious exemption for school immunizations due to measles outbreak in Disneyland	Not applicable
Georgia	Yes	GDPH Form 2208, June 2019	Chapter 511-2-2-.07 immunization chapter under rules of the GDPH	Yes and form must be signed by parent/guardian and notarized for exemption to be valid
Hawaii	Yes	HDOH Epi 7B, September 2019	Hawaii Revised Statutes 302A-1156, 302a-1157, 325-34; Hawaii Administrative Rules 11-157-5	Yes and form must be signed by parent/guardian/student aged 18 years and older
Massachusetts	Yes	No exemption form	MA School Immunization Requirements, 105 CMR 220.000	A written statement from a student or parent/guardian if the student is <18 years of age, stating that a vaccine is against sincerely held religious beliefs should be submitted and renewed annually at the start of the school year.
Rhode Island	Yes	RIDOH religious exemption form, May 2019	RIDOH Rules and Regulations 216-RICR-30-05-3	Yes and form must be signed by parent/guardian/student aged 18 years and older

Medical Exemption

All five states allow medical exemptions for adolescent school entry. Table 3 outlines medical exemption form details, immunization legislation, and identifies health care professionals authorized to complete and sign forms. California has the most stringent medical exemption policy in the country. SB 276 (2019) and SB 714 (2019) required the State Department of Public Health to develop and make available an electronic, standardized medical exemption request process through the CA Immunization Registry Medical Exemption (CAIR-ME) interface (CA Legislature, 2019). A parent or guardian must first create an account in CAIR-ME (https://cair.cdph.ca.gov/exemptions/home).

After creating an account, the parent or guardian fills in the required fields to request a medical exemption and is provided with a system generated medical exemption request number. The parent or guardian gives this request number to the physician who creates an account and enters the child's name or request number, fills out the required fields, and approves the exemption. The physician provides a 2-page form to the parent or guardian to submit to school (CDPH CAIR-ME, 2021). GA, HI, and RI require a health care professional to complete and sign the medical exemption form while MA requires a written statement from a physician stating that a child has medical contraindications (MDPH, 2021).

GA's exemption form is the simplest while HI and RI have detailed forms that include descriptions of contraindications and precautions by adolescent vaccine. It is worth noting that in-depth interviews conducted with 13 HPV vaccine policy stakeholders in five states as another component of this qualitative study asked stakeholders to rank many of the evaluated policy sub-components.

Stakeholders ranked vaccine bundling and allocating resources to implement an immunization information system for vaccine reporting as highest priority while school mandate and policy sub-components intended to increase HPV vaccine access were ranked as high priority. Philosophical and religious exemptions received the lowest priority although most states or territories permit religious exemption (44/50 states and Washington, DC) and about 30% allow philosophical exemption (NCSL, 2021).

Study participants assigned medium priority to medical exemption, which was a surprising finding.

Table 3.

Medical Exemption Policies for School Immunization Requirements in CA, GA, HI, MA, and RI

State	Medical exemption included?	Date of latest exemption form available on DOH website	Immunization Legislation	Exemption form must be signed by a physician, nurse, other healthcare professional
California	Yes	Starting in 2021- Medical exemptions must be submitted through CA Immunization Registry Medical Exemption website (CAIR-ME)	SB 276 (2019) & SB 714 (2019) required the State DPH to develop and make available an electronic, standardized medical exemption request	Must register on CAIR-ME website to be able to see the exemption request
Georgia	Yes	GDPH Form 3231 Certificate of Immunization, July 2014, HPV listed under recommended vaccines	GDPH Rules 290-5-4.05	Yes, a health care professional must evaluate adolescent and update 3231 form each year
Hawaii	Yes	HDOH Epi 8 form October 2019	Hawaii Administrative Rules 11-157-5	Yes and form must be signed by parent/guardian/student aged 18 years and older and a health care professional (MD, DO, ND, APRN-Rx, PA) with license number included. Form includes specific HPV vaccine contraindications and precautions
Massachusetts	Yes	No exemption form	MA School Immunization Requirements, 105 CMR 220.000	A written statement from a physician stating that a vaccine is medically contraindicated for a student must be submitted and renewed annually at the start of the school year.
Rhode Island	Yes	RIDOH Medical Exemption Certificate July 2017	RIDOH Rules and Regulations 216-RICR-30-05-3	Yes and form must be signed by health care professional

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