Disparities and trends in human papillomavirus (HPV) pathologic testing among oropharyngeal cancer patients in the National Cancer Database

by

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Abstract

Background: Oropharyngeal squamous cell carcinoma (OPSCC), a type of cancer that affects the mouth and throat, has an infectious disease etiology, with most cases caused by human papillomavirus (HPV). Clinical recommendations advise that all new cases of OPSCC be tested for the presence of the virus, but this guideline is not always followed. Knowledge of HPV status of OPSCC is important for guiding treatment and prognosis. With rising incidence rates of HPV-associated OPSCC, HPV testing disparities represent a critical public health concern. This study aimed to examine sociodemographic disparities and temporal trends in HPV testing for oropharyngeal cancer patients in the National Cancer Database.

Methods: Our analysis included 3,116 patients in the National Cancer Database diagnosed with oropharyngeal squamous cell carcinoma between 2013 and 2016. Exposure variables were year of diagnosis, facility type, race/ethnicity, insurance status, educational attainment, urban/rural, and median income. The outcome variable was HPV testing status. Descriptive statistics showed the distribution of HPV testing statuses across exposure variables, and chi-square testing was used to assess statistical significance. For each exposure variable, trends in HPV testing between 2013 and 2016 were examined, and Fisher's exact test was performed for each year.

Results: Across all exposure variables except urban/rural, there was a significant difference in the proportion of patients who received HPV testing. Between 2013 and 2016, the proportion of patients who were HPV tested increased incrementally and significantly (2013 =

73.6% and 2016 = 82.4%, p<0.001). HPV testing rates differed significantly by year of diagnosis and insurance status in 2014 (p=0.0003165) and 2016 (0.0349); by year of diagnosis and educational attainment in 2013 (p=0.009294); by year of diagnosis and urban/rural in 2016 (p=0.04234); by year of diagnosis and median income in 2014 (p=0.02003); by year of diagnosis and facility type in 2015 (p=0.002088); and by year of diagnosis and race/ethnicity in 2015 (p=0.03602).

Conclusions: Significant HPV testing disparities exist across time and by exposure variable for oropharyngeal squamous cell carcinoma patients in the National Cancer Database. Our findings underscore the need for increased scrutiny of HPV testing practices to ensure that every OPSCC patient receives testing.

Table of Contents

List of Tables

List of Figures

Preface

First and foremost, thank you to Dr. Angela Mazul for arranging this project for me and mentoring me every step of the way. Thank you to Dr. Jeremy Martinson for his help as an essay reader and MPH advisor. Thank you to Dr. Kathryn Demanelis for her assistance in getting this project off the ground. I would like to thank specific people for their help with data analysis and literature review – Rebecca Deek, Alexis Cenname, and Helena VonVille. None of this would have been possible without your guidance and expertise. Special thanks to Emily Prince Jones, Haley Director, and Audrey Ward for their constant support and friendship throughout my entire MPH journey. Heartfelt thanks to my parents, sister, extended family, and friends for their unwavering support over the last couple years, despite facing challenges of their own. Lastly, I would like to recognize my dad, Dr. Eric Carlson, for his dedication to providing the highest quality of care for head and neck cancer patients in Knoxville, Tennessee. His work and his patients were the inspiration for this project.

1.0 Introduction

1.1 Overview

Human papillomavirus (HPV) and oropharyngeal cancer cause a significant burden of infection and disease each year in the United States. Human papillomavirus infects most people who are sexually active, but only persists and causes cancer in a small subset. The best form of protection against HPV infection is vaccination, which has been shown effective in preventing cervical cancer. Oropharyngeal squamous cell carcinoma (OPSCC), a type of head and neck cancer, can be associated with HPV or not. The epidemiology of OPSCC has shifted over time, with an increase in HPV-associated cases. Numerous studies have shown that disparities by race, socioeconomic status, and other factors affect the survival of OPSCC patients. Furthermore, disparities exist in HPV testing for OPSCC patients, despite recommendations from clinical guidelines. To further understand HPV testing disparities, my essay examines the impact of sociodemographic variables on HPV testing status, as well as temporal trends in HPV testing.

1.2 Human Papillomavirus

Papillomaviruses are ancient viruses that have evolved over millions of years to infect humans and a wide range of animal hosts (Doorbar et al., 2015). Human papillomaviruses infect skin and mucosa and are comprised of five genera, with Alpha, Beta, and Gamma constituting the largest and most important in terms of clinical manifestations (Doorbar et al., 2015). The Alpha

genus contains several types that can be further categorized into high risk and low risk (Doorbar et al., 2015). High-risk HPV types have been shown to cause many different types of cancer in humans and are associated with a significant burden of infection and disease worldwide. Low-risk HPV types can produce benign skin lesions called papillomas (or warts), and in rare circumstances, may be associated with cancer (Egawa & Doorbar, 2017). Betapapillomaviruses mostly cause asymptomatic infections or papillomas on the skin, but may be associated with cancer in certain subgroups of people, including those who are immunocompromised or living with HIV (Egawa & Doorbar, 2017). Similar to HPVs in the Beta genus, Gammapapillomaviruses are also mostly associated with asymptomatic infections or benign papillomas of the skin (Egawa & Doorbar, 2017). Therefore, Beta and Gamma HPVs can generally be considered commensal viruses that are part of the normal skin microbiome for people who are immunocompetent (Egawa & Doorbar, 2017).

Human papillomaviruses are small, non-enveloped, double-stranded DNA viruses with an icosahedral (20-sided) shape (Doorbar et al., 2015). The genome of HPV is circular and contains around 8000 base pairs, which include eight or nine open reading frames (Doorbar et al., 2015). The L1 gene of HPV encodes for the major capsid protein and is used to distinguish HPV types, with each type having an L1 nucleotide sequence that is at least 10% different from other types (Doorbar et al., 2015). The E1 and E2 genes function in viral replication, L1 and L2 in packaging, and E4, E5, E6, and E7 in influencing cell cycle entry, host immune evasion, and virus exit from host cells (Doorbar et al., 2015).

1.2.1 High-Risk and Low-Risk HPV Types

Alphapapillomaviruses are classified into high- and low-risk types according to their propensity to cause cancer. High-risk HPV types include 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 (Brown et al., 2005). Low risk-types include 6, 11, 40, 42, 53, 54, 57, and 66 (Brown et al., 2005). High-risk types 16 and 18 are responsible for most HPV-associated cancer cases around the world, while low-risk types 6 and 11 are commonly associated with genital warts (Doorbar et al., 2015).

1.2.2 Transmission of HPV

Since HPV is a ubiquitous virus, HPV infection is incredibly common. Transmission occurs through contact with infected skin or mucosa, as the virus preferentially infects epithelial cells of those sites (McBride, 2022). Sexual transmission is one of the most common routes of HPV infection, and the majority of individuals who are sexually active will be exposed to HPV in their lifetimes (McBride, 2022). Sexual transmission of HPV can happen through various sex acts, including vaginal, anal, and oral sex. Some individuals may transmit HPV to sexual partners unknowingly since infection does not cause obvious symptoms in many people. Human papillomavirus is the most common sexually transmitted infection in the United States (Lewis et al., 2021). Lewis et al. used 2013-2016 data from the National Health and Nutrition Examination Survey (NHANES) to estimate HPV prevalence among people aged 15-59 in the United States (Lewis et al., 2021). They projected that in 2018, 77.3 million people (40% of the U.S. population) would be infected with at least one HPV type and 23.6 million people would become newly infected with HPV (Lewis et al., 2021).

Research has shown that acquisition of HPV happens soon after the initiation of sexual activity. A 2005 cohort study enrolled 60 adolescent girls aged 14-17 and followed them for an average of two years (Brown et al., 2005). All but three of the participants reported that they were sexually active (Brown et al., 2005). At the end of the study, the cumulative prevalence of HPV infection was 81.7%, and this includes HPV infections that were present at enrollment as well as incident HPV infections that were documented during follow-up (Brown et al., 2005). By the end of the study, high-risk and low-risk HPV types were detected in most participants – 76.7% had been infected with high-risk types and 56.7% had been infected with low-risk types (Brown et al., 2005). Of the 54 participants who received at least one Pap smear test, 37% had at least one abnormal result, and these abnormal results were strongly correlated with infection by high-risk HPV types (Brown et al., 2005). The investigators were also able to examine HPV persistence since their longitudinal data provided an opportunity to perform time-to-event analysis. Kaplan-Meier testing was used to estimate a median clearance time of 226 days for high-risk HPV types and 170 days for low-risk HPV types (Brown et al., 2005). Overall, the results from this study substantiate the highly contagious nature of HPV among sexually active adolescents and provide insight into HPV clearance in this population.

1.2.3 Pathogenesis of HPV Infection and Progression to Cancer

For HPV to establish infection, it needs to gain access to the basal layer of stratified squamous epithelia through tiny abrasions that disrupt the skin and/or mucosal barriers (Mittal & Banks, 2017). By infecting cells in this region, the virus is able to use the host cellular machinery for viral replication, since cells in the basal layer are continually dividing (Mittal & Banks, 2017). The HPV genome is amplified as basal cells differentiate, allowing new virions to be produced so

that nearby cells can become infected (Mittal & Banks, 2017). Extensive research has pinpointed the critical role of two HPV proteins, E6 and E7, in the development of HPV-associated cancers. These so-called "oncoproteins" are persistently expressed in high-levels in HPV-infected cancer cells (Mittal & Banks, 2017). E6 and E7 act synergistically to disrupt the cell cycle of HPV-infected host cells. The interaction of E7 with certain cell cycle regulators results in the activation of the p53 tumor suppressor pathway, which would normally lead to cell cycle arrest or apoptosis (Mittal & Banks, 2017). However, the role of the HPV E6 protein is to target the p53 protein for degradation, ensuring that the infected cell survives (Mittal & Banks, 2017). Host cells that are continually dividing due to HPV persistently stimulating the cell cycle are prone to mutation, and this can result in the accumulation of abnormal cells (Mittal & Banks, 2017). For example, the buildup of abnormal cells caused by HPV infection in the cervix can lead to cervical intraepithelial neoplasia (CIN), and can be low-grade (CIN1), moderate (CIN2), or high-grade (CIN3) (Mittal & Banks, 2017). About one-third of individuals with CIN3 will go on to develop cervical cancer in 10-20 years (McBride, 2022).

Human papillomavirus has evolved several mechanisms of evading the host immune response, including interfering with innate immunity and T cell effector function, as well as inducing the loss of human leukocyte antigen (HLA) expression from host cells (Mittal & Banks, 2017). Together, these actions support HPV infections that can become chronic, rather than acute infections that are effectively cleared by the host immune system. The virus will be cleared by the immune system within two years for about 90% of people who become infected with HPV, but chronic infection with HPV, especially high-risk types, can lead to cancer (McBride, 2022). In pre-cancerous lesions, the HPV DNA within host cells is maintained as extrachromosomal elements

called episomes, but integration of HPV DNA into the host genome has been detected in many cancerous cells (Mittal & Banks, 2017).

1.2.4 Epidemiology of HPV-Associated Cancers

In 1976, a German virologist named Harald zur Hausen hypothesized that the same papilloma viruses that were known to cause genital warts were also involved in the etiology of cervical cancer (zur Hausen, 1976). Since this momentous declaration, extensive research has established a clear association between HPV infection and many types of cancer. Besides cervical cancer, HPV can also cause penile, vulvar, vaginal, anal, and oropharyngeal cancer (de Martel et al., 2017). Pre-cancerous cervical lesions caused by HPV can be detected through Papanicolaou (or Pap smear) testing and treated through various medical procedures. However, for the other types of HPV-associated cancers (penile, anal, vulvar, vaginal, and oropharyngeal), no FDA-approved screening methods currently exist (de Martel et al., 2017).

A groundbreaking 2017 study found that around 4.5% of all incident cancer cases around the world can be attributed to HPV infection (de Martel et al., 2017). This study presented further data on the involvement of HPV infection in cancer. They estimated that in 2012, there were 570,000 new cases of HPV-associated cancers in women worldwide, and 60,000 such cases in men (de Martel et al., 2017). High-risk HPV types 16 and 18 were estimated to account for around 72% of HPV-associated cancer cases (de Martel et al., 2017). These findings highlight the profound involvement of HPV in cancer incidence around the world.

In 2023, Singh et al. used a global cancer database to estimate that there were 604,127 new cases of cervical cancer worldwide in 2020 and 341,831 deaths (Singh et al., 2023). The highest incidence rates were seen in eastern, southern, and middle Africa, followed by certain parts of

South America, Southeast Asia, and Melanesia (Singh et al., 2023). Incidence rates were relatively low in Canada, the United States, and most parts of Europe. Mortality rates were highest in eastern Africa and lowest in western Europe (Singh et al., 2023). These data highlight worldwide disparities in cervical cancer incidence and mortality. Because access to healthcare is critical in preventing, screening for, and treating cervical cancer, many resource-limited countries and areas of the world bear the burden of cervical cancer incidence and mortality.

1.2.5 HPV Vaccination

In 2006, the approval of Gardasil®, a quadrivalent vaccine against HPV types 6, 11, 16, and 18, revolutionized the prevention of cervical cancer (FUTURE II Study Group, 2007). In their phase III, randomized, double-blind, placebo-controlled trial, the FUTURE II Study Group found that the vaccine was 98% effective in preventing pre-cancerous lesions in their patient population who had no prior exposure to HPV-16 or HPV-18 (FUTURE II Study Group, 2007). The formulation of HPV vaccines consists of virus-like particles (VLPs) of the L1 major capsid protein (Schiller & Lowy, 2018). These VLPs self-assemble in the host to induce a robust immune response that is HPV-type specific (Schiller & Lowy, 2018). Fourteen years after the start of the FUTURE II study, a group of researchers confirmed the durability of the immune response in a subset of vaccine recipients from the original cohort (Kjaer et al., 2020).

In 2014, an updated version of Gardasil® called Gardasil®9 was approved, offering expanded coverage against nine oncogenic HPV types – 6, 11, 16, 18, 31, 33, 45, 52 and 58 (Mohsen et al., 2017). Importantly, these new types added to Gardasil®9 have been estimated to cause approximately 20% of cervical cancer cases (Mohsen et al., 2017). Since 2016, Gardasil®9

is the only HPV vaccine that is distributed in the United States (Meites et al., 2019). The dosing schedule for Gardasil®9 differs based on the age and immunologic status of the recipient. For individuals who receive their first dose of Gardasil®9 before their 15th birthday, the recommendation is to receive two doses, 6-12 months apart (Meites et al., 2019). For those who receive their first dose on or after their 15th birthday and those who are immunocompromised, three doses are recommended, with a 0, 1-2 month, and 6 month dosing schedule (Meites et al., 2019).

In 2019, the Advisory Committee on Immunization Practices (ACIP) released updated guidelines for HPV vaccination. Their report emphasized the importance of completing the HPV vaccination series before the initiation of sexual activity, since current HPV vaccines have only demonstrated effectiveness in preventing infections and not clearing existing infections (Meites et al., 2019). The ACIP recommends that HPV vaccination be routinely administered to adolescents of all genders at age 11 or 12, though it may be initiated in children as young as nine years old (Meites et al., 2019). The 2019 update to ACIP's guidelines declared that "catch-up" HPV vaccination is indicated for individuals up to age 26 who have not received any HPV vaccines or did not complete the full series (Meites et al., 2019). For those between ages 27 and 45 who are not fully vaccinated, the ACIP advises patients to decide together with their healthcare providers if HPV vaccination is appropriate (Meites et al., 2019).

Several studies have established the effectiveness of HPV vaccination by comparing epidemiological data before and after the implementation of population-level vaccination programs. One meta-analysis that reviewed data from 60 million individuals found that HPV vaccination significantly decreased the frequency of HPV infections and high-grade cervical lesions in girls and women, and significantly decreased the incidence of anogenital warts in girls, women, boys, and men (Drolet et al., 2019).

In 2019, the National Immunization Survey reported the estimated rates of HPV vaccination coverage by state for adolescents 13-17 years old (Pingali et al., 2023). The overall estimate for the United States for up-to-date HPV vaccination in this age group was 54.2% (Pingali et al., 2023). Rates varied widely among states, with Rhode Island having the highest coverage estimate at 78.9%, and Mississippi having the lowest at 30.5% (Centers for Disease Control and Prevention, n.d.). Currently, HPV vaccination for schoolchildren is mandated in five states and jurisdictions – Hawaii, Virginia, Rhode Island, Washington, D.C., and Puerto Rico (National Conference of State Legislators, n.d.). To address lagging HPV vaccination rates, several states have implemented policies short of mandatory vaccination; for example, Iowa and Texas mandate that information on HPV vaccination be included in school curricula (Hoss et al., 2019).

A 2023 study by Khalil et al. examined HPV vaccination status by several sociodemographic factors among a large patient population from the University of Pittsburgh Medical Center. The investigators found that 33.6% of female patients aged 18-26 had completed the HPV vaccination series compared to 25.4% of males (Khalil et al., 2023). Black patients were 35% more likely to initiate HPV vaccination but 11% less likely to complete it, compared to white patients (Khalil et al., 2023). The findings of this study confirm that HPV vaccination rates are far behind the Healthy People 2030 goal of 80% and that disparities exist for vaccination initiation and completion (Khalil et al., 2023). Barriers to optimal HPV vaccination rates include issues with healthcare access, lack of awareness of HPV and cancer, stigma surrounding HPV as a sexually transmitted infection, and vaccine hesitancy (Khalil et al., 2023). Many parents and guardians of adolescents express concerns over the safety and necessity of HPV vaccination. A 2020 study by Szilagyi et al. found that around 23% of parents who were surveyed were hesitant about HPV

vaccination, and this hesitancy was strongly correlated with adolescents not receiving HPV vaccination (Szilagyi et al., 2020).

1.3 Oropharyngeal Squamous Cell Carcinoma

Oropharyngeal cancer is a type of head and neck cancer that affects the anatomical regions of the oropharynx, which includes the palatine tonsils, soft palate, tongue base, and posterior pharyngeal wall (Westra & Lewis, 2017). Oropharyngeal squamous cell carcinoma (OPSCC) is a type of oropharyngeal cancer that specifically affects the epithelial cells that line the oropharynx (Ferris & Westra, 2023). The clinical management of oropharyngeal cancer was transformed with the release of the 2017 edition of the World Health Organization/International Agency for Research on Cancer's *Classification of Tumors* reference book (Westra & Lewis, 2017). For the first time, an edition of this book included a separate chapter for the oropharynx, recognizing it as distinct from the oral cavity, and acknowledged that HPV-associated oropharyngeal cancer was a discrete type of cancer (Westra & Lewis, 2017). This update signaled that substantial changes were needed in the clinical practice of head and neck cancer (Westra & Lewis, 2017). Prior to this update, oral cavity cancer and oropharyngeal cancer had typically been grouped together as "oral cancer," despite important distinctions (Westra & Lewis, 2017). For example, although both the oral cavity and oropharynx are lined with stratified squamous epithelium, only the oropharynx contains tonsillar tissue, which is particularly susceptible to HPV infection (Westra & Lewis, 2017).

1.3.1 Epidemiology of Oropharyngeal Cancer

Using data from a global cancer database, Lorenzoni et al. estimated that there were 98,412 incident cases of oropharyngeal cancer and 48,143 deaths worldwide in 2020 (Lorenzoni et al., 2022). The highest age-standardized incidence rates for men were in Romania, Belarus, Denmark, and the Republic of Moldova, and for women were in Denmark, France, Hungary, and Czechia (Lorenzoni et al., 2022). Other countries with high age-standardized incidence rates were Australia, Cuba, the United States, Brazil, the Russian Federation, India, Turkmenistan, and Bangladesh (Lorenzoni et al., 2022). Areas with the lowest age-standardized incidence rates for both sexes included most African countries, China, and many western Asian countries (Lorenzoni et al., 2022). The highest age-standardized mortality rates for men were in Slovenia, Belarus, Romania, Slovakia, and the Republic of Moldova, and for women were in Hungary, Denmark, Namibia, Montenegro, and Bangladesh (Lorenzoni et al., 2022). The lowest age-standardized mortality rates were in most African countries and western Asia (Lorenzoni et al., 2022). Despite having some of the highest incidence rates, northern Europe and northern America were not among the five areas with the highest mortality rates (Lorenzoni et al., 2022).

1.4 HPV and OPSCC

In the mid-1980s, HPV was detected in head and neck squamous cell carcinoma, but it wasn't until the year 2000 that the accumulation of compelling evidence led to the recognition of HPV's role in causing OPSCC (Ferris & Westra, 2023). In 2018, the CDC declared in its Morbidity and Mortality Weekly Report that as of 2015, oropharyngeal squamous cell carcinoma

had surpassed cervical cancer as the most common HPV-associated cancer in the United States (Van Dyne et al., 2018). Between 1999 and 2015, incidence rates for OPSCC in the U.S. increased by 2.7% per year in men and 0.8% per year in women (Van Dyne et al., 2018). Thanks to screening efforts, cervical cancer incidence rates in the U.S. declined by 1.6% per year between 1999 and 2015, while HPV had been driving an increase in the incidence of oropharyngeal cancer (Van Dyne et al., 2018). Studies have found that evidence of HPV infection is present in around 70% of oropharyngeal cancer cases (Van Dyne et al., 2018).

1.4.1 HPV-Positive versus HPV-Negative OPSCC

Once a consensus was reached that HPV played a causal role in the development of oropharyngeal cancer, HPV-positive and HPV-negative oropharyngeal cancers began to be treated as separate entities, both clinically and epidemiologically. In fact, HPV status of OPSCC is considered the most influential prognostic factor for oropharyngeal cancer patients, with HPV positivity conferring a more favorable prognosis than negative HPV status (Ferris & Westra, 2023). Treatment options for oropharyngeal cancer include surgery, radiation, chemotherapy, immunotherapy, or a combination of therapies. Clinical trials have shown that treatment de-escalation for patients with HPV-associated cancers may be appropriate, due to the receptiveness of HPV-positive cancers to treatment (Mehanna et al., 2020). Treatment de-escalation, which involves using lower doses of radiation or chemotherapy for HPV-positive cancers, may be effective in treating the cancer without causing as severe of side effects in patients (Mehanna et al., 2020).

Epidemiological data reveals notable differences between patients with HPV-positive and HPV-negative OPSCC. Incidence rates of HPV-associated cancers are increasing in high-income

countries, with younger, white males of high socioeconomic status particularly at risk (Lorenzoni et al., 2022). In the U.S., HPV-negative OPSCC is more commonly seen in Black versus white individuals and older versus younger individuals (Young et al., 2015). Incidence of HPV-positive OPSCC is strongly associated with a high number of lifetime vaginal or oral sex partners (Ferris & Westra, 2023). Tobacco use and alcohol consumption are major risk factors for HPV-negative OPSCC (Ferris & Westra, 2023). As smoking has become less prevalent in the U.S. over the last few decades, incidence rates of HPV-negative OPSCC have declined (Young et al., 2015).

1.4.2 Testing for HPV in OPSCC

In 2012, the National Comprehensive Cancer Network recommended that all incident cases of oropharyngeal cancer be tested for the presence of HPV (Caudell et al., 2022). They specifically recommended that a type of testing called p16 immunohistochemistry (IHC) be used, noting that expression of p16 is a reliable indicator of HPV positivity (Caudell et al., 2022). Other ways to test for HPV in OPSCC are polymerase chain reaction (PCR) and in situ hybridization (ISH) (Caudell et al., 2022). These three tests have varying levels of sensitivity and specificity, with IHC and PCR having the highest sensitivity and ISH having the highest specificity (Caudell et al., 2022).

1.5 Disparities in HPV-Associated OPSCC

1.5.1 Disparities in OPSCC Patient Outcomes

Disparities in oropharyngeal cancer have been widely reported. Studies have shown that race, socioeconomic status, gender, urban/rural categorization, insurance status, and access to healthcare can disproportionately affect outcomes for OPSCC patients. In 2022, Baliga et al. used the National Cancer Database to compare survival rates for Black versus white patients with OPSCC (Baliga et al., 2023). The investigators found that among patients with OPSCC, Black individuals had a 5-year overall survival rate of 23%, compared to 42% for white patients ($p<0.0001$) (Baliga et al., 2023). Significant differences were still seen after stratification by HPV status. For cases of HPV-associated OPSCC, Black patients had a 5-year overall survival rate of 39%, compared to 65% for white patients ($p<0.0001$) (Baliga et al., 2023). For cases of HPV-negative OPSCC, Black patients had a 5-year overall survival rate of 13%, compared to 36% for white patients ($p<0.0001$) (Baliga et al., 2023). Another study used SEER data to show survival disparities by race and insurance status for OPSCC patients, with Hispanic patients having a higher risk of death than non-Hispanic white patients, and those on Medicaid and the uninsured having a higher risk of death than those with insurance other than Medicaid (Osazuwa-Peters et al., 2021).

A 2020 analysis by Clarke et al. found that Black rural patients had significantly worse survival than white urban patients (Clarke et al., 2020). Furthermore, they elucidated that urban/rural status affected survival outcomes to a greater extent for Black patients compared to white patients (Clarke et al., 2020). In 2021, Mazul et al. found that survival of Black female patients with HPV-associated OPSCC was far worse than survival for any other race and gender group, providing evidence of an interaction between race and gender in OPSCC survival (Mazul

et al., 2021). Further evidence of interaction between sociodemographic variables was reported by Yan et al. in 2023, when they found that survival of Black OPSCC patients of low socioeconomic status was much worse compared to patients of other races and low socioeconomic status (Yan et al., 2023). Mounting evidence has demonstrated that survival of OPSCC patients is impacted by a variety of factors, and that certain groups experience disproportionately worse outcomes and prognosis compared to other groups.

1.5.2 Disparities in HPV Testing for OPSCC Patients

In addition to inequities that affect outcomes for OPSCC patients, recent research has shed light on disparities in HPV testing for OPSCC patients. In 2020, Mazul et al. used the National Cancer Database to determine whether certain sociodemographic factors were associated with HPV testing status between 2013 and 2015 (Mazul et al., 2020). They found that 12.0% of OPSCC patients in their analysis had not been tested for HPV, with the highest proportion of untested patients being diagnosed in 2013 (Mazul et al., 2020). Insurance status affected the likelihood of being tested, with patients on Medicaid and the uninsured being more likely not to receive testing than patients with private insurance (Mazul et al., 2020). Women were more likely not to receive testing than men, and higher age was associated with a higher likelihood of not being tested (Mazul et al., 2020). After the National Comprehensive Cancer Network put forth recommendations in 2012 that all incident OPSCC be tested for HPV, Mazul et al. were one of the first to show that significant testing disparities exist in oropharyngeal cancer.

In 2021, Husain et al. examined HPV testing rates among oropharyngeal cancer patients in the National Cancer Database (NCDB) and Surveillance, Epidemiology, and End Results (SEER) program. The researchers sought to measure adherence to clinical guidelines as well as investigate

the presence of sociodemographic disparities in HPV testing status. They found that HPV testing rates varied by race in both databases, with white patients having higher rates than Black patients. Testing rates also differed by insurance status, with privately insured patients more likely to be tested than patients on Medicare, Medicaid, or other government insurance. Patients who lived in areas with lower educational attainment had lower testing rates than those in areas of high educational attainment. Age was also a variable that revealed testing disparities, with older patients less likely to be tested than younger ones. The facility types where patients received care impacted their likelihood of being tested for HPV, with community hospitals and comprehensive community cancer centers having lower testing rates than academic hospitals and NCI-designated comprehensive cancer centers. The researchers found that testing uptake increased over time between 2013 and 2016, but rates were still lower than 100% (Husain et al. 2021).

In their discussion, Husain et al. posit that cost and access to resources may be reasons why HPV testing is not always performed. However, the disparities that their analysis revealed persisted even after adjusting for sociodemographic factors and year of diagnosis, providing evidence for possible biases in the clinical management of oropharyngeal cancer patients. The authors point to the growing body of evidence that supports knowledge of HPV status for guiding treatment and prognosis of OPSCC patients. They also draw attention to coding issues with the HPV testing variable itself since many patients were coded as 999 (unknown HPV testing status). Because the HPV testing variable does not give information on the type of HPV testing used, this allows for the possibility of patients being incorrectly coded due to registrar errors. For example, p16 immunohistochemistry testing is often used as a proxy for HPV status, but some registrars may not be aware that p16 positivity indicates HPV positivity. In closing, the authors call for increased

HPV testing among OPSCC patients, decreased disparities in testing, and changes in the HPV testing variable to allow for more consistent and accurate coding (Husain et al., 2021).

1.6 Gaps in Knowledge

Very little research has been done to determine factors that are associated with receipt of HPV testing for oropharyngeal cancer patients. While Husain et al. did examine testing trends across the years 2013-2016, they did not assess whether HPV testing uptake was differential by year of diagnosis and insurance status, race/ethnicity, educational attainment, facility type, urban/rural, and median income. A full understanding of the role of these factors is critical for addressing potential disparities in HPV testing for OPSCC patients. Furthermore, the effect of year of diagnosis on HPV testing is important since we were interested in assessing how testing uptake changed in the years following the 2012 recommendation that all new cases of OPSCC be tested for HPV.

1.7 Public Health Significance

Suboptimal guideline adherence and disparities in HPV testing for oropharyngeal cancer patients represent critical public health concerns for many reasons. Most importantly, the existence of disparities in HPV testing means that outcomes for OPSCC patients are affected. If patients whose cancers are HPV-positive are not tested for HPV, they may be unnecessarily exposed to higher doses of chemotherapy and radiation, instead of undergoing treatment de-escalation in

clinical trials. Furthermore, because knowledge of HPV status for OPSCC patients can guide eligibility for clinical trials, patients who are not tested may be disproportionately excluded from participating in these trials. Healthcare providers can use knowledge of HPV status to inform prognosis, since HPV-positive cancers are associated with better prognosis compared to HPV-negative cancers. Improving rates of HPV testing is especially important now that incidence rates for HPV-associated OPSCC are rising.

Additionally, HPV testing for OPSCC patients has implications for HPV vaccination policy. Numerous studies have provided overwhelming evidence that HPV vaccination is effective in preventing cervical cancer, which has spurred the development of HPV vaccination policy in the United States. In order to leverage the data to show that HPV vaccination is also effective in reducing the incidence of OPSCC, robust and accurate reporting of HPV status for oropharyngeal cancer patients is essential. In 2020, the FDA added OPSCC to the list of indications for HPV vaccination, which supports HPV vaccination as a prevention measure for oropharyngeal cancer (Zhou et al., 2021). Future research will undoubtedly investigate the impact of HPV vaccination on OPSCC incidence.

2.0 Objectives

The objective of this study was to build on the analysis of Husain et al. by examining sociodemographic disparities and temporal trends in HPV testing for oropharyngeal cancer patients in the National Cancer Database. First, we aimed to determine whether disparities existed in HPV testing status by year of diagnosis, insurance status, race/ethnicity, educational attainment, facility type, and median income. Our second aim was to examine whether the percentage of patients who were HPV tested differed significantly by year of diagnosis and insurance status, race/ethnicity, educational attainment, facility type, urban/rural, and median income. We hypothesized that HPV testing rates would increase between 2013 and 2016, and that our analysis would reveal testing disparities by race, insurance status, and other variables, as documented by prior research.

3.0 Methods

3.1 Data Source and Study Population

The data source for this analysis was a Participant User Data File (PUF) requested from the National Cancer Database (NCDB). The PUF contains data from head and neck cancer patients, including thyroid cancer patients, that is de-identified and Health Insurance Portability and Accountability Act (HIPAA)-compliant (American College of Surgeons, n.d.-b). The National Cancer Database is the largest clinical registry in the world and gathers data on around 70% of incident cancer cases in the United States (Bilimoria et al., 2008). Hospitals and medical centers contributing to NCDB are accredited by the Commission on Cancer, which categorizes cancer programs based on factors such as facility type and number of cancer cases recorded yearly (American College of Surgeons, n.d.-a).

3.2 Inclusion and Exclusion Criteria

Figure 1 outlines how cases were excluded from the NCDB PUF to end up with the final subset of 3116 OPSCC patients. The NCDB PUF contains data for cancer cases diagnosed between 2004 and 2020, but only those diagnosed between 2013 and 2016 were included in this analysis. Since we were only interested in studying oropharyngeal squamous cell carcinoma, we filtered the dataset further to only include those cases. This was done by filtering by the primary site codes (C019, C090, C091, C098-C104, C108, C109, C142) and histology codes (8073–8079 and 8083–

8084) that correspond to OPSCC. Additionally, we excluded patients for whom HPV testing status was coded as "not applicable" (CS site-specific factor 10 = 988; n = 3), since these were not relevant to our analysis.

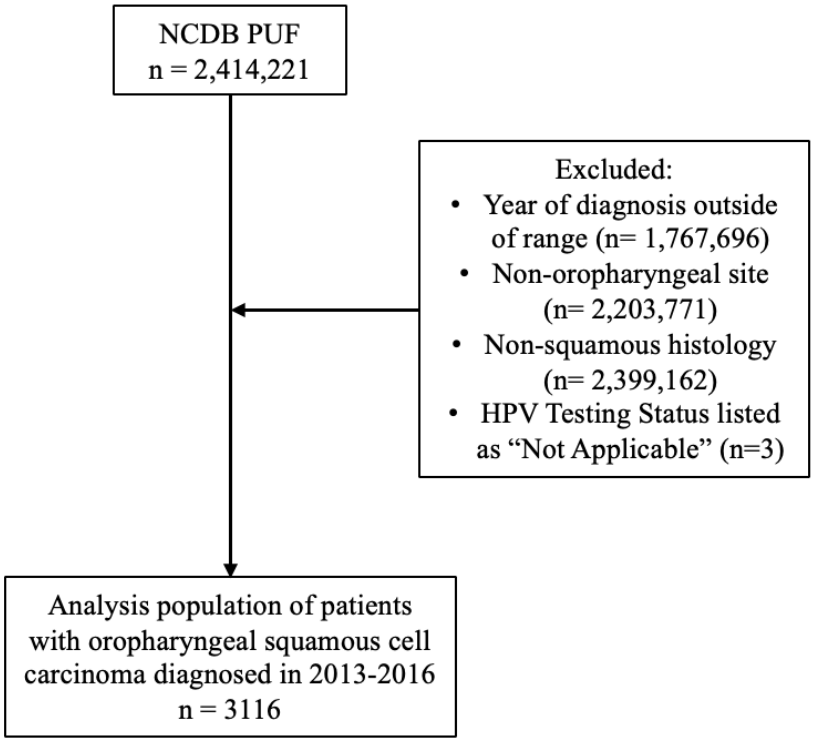

Figure 1 – CONSORT Diagram: because Patients May Fall Into Multiple Exclusion Categories, the Total Number of Exclusions Exceeds the Total Number of Patients

3.3 Study Variables

The outcome variable for this analysis was HPV testing status, which is coded within the American Joint Committee on Cancer Collaborative Stage (CS) site-specific factor 10 variable. This coding has multiple levels, with the following corresponding to known testing status: 0, 10,

20, 30, 40, 50, 60, 70, and 997 (National Cancer Institute's Surveillance, Epidemiology, and End Results program, n.d.). We grouped all these patients together as "HPV Tested" since our primary aim was to examine HPV testing status, regardless of whether the results were positive or negative for the virus. When HPV testing was not performed, this was denoted by the code 998. The code 999 was used when HPV testing status was unknown. For our analysis, we created an HPV testing status variable that included two groups: 1) those who were tested, and 2) those who were not tested together with those coded as 999 (unknown). Since we were also interested in examining unknown HPV testing status, we created another HPV testing status variable that included three groups: 1) those who were tested, 2) those who were not tested, and 3) those coded as 999 (unknown).

The exposure variables for our analysis were year of diagnosis, facility type, race/ethnicity, insurance status, educational attainment, urban/rural, and median income. The years of diagnosis included in this analysis were 2013, 2014, 2015, and 2016. Four different facility types, as designated by the American College of Surgeons, were examined in this analysis: Community Cancer Program, Comprehensive Community Cancer Program, Academic/Research Program (including NCI-designated Comprehensive Cancer Centers), and Integrated Network Cancer Program. Community Cancer Programs record between 101 and 499 incident cancer cases per year; Comprehensive Community Cancer Programs record 500 or more incident cancer cases per year; Academic/Research Programs have four or more program areas for postgraduate medical education and record more than 500 incident cancer cases per year; and Integrated Network Cancer Programs provide integrated and comprehensive cancer care services (American College of Surgeons, n.d.-a).

Race and ethnicity were grouped as White, Black, Other (including several Asian racial groups), and Hispanic. Insurance status included not insured, private insurance/managed care, Medicaid, Medicare, and other government. Educational attainment was estimated using group-level data from the 2016 American Community Survey, and patients were categorized based on the percentage of adults 25 years or older in their zip code who did not possess a high school diploma (17.6%+, 10.9%-17.5%, 6.3%-10.8%, and <6.3%) (Commission on Cancer, n.d.). For urban/rural groupings, three categories (urban, metro, and rural) were used, based on population data from the USDA Economic Research Service in 2013 (Commission on Cancer, n.d.). Median income was estimated using group-level data from the 2016 American Community Survey, and patients were categorized into levels based on median household income for their area of residence (<$40,227; $40,227-50,353; $50,354-63,332; and $63,333+) (Commission on Cancer, n.d.).

3.4 Statistical Analysis

Descriptive statistics were conducted to show the percentages of each HPV testing status (not tested, tested, and unknown) within each category of our exposure variables. Categories within each variable included: not insured, private insurance/managed care, Medicaid, Medicare, and Other Government for insurance status; Community Cancer Program, Comprehensive Community Cancer Program, Academic/Research Program, and Integrated Network Cancer Program for facility type; white, Black, Hispanic, and other for race/ethnicity; urban, metro, and rural for urban/rural; 17.6%+, 10.9%-17.5%, 6.3%-10.8%, and <6.3% of adults 25 years or older in a patient's zip code without a high school diploma for educational attainment; and <$40,227, $40,227-50,353, $50,354-63,332, and $63,333+ median income for area of residence for median

income. Chi-square testing was used to assess statistical significance for the distribution of HPV testing statuses across variables. For each exposure variable, trends in HPV testing between 2013 and 2016 were examined, and Fisher's exact test was performed for each year to assess statistical significance. RStudio version 2023.06.1+524 was used for all analyses, and a p-value of <0.05 was considered statistically significant.

4.0 Results

4.1 Sociodemographic Characteristics of Study Population

This study included 3116 individuals with diverse sociodemographic characteristics. Our analysis showed that the proportion of patients who were HPV tested differed significantly across all variables except urban/rural (Table 1). Between 2013 and 2016, the proportion of patients who were HPV tested increased incrementally and significantly (2013 = 73.6% and 2016 = 82.4%, $p<0.001$). For insurance status, patients with private insurance/managed care had the highest proportion who received HPV testing (80.8%), whereas patients on Medicaid had the lowest (70.8%, $p=0.007$). Patients who lived in areas with the lowest educational attainment (17.6%+ of adults with no high school diploma) had the lowest proportion who were HPV tested (69.9%), and those who lived in areas where 6.3%-10.8% of adults had no high school diploma had the highest proportion (80.8%, $p<0.001$).

The proportion of patients who received HPV testing was similar among those from urban, metro, and rural areas ($p=0.345$), but patients from rural areas had the lowest proportion who were tested at 73.1%. Patients who lived in areas with the lowest median income (<$40,227) had the lowest proportion who were HPV tested (70.2%), and patients who lived in areas with median income between $50,354 and $63,332 had the highest (80.9%, $p<0.001$). For facility type, patients whose cancer cases were reported at Community Cancer Programs had the lowest proportion who were HPV tested (69.4%), and those whose cases were reported at Academic/Research Programs had the highest (79.5%, $p<0.001$). Finally, Hispanic patients had the lowest proportion who received HPV testing (70.1%), while white patients had the highest (78.1%, $p<0.031$).

Table 1 – Summary Statistics for Sociodemographic Variables Stratified by HPV Testing Status (n=3116)

Variable	Not Tested (N=224)	Tested (N=2410)	Unknown (N=482)	Chi-square p-value	Total* (N=3116)
Year of Diagnosis				<0.001	
2013	50 (6.6%)	556 (73.6%)	149 (19.7%)		755 (24.2%)
2014	68 (8.7%)	586 (75.2%)	125 (16.0%)		779 (25.0%)
2015	55 (6.8%)	633 (78.1%)	123 (15.2%)		811 (26.0%)
2016	51 (6.6%)	635 (82.4%)	85 (11.0%)		771 (24.7%)
Insurance Status				0.007	
Not Insured	12 (11.4%)	80 (76.2%)	13 (12.4%)		105 (3.4%)
Private Insurance/ Managed Care	94 (6.1%)	1254 (80.8%)	204 (13.1%)		1552 (50.9%)
Medicaid	21 (9.6%)	155 (70.8%)	43 (19.6%)		219 (7.2%)
Medicare	87 (8.1%)	814 (75.5%)	177 (16.4%)		1078 (35.3%)
Other Government	8 (8.3%)	73 (76.0%)	15 (15.6%)		96 (3.1%)
Educational Attainment				<0.001	
17.6%+	42 (8.8%)	332 (69.9%)	101 (21.3%)		475 (17.7%)
10.9%-17.5%	50 (7.5%)	504 (75.9%)	110 (16.6%)		664 (24.8%)
6.3%-10.8%	40 (4.9%)	655 (80.8%)	116 (14.3%)		811 (30.3%)
<6.3%	59 (8.1%)	574 (78.8%)	95 (13.0%)		728 (27.2%)
Urban/rural				0.345	
Metro	181 (7.2%)	1962 (77.5%)	388 (15.3%)		2531 (83.6%)
Urban	27 (6.1%)	344 (77.1%)	75 (16.8%)		446 (14.7%)
Rural	7 (13.5%)	38 (73.1%)	7 (13.5%)		52 (1.7%)
Median Income				< 0.001	
<$40,227	47 (11.7%)	283 (70.2%)	73 (18.1%)		403 (15.1%)
$40,227-50,353	38 (6.3%)	451 (74.7%)	115 (19.0%)		604 (22.6%)
$50,354-63,332	42 (6.5%)	526 (80.9%)	82 (12.6%)		650 (24.4%)
$63,333+	64 (6.3%)	798 (78.9%)	150 (14.8%)		1012 (37.9%)
Facility Type				< 0.001	
Community Cancer Program	6 (4.1%)	102 (69.4%)	39 (26.5%)		147 (4.8%)
Comprehensive Community Cancer Program	55 (5.5%)	785 (77.8%)	169 (16.7%)		1009 (32.7%)
Academic/Research Program	92 (6.4%)	1141 (79.5%)	202 (14.1%)		1435 (46.5%)
Integrated Network Cancer Program	70 (14.1%)	358 (71.9%)	70 (14.1%)		498 (16.1%)
Race				0.031	
White	187 (6.8%)	2159 (78.1%)	418 (15.1%)		2764 (88.7%)
Black	15 (9.6%)	113 (72.4%)	28 (17.9%)		156 (5.0%)
Other	7 (16.7%)	30 (71.4%)	5 (11.9%)		42 (1.3%)
Hispanic	15 (9.7%)	108 (70.1%)	31 (20.1%)		154 (4.9%)

Table 1 legend

- Unknown HPV testing status = coded as 999
- p-values represent chi-square comparison of these groups under the null hypothesis that there is no difference in the proportion of patients who received HPV testing
- *Column percents
- Because some variables might not be recorded for every patient (for example, facility type), the values may not add to the same total

4.2 Temporal Trends in HPV Testing by Exposure Variable

For our analysis, we also examined trends in HPV testing over time for each of the exposure variables. First, we examined how rates of HPV testing differed by insurance status between 2013 and 2016 (Figure 2). For OPSCC patients who were diagnosed in 2013, those with private insurance/managed care had the highest rate of HPV testing at 76.61%. Rates increased slightly over time for this group and ended at 83.76% in 2016. Patients in the insurance category "other government" initially had the lowest HPV testing rate in 2013 (70.0%), then experienced a drop in 2014 before increasing dramatically over the next two years and ended as the group with the highest rate in 2016 (94.44%). HPV testing rates for patients on Medicaid started at 75.0% in 2013, dropped in 2014, rose in 2015, and dropped again in 2016, positioning this group as the category with the lowest rate in 2016 (69.23%). Rates for patients on Medicare were 72.58% in 2013 and 82.03% in 2016. Lastly, the group of patients who were not insured had an HPV testing rate of 75.0% in 2013 and 78.95% in 2016. Fisher's exact test was performed for each of the four years of diagnosis to examine if the differences in HPV testing rates among groups were statistically significant. This testing revealed significant differences for 2014 and 2016 ($p=0.0003165$ and $p=0.0349$, respectively).

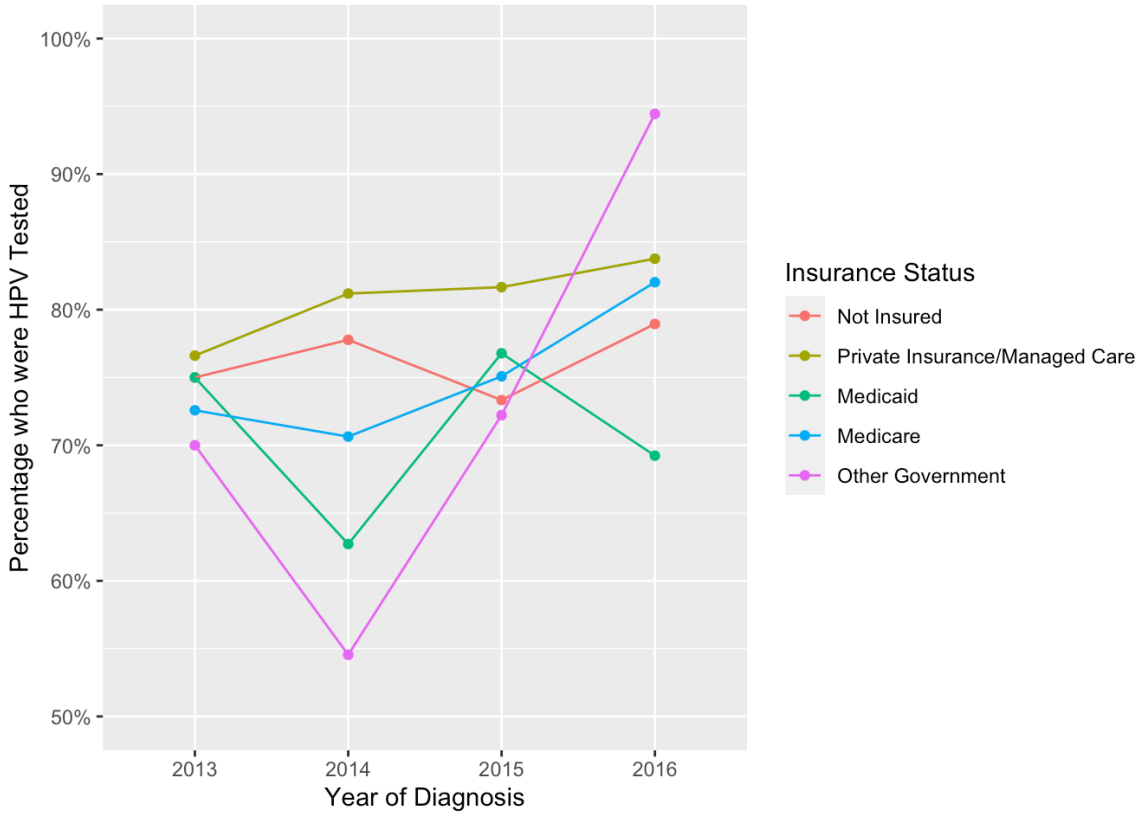

Figure 2 – Percentage who were HPV Tested by Year of Diagnosis and Insurance Status

Next, we examined differences in HPV testing rates for various categories of educational attainment (Figure 3). In 2013, the two groups of patients who lived in areas with the highest levels of educational attainment (<6.3% and 6.3%-10.8% with no high school diploma) had the highest HPV testing rates (78.62% and 79.59%, respectively). The testing rate for the group with the highest educational attainment (<6.3% with no high school diploma) stayed fairly constant over time and ended at 79.78% in 2016. The rate for the group with the second highest educational attainment (6.3%-10.8% with no high school diploma) increased more considerably over time, ending at 84.16% in 2016. For patients who lived in areas with between 10.9% and 17.5% of adults without high school diplomas, the rate of HPV testing started at 70.0% in 2013 and increased substantially to 84.66% in 2016. Lastly, patients in the group with lowest education attainment had

the lowest HPV testing rate in 2013 (65.22%), and while this increased to 77.98% in 2016, they were also the group with the lowest rate in 2016. Fisher's exact test indicated that the only year with a significant difference in HPV testing among the categories of educational attainment was 2013 (p=0.009294).

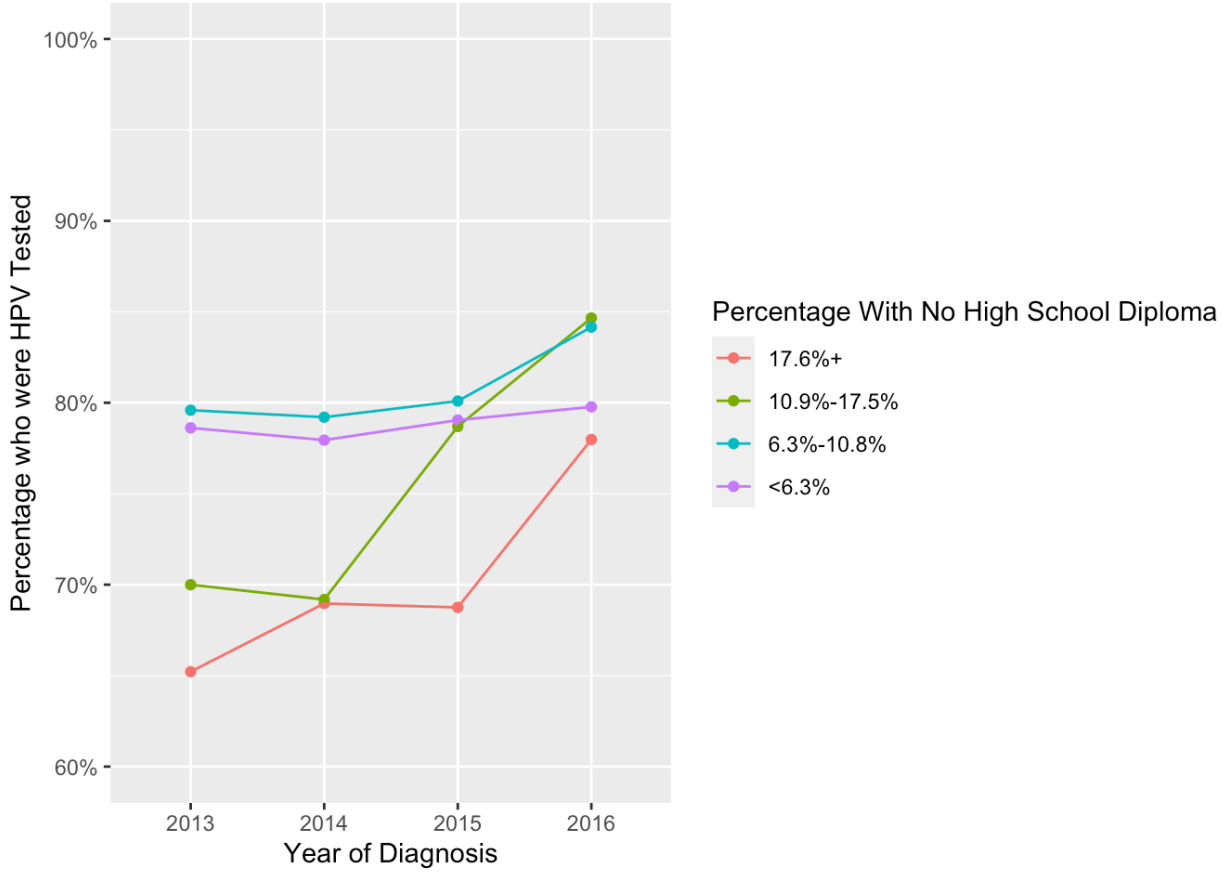

Figure 3 – Percentage who were HPV Tested by Year of Diagnosis and Educational Attainment

The next variable in our analysis was urban/rural categorization (Figure 4). The rates of HPV testing among patients who lived in urban, metro, and rural areas were initially similar in 2013 (71.93%, 73.81%, and 75.0%, respectively). However, rates for patients in metro and urban areas steadily increased over time, whereas rates for rural patients exhibited a different pattern. In

2014, rates for rural patients dropped slightly, increased drastically in 2015, and then declined markedly in 2016 to 63.16%, making them the group with the lowest rate of HPV testing in 2016. Patients from metro areas had the highest testing rate (83.39%) in 2016, with urban patients following closely behind (78.51%). Fisher's exact test showed that 2016 was the only year in which HPV testing rates differed significantly among urban, metro, and rural patients (p=0.04234).

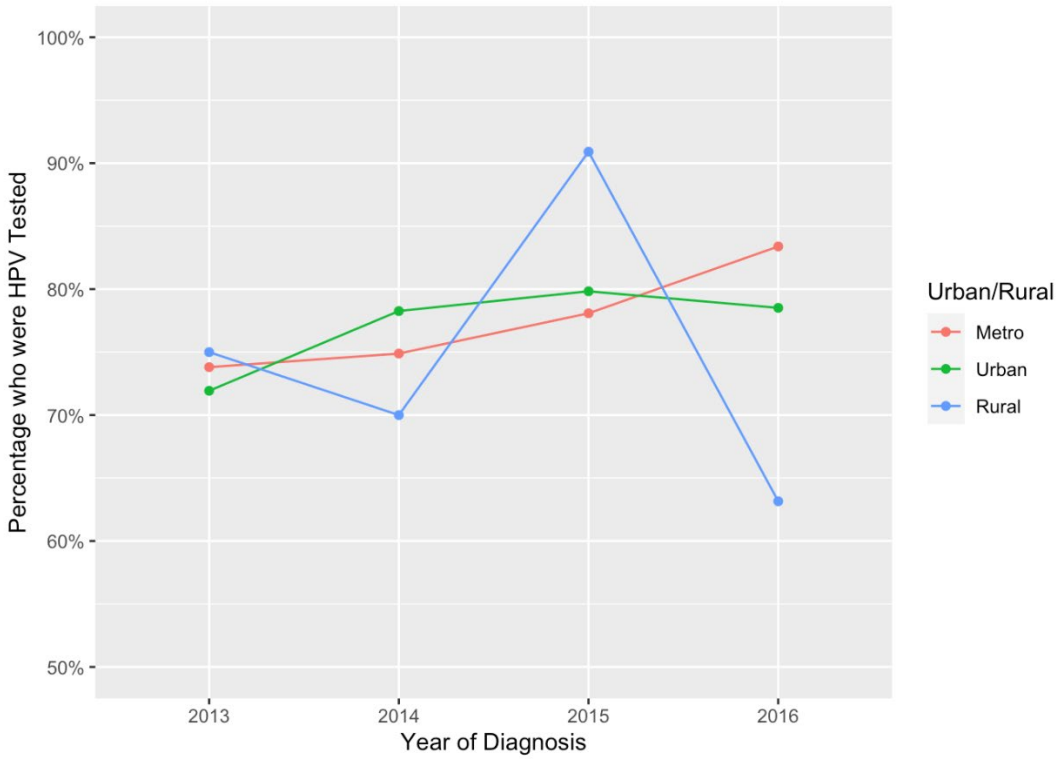

Figure 4 – Percentage who were HPV Tested by Year of Diagnosis and Urban/Rural Categorization

We also included median income in our analysis of temporal trends in HPV testing (Figure 5). In 2013, patients who lived in areas with the highest median income ($63,333+) had the highest rate of HPV testing (77.52%), and patients who lived in areas with the lowest median income (<$40,227) had the lowest testing rate (68.32%). Rates for the group with the highest median income ($63,333+) changed slightly over the next two years and increased to 83.47% in 2016. For

the group of patients who lived in areas where the median income was between $50,354 and $63,332, the rate of HPV testing increased incrementally from 2013 to 2016, and their rate was the highest of all the groups in 2016 (87.20%). The patients who lived in areas with the lowest median income (<$40,227) experienced a decrease in HPV testing rates from 2013 to 2014, and then an increase in 2015 and 2016. The lowest HPV testing rate for 2016 was roughly the same between the two groups of patients from areas with the lowest median incomes – 77.33% for the group with median incomes between $40,227 and $50,353, and 77.36% for the group with median incomes lower than $40,227. Fisher's exact test determined that 2014 was the only year in which HPV testing rates differed significantly by median income among the four groups (p=0.02003).

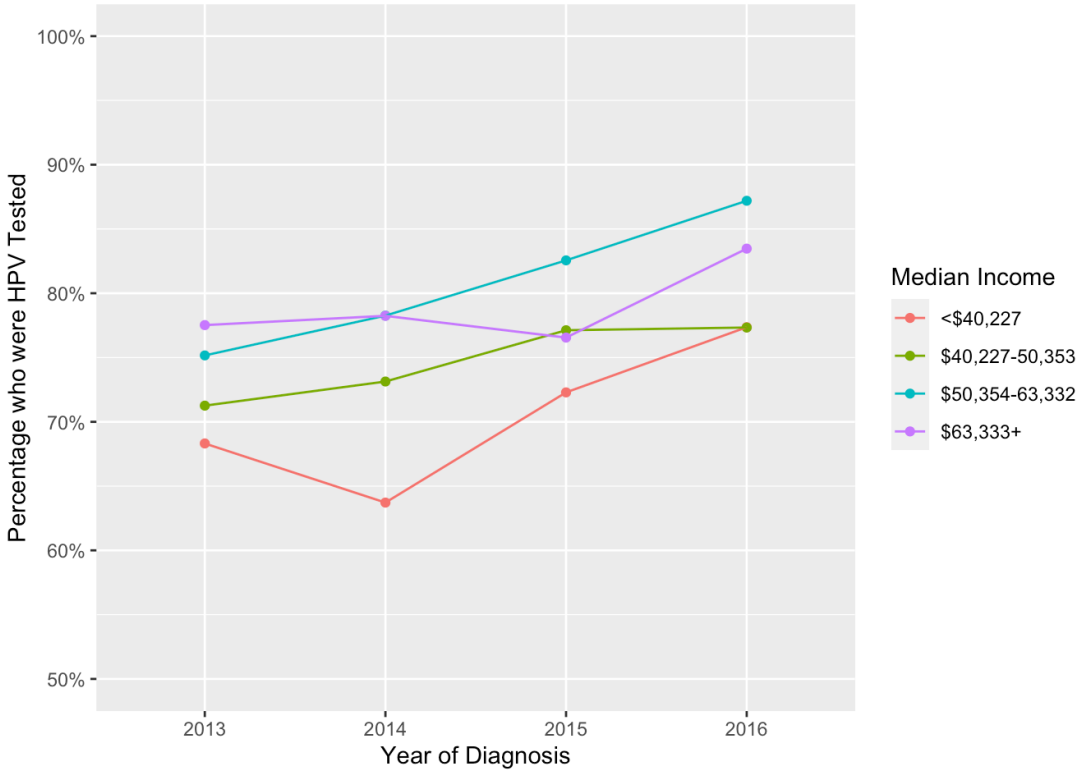

Figure 5 – Percentage who were HPV Tested by Year of Diagnosis and Median Income

The type of facility where cancer cases were recorded was examined next (Figure 6). Academic/Research Programs had the highest HPV testing rate in 2013 at 77.71%, and rates steadily increased over time, ending at 83.33% in 2016. Rates for Integrated Network Cancer Programs started at 73.08% in 2013, reached their lowest point at 65.87% in 2015, and rose to 76.85% in 2016. For Comprehensive Community Cancer Programs, HPV testing rates increased consistently over time, starting at 69.55% in 2013 and ending at 83.78% in 2016. Community Cancer Programs had the lowest HPV testing rate in 2013 (61.74%), but increased incrementally each year, ending at 76.74% in 2016. Fisher's exact test showed that HPV testing rates only differed significantly among facility types in the year 2015 (p=0.002088).

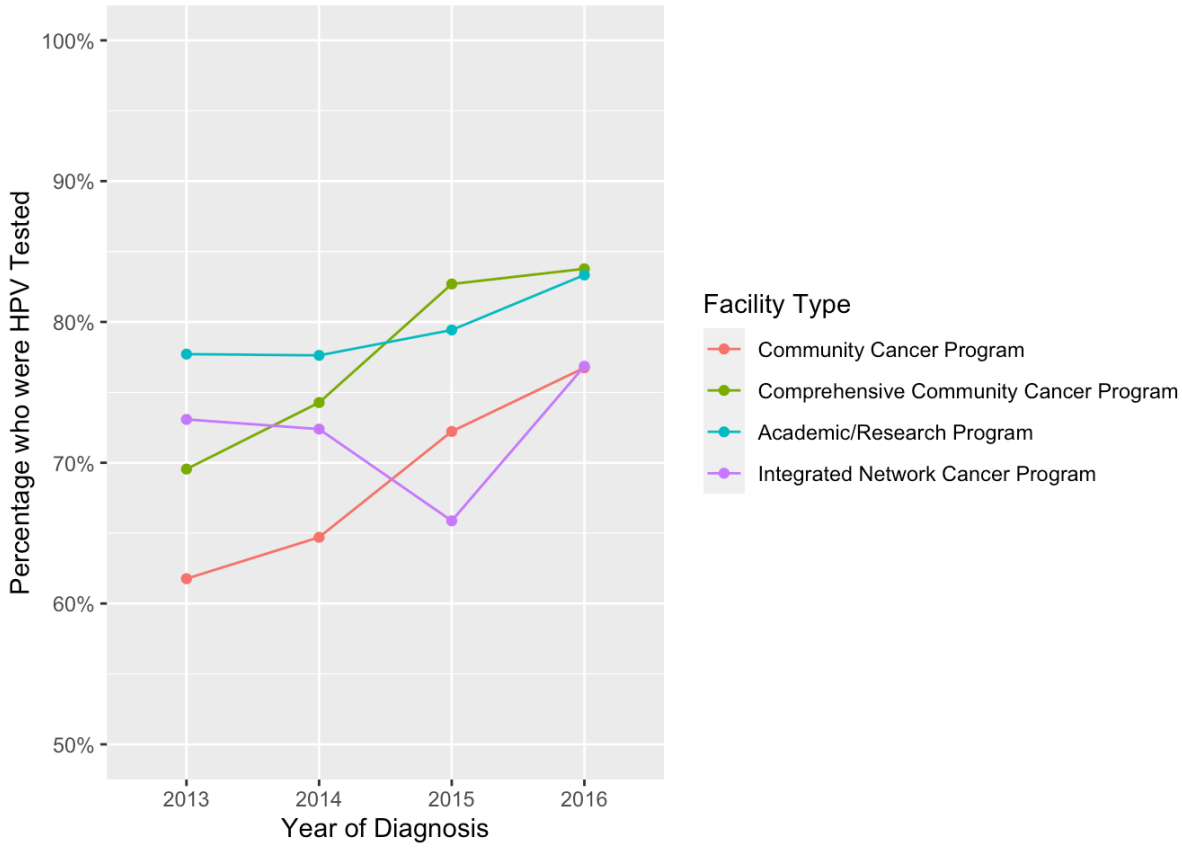

Figure 6 – Percentage who were HPV Tested by Year of Diagnosis and Facility Type

Race was the final variable we examined in this stratified analysis (Figure 7). The highest HPV testing rate in 2013 was among white patients, at 74.62%. The rate for white patients increased slightly each year, ending at 82.32% in 2016. Black patients had the lowest HPV testing rate in 2013 (63.16%), and their rate dropped slightly in 2014 before rising sharply between 2014 and 2015. In 2016, Black patients had the highest HPV testing rate of all the groups, at 84.62%. For Hispanic patients and those in the "Other" category, HPV testing rates followed a similar pattern between 2013 and 2016. The rate for Hispanic patients was 68.18% in 2013, increased slightly in 2014, and decreased considerably to 60.0% in 2015 before sharply rising to 82.35% in 2016. For patients of other races, the HPV testing rate was 73.3% in 2013, decreased markedly between 2013 and 2015, and rose to 75.0% in 2016. According to Fisher's exact test, 2015 was the only year in which HPV testing rates differed significantly among the four racial/ethnic categories ($p=0.03602$).

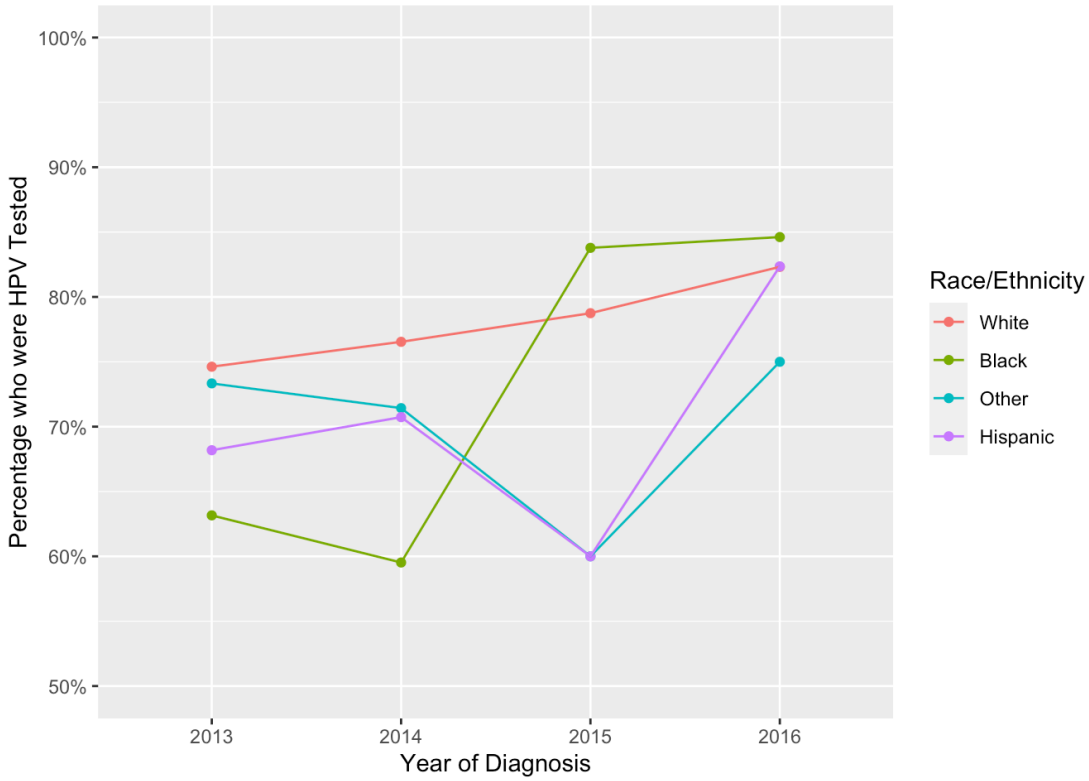

Figure 7 – Percentage who were HPV Tested by Year of Diagnosis and Race/Ethnicity

5.0 Discussion

Our findings demonstrate that significant disparities exist by year of diagnosis and by exposure variable for oropharyngeal squamous cell carcinoma patients in the National Cancer Database. Furthermore, the results of our analysis align with the findings of Husain et al. in their 2021 study that examined HPV testing disparities and guideline adherence for OPSCC patients. Both our analysis and the Husain et al. study found that HPV testing rates increased between 2013 and 2016 and that there were sociodemographic testing disparities by race, insurance status, educational attainment, and facility type.

As Husain et al. described, limitations in our study include issues with the HPV testing variable itself. The HPV testing statuses that were coded as 999 (unknown) could potentially introduce misclassification bias if patients who were truly tested or truly not tested were improperly grouped into unknown testing status. There is a possibility for selection bias, since the patients who were included in the National Cancer Database and into our analysis may be systematically different from patients who were excluded. Furthermore, selection bias could have also been introduced if the distribution of facility types that recorded cancer cases in NCDB changed significantly between 2013 and 2016. Additionally, there may be issues with generalizability of our study findings as those who were included in our analysis may not be representative of the broader population of oropharyngeal cancer patients in the United States.

Ideally, we would expect to see HPV testing rates increase over time for all patients, but this was not always the case in our analysis. For many categories of sociodemographic variables, testing rates declined over time, and sometimes even ended lower than where they began. For example, the HPV testing rate for patients on Medicaid started at 75% in 2013 but ended at 69.23%

in 2016. For patients who lived in rural areas, HPV testing rates were erratic, with an initial increase from 70% to 90.92% between 2014 and 2015, but a sharp decline from 90.92% in 2015 to 63.16% in 2016. These decreases in HPV testing rates and downward trends in testing over time are concerning for subgroups of patients who are being disproportionately affected by substandard HPV testing. The results of Fisher's exact test for insurance status and urban/rural indicate that testing disparities among categories of these variables were significant in 2016, the last year of our analysis. This finding is concerning because rates should be at their highest and most similar among all subgroups in 2016. This data signifies the need for increased consideration of HPV testing for patients with certain sociodemographic characteristics who are diagnosed with OPSCC.

Issues regarding equitable access to treatments have become widespread across many types of cancer and chronic diseases in the United States. For example, novel breast cancer treatments are typically only accessible to patients who are insured or can afford to pay for them out-of-pocket (Chopra et al., 2023). Additionally, access to antiretroviral therapy (ART) for HIV has been complicated by affordability and access to healthcare (Bouabida et al., 2023). These barriers can lead to disparities in patient outcomes based on income and insurance coverage. Our analysis of HPV testing uptake revealed that nearly all OPSCC patient groups in the NCDB between 2013 and 2016 were affected by substandard HPV testing. However, given that certain subgroups were affected disproportionately by these testing inequities, targeted interventions should be prioritized for them going forward. Our analysis showed that special attention should be paid to increase HPV testing rates for marginalized groups of OPSCC patients, including those on Medicaid and the uninsured, those who live in areas with low median income and educational attainment, rural patients, and patients from racial/ethnic minority groups.

Qualitative research may be a valuable way to identify barriers to HPV testing from the perspective of healthcare providers and administrators. In 2013, Maniakas et al. distributed an online survey to three medical associations in North America (Maniakas et al., 2014). Respondents included a wide range of head and neck cancer providers, including head and neck surgeons, radiation oncologists, medical oncologists, and pathologists (Maniakas et al., 2014). Results showed that 67% of respondents reported that they systematically test for HPV in OPSCC cases (Maniakas et al., 2014). Interestingly, physicians who practiced at academic medical centers were more likely to use HPV testing compared to physicians who practiced at non-academic centers (83.3% vs 39.7%, $p<0.001$) (Maniakas et al., 2014). This aligns with our finding that the OPSCC patients in our analysis population who were diagnosed at academic medical centers had some of the highest rates of HPV testing between 2013 and 2016, compared to patients diagnosed at other facility types. Survey respondents in the Maniakas et al. study identified cost of HPV testing, perceived lack of relevance, and insufficient time as obstacles to HPV testing (Maniakas et al., 2014). The researchers acknowledged that a low response rate (15.2%) was a major limitation of their study, which highlights the need for further qualitative research in this area (Maniakas et al., 2014).

Our analysis did reveal some encouraging findings, including improved HPV testing rates over time for some historically marginalized groups. For example, while testing rates for Black patients initially slightly declined, they sharply increased between 2014 and 2015, even exceeding the rates for whites, Hispanics, and patients of other races in 2015 and 2016. Patients in the "other government" insurance category experienced some of the highest HPV testing rates of all variables in 2016, at 94.44%. Overall, HPV testing rates were higher in 2016 than 2013 for all but one category of insurance status (not insured, private insurance/managed care, Medicare, and other

government), all categories of educational attainment (17.6%+, 10.9%-17.5%, 6.3%-10.8%, and <6.3% of adults 25 years or older in a patient's zip code without a high school diploma), all but one category of urban/rural (urban and metro), all categories of median income (<$40,227; $40,227-50,353; $50,354-63,332; and $63,333+), all categories of facility type (Community Cancer Program, Comprehensive Community Cancer Program, Academic/Research Program, and Integrated Network Cancer Program), and all categories of race/ethnicity (white, Black, Hispanic, and other).

The findings of this study provide evidence for policymakers, regulatory organizations, and healthcare providers that HPV testing disparities and substandard guideline adherence are important issues in the management of oropharyngeal cancer. Certain groups of OPSCC patients diagnosed between 2013 and 2016 were less likely to receive HPV testing compared to other groups, and HPV testing did not uniformly increase for all patients between those years. Public health interventions should focus on strategies to increase HPV testing uptake, identify barriers to HPV testing, and reduce disparities to ensure that every patient diagnosed with oropharyngeal squamous cell carcinoma receives the highest quality of care.

Appendix A – Supplementary Tables

Percentage of patients who were HPV tested by year of diagnosis and insurance status

Appendix Table 1

Year of Diagnosis	Insurance Status	Percentage who were HPV tested
2013	Not Insured	75
2013	Private Insurance/Managed Care	76.6129
2013	Medicaid	75
2013	Medicare	72.58065
2013	Other Government	70
2014	Not Insured	77.77778
2014	Private Insurance/Managed Care	81.19048
2014	Medicaid	62.71186
2014	Medicare	70.6383
2014	Other Government	54.54545
2015	Not Insured	73.33333
2015	Private Insurance/Managed Care	81.66259
2015	Medicaid	76.78571
2015	Medicare	75.08651
2015	Other Government	72.22222
2016	Not Insured	78.94737
2016	Private Insurance/Managed Care	83.76068
2016	Medicaid	69.23077
2016	Medicare	82.02614
2016	Other Government	94.44444
2016	Private Insurance/Managed Care	83.76068
2016	Medicaid	69.23077
2016	Other Government	94.44444

Percentage of patients who were HPV tested by year of diagnosis and educational attainment

Appendix Table 2

Year of Diagnosis	Percentage with no high school diploma	Percentage who were HPV tested
2013	17.6%+	65.21739
2013	10.9%-17.5%	70
2013	6.3%-10.8%	79.59184
2013	<6.3%	78.62069
2014	17.6%+	68.96552
2014	10.9%-17.5%	69.18239
2014	6.3%-10.8%	79.20792
2014	<6.3%	77.94872
2015	17.6%+	68.75
2015	10.9%-17.5%	78.69822
2015	6.3%-10.8%	80.09479
2015	<6.3%	79.04762
2016	17.6%+	77.98165
2016	10.9%-17.5%	84.65909
2016	6.3%-10.8%	84.15842
2016	<6.3%	79.77528

Percentage of patients who were HPV tested by year of diagnosis and urban/rural

Appendix Table 3

Year of Diagnosis	Urban/rural	Percentage who were HPV tested
2013	Metro	73.8056
2013	Urban	71.92982
2013	Rural	75
2014	Metro	74.88515
2014	Urban	78.26087
2014	Rural	70
2015	Metro	78.08219
2015	Urban	79.83193
2015	Rural	90.90909
2016	Metro	83.38762
2016	Urban	78.5124
2016	Rural	63.15789

2013	Metro	73.8056
2013	Urban	71.92982
2013	Rural	75
2014	Metro	74.88515

Percentage of patients who were HPV tested by year of diagnosis and median income

Appendix Table 4

Year of Diagnosis	Median income	Percentage who were HPV tested
2013	<$40,227	68.31683
2013	$40,227-50,353	71.25749
2013	$50,354-63,332	75.1634
2013	$63,333+	77.52294
2014	<$40,227	63.71681
2014	$40,227-50,353	73.13433
2014	$50,354-63,332	78.26087
2014	$63,333+	78.24427
2015	<$40,227	72.28916
2015	$40,227-50,353	77.12418
2015	$50,354-63,332	82.55814
2015	$63,333+	76.55172
2016	<$40,227	77.35849
2016	$40,227-50,353	77.33333
2016	$50,354-63,332	87.19512
2016	$63,333+	83.47107

Percentage of patients who were HPV tested by year of diagnosis and facility type

Appendix Table 5

Year of Diagnosis	Facility type	Percentage who were HPV tested
2013	Community Cancer Program	61.76471
2013	Comprehensive Community Cancer Program	69.54733
2013	Academic/Research Program	77.71261
2013	Integrated Network Cancer Program	73.07692

2014	Community Cancer Program	64.70588
2014	Comprehensive Community Cancer Program	74.27386
2014	Academic/Research Program	77.62431
2014	Integrated Network Cancer Program	72.38806
2015	Community Cancer Program	72.22222
2015	Comprehensive Community Cancer Program	82.69231
2015	Academic/Research Program	79.42708
2015	Integrated Network Cancer Program	65.87302
2016	Community Cancer Program	76.74419
2016	Comprehensive Community Cancer Program	83.77358
2016	Academic/Research Program	83.33333
2016	Integrated Network Cancer Program	76.85185

Percentage of patients who were HPV tested by year of diagnosis and race

Appendix Table 6

Year of Diagnosis	Race	Percentage who were HPV tested
2013	White	74.62006
2013	Black	63.15789
2013	Other	73.33333
2013	Hispanic	68.18182
2014	White	76.53959
2014	Black	59.52381
2014	Other	71.42857
2014	Hispanic	70.73171
2015	White	78.74659
2015	Black	83.78378
2015	Other	60
2015	Hispanic	60
2016	White	82.31884
2016	Black	84.61538
2016	Other	75
2016	Hispanic	82.35294

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